Cellular Distribution and Functions of P2 Receptor Subtypes in Different Systems

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This review is aimed at providing readers with a comprehensive reference article about the distribution and function of P2 receptors in all the organs, tissues, and cells in the body. Each section provides an account of the early history of purinergic signaling in the organ/cell up to 1994, then summarizes subsequent evidence for the presence of P2X and P2Y receptor subtype mRNA and proteins as well as functional data, all fully referenced. A section is included describing the plasticity of expression of P2 receptors during development and aging as well as in various pathophysiological conditions. Finally, there is some discussion of possible future developments in the purinergic signaling field.

KEY WORDS: Purinergic, P2X, P2Y, Plasticity, Neuron, Smooth muscle, Epithelium, Endothelium.

I. Introduction

In 1929 Drury and Szent-Györgyi published a seminal paper describing the potent actions of adenine compounds. Some decades later, adenosine 5′-triphosphate (ATP) was proposed as the transmitter responsible for non-adrenergic, noncholinergic (NANC) transmission in the gut and bladder and the term "purinergic" was introduced (Burnstock, 1972). The fact that ATP was recognized primarily for its important intracellular roles in many biochemical processes coupled to the intuitive feeling that such a ubiquitous

and simple compound was unlikely to be utilized as an extracellular messenger fueled early resistance to this concept, even though powerful extracellular enzymes involved in the breakdown of ATP were known to be present.

Implicit in the concept of purinergic neurotransmission was the existence of postjunctional purinergic receptors; in addition, the potent actions of extracellular ATP on many different cell types also implicated membrane receptors. The first definition of purinergic receptors was put forward in 1976 (Burnstock, 1976) followed 2 years later by a proposed basis for distinguishing two types of purinoceptor, identified as P1 and P2 (for adenosine and ATP/adenosine diphosphate [ADP], respectively) (Burnstock, 1978). Concurrent with this, two subtypes of the P1 (adenosine) receptor were recognized (Londos *et al.*, 1980; Van Calker *et al.*, 1979); four subtypes of P1 receptors have subsequently been cloned, namely A_1, A_{2A}, A_{2B}, and A_3 (Fredholm *et al.*, 2001; Ralevic and Burnstock, 1998). It was not until 1985 that the existence of two types of P2 receptors (P2X and P2Y) was proposed (Burnstock and Kennedy, 1985). The following year two further P2 purinoceptor subtypes were tentatively identified, namely a P2T receptor selective for ADP on platelets and a P2Z receptor on macrophages (Gordon, 1986). Further subtypes of P2 receptors followed, perhaps the most important being the P2U receptor that could recognize pyrimidines such as uridine triphosphate (UTP) as well as ATP (O'Connor *et al.*, 1991). At a meeting in 1994, Williams made the point that a classification of P2 purinoceptors based on a "random walk through the alphabet" was not satisfactory, and Abbracchio and Burnstock (1994) proposed that purinoceptors should belong to two major families: a P2X family of ligand-gated ion channel receptors and a P2Y family of G protein-coupled receptors, the classification formed on the basis of transduction mechanism studies (Dubyak, 1991) and the cloning of nucleotide receptors (Brake *et al.*, 1994; Lustig *et al.*, 1993; Valera *et al.*, 1994; Webb *et al.*, 1993). This nomenclature has been widely adopted, and currently seven P2X subtypes and about eight P2Y receptor subtypes are recognized, including receptors that are sensitive to pyrimidines as well as purines (Burnstock, 2003a; Ralevic and Burnstock, 1998).

It is widely recognized that purinergic signaling is a primitive system (Burnstock, 1996a) involved in both neuronal and non-neuronal mechanisms (Abbracchio and Burnstock, 1998), including exocrine and endocrine secretion, immune responses, inflammation, pain, platelet aggregation, and endothelial-mediated vasodilatation (Burnstock, 1997, 2000a, 2003b; Dubyak and el-Moatassim, 1993; Gordon, 1986; Olsson and Pearson, 1990). Receptors for purines and pyrimidine nucleotides are involved in both short-term signaling, such as neurotransmission and secretion, and long-term (trophic) signaling, such as cell proliferation, differentiation, and programmed cell death that occur during development and regeneration

(Burnstock, 2001a, 2002; Neary *et al.*, 1996). P2 receptors show plasticity of expression during development and aging, following trauma or surgery, and in disease (see Section III).

This review is devoted to describing the cell and molecular biology of P2 receptor subtypes in all the body systems. Our approach has been to deal with each system in the following way: We begin with a historical introduction of the early descriptions of the actions of ATP, covering the literature up to 1994 when the first clear framework for P2 receptor subtyping into P2X ionotropic and P2Y metabotropic families was put forward (Abbracchio and Burnstock, 1994). A table follows summarizing the distribution of P2 receptor mRNA, protein, and functional receptors (receptor mRNA as seen with Northern blots, reverse transcriptase-polymerase chain reaction [RT-PCR], or *in situ* hybridization; protein as seen with immunostaining, Western blots, or autoradiography/ligand binding, and identification of functional P2 receptor subtypes as seen by pharmacology/electrophysiology, Ca^{2+} imaging, and biochemistry). The functions claimed for the receptors identified are included in the table, as well as the key references. Finally, there is a section concerned with the sources of ATP that could act on the receptors and a brief summary of the main purinergic signaling features of the system.

A. Current Status of P2 Receptor Subtypes

1. *P2X receptors*: Members of the existing family of ionotropic $P2X_{1-7}$ receptors exhibit a subunit topology of: intracellular N- and C-termini possessing consensus binding motifs for protein kinases; two transmembrane spanning regions, the first (TM1) being involved with channel gating and the second (TM2) lining the ion pore; a large extracellular loop, with 10 conserved cysteine residues forming a series of disulfide bridges; a hydrophobic H5 region close to the pore vestibule, for possible receptor/channel modulation by cations (magnesium, calcium, zinc, copper, and proton ions); and an ATP-binding site, which may involve regions of the extracellular loop adjacent to TM1 and TM2 (see Fig. 1a). The $P2X_{1-7}$ receptors show 30–50% sequence identity at the peptide level. The stoichiometry of $P2X_{1-7}$ receptors is thought to involve three subunits that form a stretched trimer (Khakh *et al.*, 2001).

The pharmacology of the recombinant P2X receptor subtypes expressed in oocytes or other cell types displays significant differences from the pharmacology of P2X-mediated responses in naturally occurring sites. There are several contributing factors that may explain these differences. The trimer ion pore may form heteromultimers as well as homomultimers. For example, heteromultimers of $P2X_2$ and $P2X_3$ receptor subtypes ($P2X_{2/3}$) are clearly established in nodose ganglia (Lewis *et al.*, 1995; Radford *et al.*, 1997), $P2X_{4/6}$

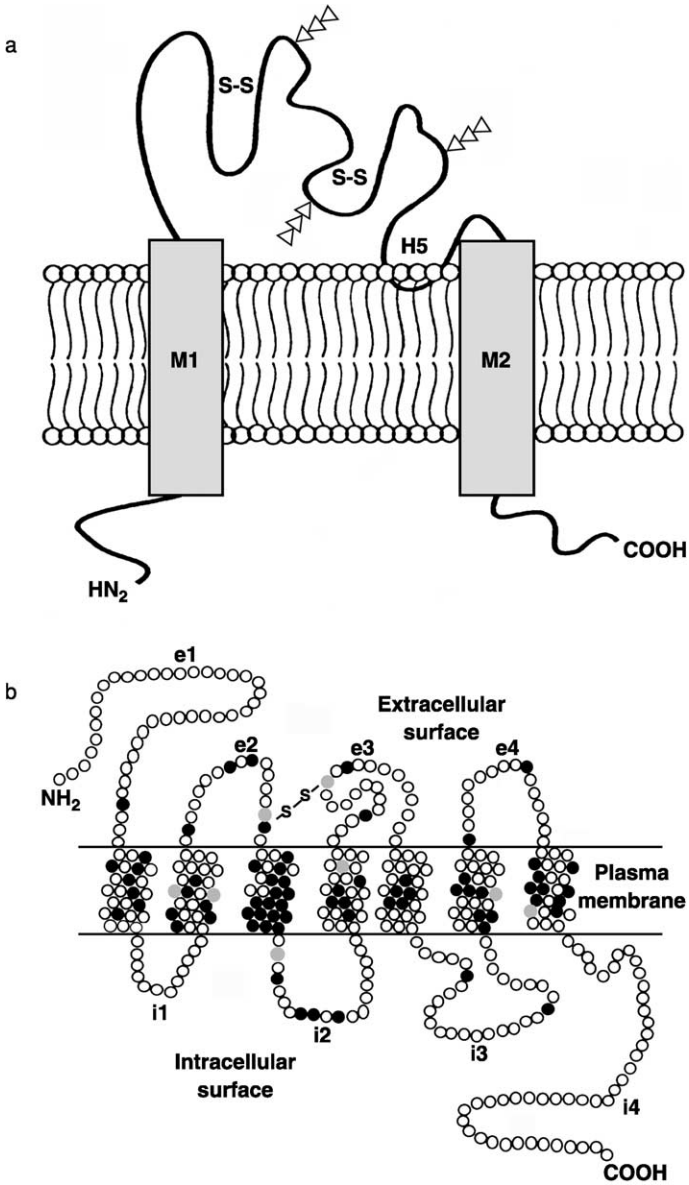

FIG. 1 (a) Diagram depicting the transmembrane topology for P2X receptor protein showing both N-terminus and C-terminus in the cytoplasm. Two putative membrane-spanning segments (M1 and M2) traverse the lipid bilayer of the plasma membrane and are connected by a hydrophilic segment of 270 amino acids. This putative extracellular domain is shown containing two disulfide-bonded loops (S–S) and three N-linked glycosyl chains (triangles). (From Brake

in central nervous system (CNS) neurons (Lê *et al.*, 1998), $P2X_{1/5}$ in some blood vessels (Haines *et al.*, 1999; Torres *et al.*, 1998), and $P2X_{2/6}$ in the brain stem (King *et al.*, 2000b). $P2X_7$ does not form heteromultimers, and $P2X_6$ will not form a functional homomultimer (North and Surprenant, 2000; Torres *et al.*, 1999). Second, spliced variants of P2X receptor subtypes may be a contributing factor. For example, a splice variant of the $P2X_4$ receptor, while on its own nonfunctional, can potentiate the actions of ATP through the full-length $P2X_4$ receptors (Townsend-Nicholson *et al.*, 1999). Third, the presence of powerful ectoenzymes that rapidly break down purines and pyrimidines in native tissues is not a factor when examining recombinant receptors (Zimmermann, 1996).

Within the P2X receptor family there are many pharmacological and operational differences between individual receptor subtypes. The kinetics of activation, inactivation, and deactivation also vary considerably among P2X receptors. Calcium permeability is high for some P2X subtypes, a property that may be functionally important. For a more specific review of P2X receptor molecular biology, cell biology, physiology, and biophysics, the reader is referred to North (2002).

2. *P2Y receptors*: Metabotropic $P2Y_{1-14}$ receptors have a characteristic subunit topology of an extracellular N-terminus and an intracellular C-terminus, the latter possessing consensus binding motifs for protein kinases; seven transmembrane-spanning regions that help to form the ligand docking pocket; a high level of sequence homology between some transmembrane-spanning regions, in particular TM3, TM6, and TM7; the intracellular loops and C-terminus posses structural diversity among P2Y subtypes, so influencing the degree of coupling with $G_{q/11}$, G_s, and G_i proteins (see Fig. 1b). Each P2Y receptor binds to a single heterotrimeric G protein (typically $G_{q/11}$), although $P2Y_{11}$ can couple to both $G_{q/11}$ and G_s whereas $P2Y_{12}$ couples to G_i and $P2Y_{14}$ to $G_{i/0}$. Under certain conditions P2Y receptors may form homo- and heteromultimeric assemblies, and many tissues express multiple P2Y subtypes (King *et al.*, 2000a). P2Y receptors show a low level of sequence homology at the peptide level (19–55% identical) and, consequently, show significant differences in their pharmacological and operational profiles. $P2Y_1$, $P2Y_6$, and $P2Y_{12}$ receptors are activated principally by nucleoside diphosphates, while $P2Y_2$ and $P2Y_4$ are activated mainly by nucleoside

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et al., 1994; reproduced with permission from Nature.) (b) Schematic diagram of the sequence of the $P2Y_1$ receptor showing its differences from $P2Y_2$ and $P2Y_3$ receptors. Filled circles represent amino acid residues that are conserved among the three receptors. (Modified from Barnard *et al.* (1994). *Trends Pharmacol. Sci.* **15,** 67–70; reproduced with permission from Elsevier Science.)

triphosphates. $P2Y_2$, $P2Y_4$, and $P2Y_6$ receptors are activated by both purine and pyrimidine nucleotides and $P2Y_1$, $P2Y_{11}$, and $P2Y_{12}$ receptors are activated by purine nucleotides alone. In response to nucleotide activation, recombinant P2Y receptors either activate phospholipase C (PLC) and release intracellular calcium ($[Ca^{2+}]_i$) or affect adenylyl cyclase and alter cAMP levels. To date there is insufficient evidence to indicate that the $P2Y_5$, $P2Y_9$, and $P2Y_{10}$ sequences are nucleotide receptors or affect intracellular signaling cascades. Endogenous P2Y receptors show a great diversity in intracellular signaling and can activate phospholipases A_2, C, and D, major excreted protein (MEP)/mitogen-activated protein (MAP) kinase, Rho-dependent kinase and tyrosine kinase, as well as coupling both positively and negatively to adenylyl cyclase.

At mammalian $P2Y_1$ receptors, 2-methylthioADP (2-MeSADP) is a potent agonist (Hechler *et al.*, 1998) and N^6-methyl-2′-deoxyadenosine 3′,5′-bisphosphate (MRS 2179) a potent antagonist (Boyer *et al.*, 1998); N^6-methyl-1,5-anhydro-2-(adenin-9-yl)-2,3-dideoxy-D-arabinohexitol-4,6-bis (diammonium phosphate) (MRS 2269) and MRS 2286 have been identified as selective antagonists (Brown *et al.*, 2000). ATP and UTP are equipotent at $P2Y_2$ and $P2Y_4$ receptors in the rat, but the two receptors can be distinguished with antagonists, as suramin blocks $P2Y_2$, while Reactive Blue 2 blocks $P2Y_4$ receptors (Bogdanov *et al.*, 1998b; King *et al.*, 1998a). $P2Y_6$ is uridine diphosphate (UDP)-selective, while $P2Y_7$ has been revealed to be a leukotriene receptor (Yokomizo *et al.*, 1997). $P2Y_8$ is a receptor cloned from frog embryos, at which all the nucleotides are equipotent (Bogdanov *et al.*, 1997), but no mammalian homologue has been identified to date, apart from a recent report of $P2Y_8$ mRNA in undifferentiated HL60 cells (Adrian *et al.*, 2000). $P2Y_{11}$ is unusual in that two transduction pathways can be activated, adenylate cyclase as well as inositol triphosphate (IP_3), which is the second messenger system used by the majority of the P2Y receptors. The $P2Y_{12}$ receptor found on platelets was not cloned until more recently (Hollopeter *et al.*, 2001), although it has only 19% homology with the other P2Y receptor subtypes. This receptor together with $P2Y_{13}$ and $P2Y_{14}$ may represent a subgroup of P2Y receptors for which transduction is entirely through adenylate cyclase (Abbracchio *et al.*, 2003; Communi *et al.*, 2001a,b; Zhang *et al.*, 2002). A receptor on C6 glioma cells and possibly a receptor in the midbrain, selective for a diadenosine polyphosphate, also may operate through adenylate cyclase. An interesting question that has arisen by analogy with other G protein-coupled receptors is whether dimers can form between the P2Y subtypes. For a specific review of P2Y receptor biology and physiology, see Lazarowski (2003).

Table I summarizes the structure and properties of current receptor subtypes while Table II summarizes the current status of P2 receptor subtype agonists and antagonists.

TABLE I

Characteristics of Receptors for Purines and Pyrimidines[a, b]

Receptor		Main distribution	Agonists	Antagonists	Transduction mechanisms
P2X	$P2X_1$	Smooth muscle, platelets, cerebellum, dorsal horn spinal neurons	α,β-meATP = ATP = 2-MeSATP (rapid desensitization)	TNP-ATP, IP_5I, NF023	Intrinsic cation channel (Ca^{2+} and Na^+)
	$P2X_2$	Smooth muscle, CNS, retina, chromaffin cells, autonomic and sensory ganglia	ATP ≥ ATPγS ≥ 2-MeSATP >> α,β-meATP (pH + zinc sensitive)	Suramin, PPADS	Intrinsic ion channel (particularly Ca^{2+})
	$P2X_3$	Sensory neurons, NTS, some sympathetic neurons	2-MeSATP ≥ ATP ≥ α,β-meATP (rapid desensitization)	TNP-ATP, suramin, PPADS	Intrinsic cation channel
	$P2X_4$	CNS, testis, colon	ATP >> α,β-meATP	—	Intrinsic ion channel (especially Ca^{2+})
	$P2X_5$	Proliferating cells in skin, gut, bladder, thymus, spinal cord	ATP >> α,β-meATP	Suramin, PPADS	Intrinsic ion channel
	$P2X_6$	CNS, motor neurons in spinal cord	(Does not function as homomultimer)	—	Intrinsic ion channel
	$P2X_7$	Apoptotic cells in immune cells, pancreas, skin, etc.	Bz-ATP > ATP ≥ 2-MeSATP >> α,β-meATP	KN-62, KN04 Coomassie brilliant blue	Intrinsic cation channel and a large pore with prolonged activation
P2Y	$P2Y_1$	Epithelial and endothelial cells, platelets, immune cells, osteoclasts	2-MeSADP > 2-MeSATP = ADP > ATP	MRS 2279, MRS 2179	G_q/G_{11}; PLCβ activation
	$P2Y_2$	Immune cells, epithelial and endothelial cells, kidney tubules, osteoblasts	UTP = ATP	Suramin	G_q/G_{11} and possibly G_i; PLCβ activation
	$P2Y_4$	Endothelial cells	UTP ≥ ATP	Reactive Blue 2, PPADS	G_q/G_{11} and possibly G_i; PLCβ activation
	$P2Y_6$	Some epithelial cells, placenta, T cells, thymus	UDP > UTP >> ATP	Reactive Blue 2, PPADS, suramin	G_q/G_{11}; PLCβ activation

(*continued*)

TABLE I (*continued*)

Receptor	Main distribution	Agonists	Antagonists	Transduction mechanisms
$P2Y_{11}$	Spleen, intestine, granulocytes	AR-C67085MX > Bz-ATP ≥ ATPγS > ATP	Suramin, Reactive Blue 2	G_q/G_{11} and G_s; PLCβ activation
$P2Y_{12}$	Platelets, glial cells	ADP = 2-MeSADP	AR-C67085MX, AR-C69931MX	G_i (2); inhibition of adenylate cyclase
$P2Y_{13}$	Spleen, brain, lymph nodes, bone marrow	ADP = 2-MeSADP >> ATP and 2-MeSATP		G_i
$P2Y_{14}$	Placenta, adipose tissue, stomach, intestine, discrete brain regions	UDP-glucose = UDP-galactose		$G_{i/o}$

[a]Modified, with permission, from Burnstock (2003a).

[b]ATP, adenine-5′-triphosphate; ADP, adenosine-5′-diphosphate; 2-MeSATP, 2-methylthioadenosine 5′-triphosphate; 2-MeSADP, 2-methylthio ADP; α,β-meATP, α,β-methylene ATP; Bz-ATP, benzoyl ATP; UTP, uridine triphosphate, UDP, uridine diphosphate; PPADS, pyridoxal-phosphate-6-azophenyl-2′,4′-disulfonic acid; NF023, 8,8′-[carbonylbis(imino-3,1-phenylenecarbonyl-imino)] bis-(1,3,5-naphthalene trisulfonate); MRS 2179, N^6-methyl-2′-deoxyadenosine 3′,5′-bisphosphate; MRS 2279, 2-chloro-N^6-methyl-(*N*)-methanocarba-2′-deoxyadenosine-3′,5′-bisphosphate; TNP-ATP, trinitrophenol-ATP; KN-62, 1-[*N*,*O*-bis(5-isoquinolinesulfonyl)-*N*-methyl-L-tyrosyl]-4-phenylpiperazine; AR-C67085 MX, 2-propylthio-D-β-γ-dichloromethylene ATP; IP_5I, diinosine pentaphosphate.

TABLE II

Mammalian P2 Receptors and Assessment of Activities of Agonists and Antagonists[a,b]

	$P2X_1$	$P2X_2$	$P2X_3$	$P2X_4$	$P2X_5$	$P2X_6$	$P2X_7$	$P2X_{2/3}$	$P2X_{1/5}$	$P2X_{4/6}$	$P2Y_1$	$P2Y_2$	$P2Y_4$	$P2Y_6$	$P2Y_{11}$	$P2Y_{12}$	$P2Y_{13}$	$P2Y_{14}$
Agonists																		
ATP	✓✓✓	✓✓	✓✓✓	✓✓	✓✓	✓	✓	✓✓✓	✓✓✓	✓✓	✓	✓✓✓	✓✓	—	✓			
ADP	✓	—	✓	—	—	—	—		✓✓		✓✓		✓			✓✓	✓✓	
2-MeSATP	✓✓✓	✓✓	✓✓✓	✓✓	✓✓	✓	✓				✓✓		✓	✓	✓	✓	✓✓	
PAPET-ATP	✓✓	✓	✓✓✓	✓							✓✓✓[c]							
2-MeSADP				✓							✓✓✓[c]			✓✓		✓✓✓	✓✓✓	
HT-AMP	✓✓	—	✓✓✓	✓✓							✓✓							
α,β-meATP	✓✓✓[c]	—	✓✓✓[c]	✓	✓	✓	—	✓✓✓	✓✓	✓			—					
β,γ-meATP	✓✓	—	✓✓	—	✓		—						—					
ATPγS	✓✓	✓✓	✓✓	✓	✓✓	✓	—				✓	✓	✓		✓✓✓	✓		
ATPβS											✓✓				✓	✓✓		
Bz-ATP	✓✓✓	✓✓	✓	✓✓✓	✓✓		✓✓						✓ [antag]		✓✓✓			
UDP-glucose																		✓✓✓[c]
UDPβS														✓✓✓[c]				
2-dATP															✓✓			
Ap_4A	✓✓✓	✓	✓✓✓	✓	✓							✓✓	✓✓					
UTP	—	—	—	—	✓							✓✓✓	✓✓✓	✓				
UTPγS												✓✓✓[c]						
UDP					—							✓	✓✓	✓✓✓				
CTP	✓	✓	✓	—	✓								✓✓					
Antagonists																		
PPADS	✓✓	✓✓	✓✓	—	✓✓	✓	✓					✓	✓	✓✓				
isoPPADS	✓✓	✓✓	✓✓															
PPNDS	✓✓[c]																	
Suramin	✓✓	✓	✓	—	✓✓	—	—				✓	✓	—	—	✓✓	✓		
NF023	✓✓[c]	✓	✓															
Reactive Blue 2	✓	✓✓	✓	—	✓						✓		✓	✓✓	✓	✓✓		
MRS 2179	✓	—	✓	—							✓✓✓	—	—	—				

(*continued*)

TABLE II (*continued*)

	$P2X_1$	$P2X_2$	$P2X_3$	$P2X_4$	$P2X_5$	$P2X_6$	$P2X_7$	$P2X_{2/3}$	$P2X_{1/5}$	$P2X_{4/6}$	$P2Y_1$	$P2Y_2$	$P2Y_4$	$P2Y_6$	$P2Y_{11}$	$P2Y_{12}$	$P2Y_{13}$	$P2Y_{14}$
MRS 2279	—		—								✓✓✓[c]							
TNP-ATP	✓✓✓[c]	✓	✓✓✓[c]	✓	✓		✓											
KN-62							✓✓✓(h)											
AR-C67085MX															✓✓[c] [ag]	✓✓✓[c]		
2-MeSAMP																✓✓		
Brilliant Blue G	✓	✓	—				✓✓✓(r)											
Ip_5I	✓✓✓[c]	—	✓	—														
MRS 2257	✓✓✓[c]		✓✓[c]															
NF279	✓✓✓[c]	✓	✓	—			✓											
NF449	✓✓✓	✓✓									✓	✓						

[a]Modified with permission, from Burnstock (2003a).

[b]Number of ticks (✓) indicates relative potency with respect to agonist/antagonist concentration. Agonists: ✓✓✓, <1 μ*M*; ✓✓, 1–10 μ*M*; ✓, >10 μ*M*; —, virtually inactive. Antagonists: ✓✓✓, <10 n*M*; ✓✓, 10–300 n*M*; ✓, >300 n*M*; —, virtually inactive. h, human; r, rat; PAPET-ATP, 2-[2-(4-aminophenyl)ethylthio]adenosine 5′-triphosphate; HT-AMP, 2-(hexylthio)adenosine 5′-monophosphate; Ap_4A, P^1, P^4-di-(adenosine-5′)-tetraphosphate; 2-dATP, deoxyATP; CTP, cytidine triphosphate; iso-PPADS, pyridoxal-phosphate-6-azophenyl-2′,5′-disulfonic acid; PPNDS, pyridoxal-5′-phosphate-6-(2′-naphthylazo-6′-nitro-4′,8′-disulfonate); MRS 2257, pyridoxal-5′-phosphonate-6-azophenyl-3′,5′-bismethyl phosphonate; NF279, [8,8′-[carbonylbis(imino-4,1-phenylene carbonylimino-4,1-phenylene carbonylimino)]bis(1,3,5-naphthalenetrisulphonic acid)]; NF449, 4,4′,4″,4‴-[carbonyl-bis[imino-5,1,3-benzenetriyl bis(carbonylimino)]]tetrakis(benzene-1,3-disulfonate).

[c]Selective agonist or antagonist.

II. Distribution and Functions of P2 Receptor Subtypes in Different Organs, Cells, and Tissues

A. Respiratory System

1. Lung

ATP (probably via adenosine) has been known as a bronchodilating agent for many years (Venugopalan *et al.*, 1986). Similarly, the presence of both vasoconstricting P2X receptors and vasodilating P2Y receptors in pulmonary vessels has long been recognized in both rats and humans (Liu *et al.*, 1989a,b).

ATP exerts various effects upon airway epithelial cells. Alveolar type II cells synthesize and secrete surfactant in response to a variety of secretagogues, of which ATP is a particularly potent example. The earliest report that ATP can stimulate surfactant release was in 1983 (Gilfillan *et al.*, 1983) and was soon followed by Rice and Singleton (1986), whose data provided evidence for ATP regulating surfactant secretion and release from alveolar type II cells in rats via a P2 receptor. Further studies characterized the P2 receptor as a P2Y receptor (Rice, 1990; Rice and Singleton, 1987, 1989).

ATP also activates epithelial cells with different phenotypes. Ciliated epithelial cells are important as defense against pathogenic microbes and microparticles. Some patients suffering from chronic bronchitis and bronchiectasis also showed an increase in ciliary activity in response to ATP (Rossman *et al.*, 1980). This effect is not limited to impaired cilia; indeed, ATP has been shown to enhance mucociliary transport in healthy subjects (Saano *et al.*, 1991; Yoshitsugu *et al.*, 1993). Goblet cells are also important in airway defense, and these cells were induced to synthesize and secrete mucins in response to applied ATP, via a cell surface P2 receptor (Davis *et al.*, 1992; Kim and Lee, 1991; Kim *et al.*, 1993a).

The distribution and function of P2 receptor subtypes in the lung are summarized in Table III with descriptions of receptor subtype mRNA (as seen with Northern blots, RT-PCR, or *in situ* hybridization), protein (as seen with immunostaining, Western blots, or autoradiography/ligand binding), and identification of P2 receptor subtypes of the lung based on the pharmacological or chemical profile (as seen by pharmacology/electrophysiology, Ca^{2+} imaging, and biochemistry). The functions claimed for the receptors identified are included in Table III, as well as the key references (cf. Table XXIV).

ATP was released from airway epithelial cells both under basal conditions and following stimulation with hypotonic conditions (Donaldson *et al.*, 2000; Guyot and Hanrahan, 2002; Taylor *et al.*, 1998), and human airway epithelial cells have been found to contain ecto-adenylate kinase thought to prolong

TABLE III
Lung[a]

Cellular component	Receptor mRNA		Receptor protein		Pharmacological and biochemical profile		Function	References
Whole lung			$P2X_4$ (E)					Bo *et al.*, 2003[b]
Airway smooth muscle								
Lung slices						$P2Y_2$ (G) or $P2Y_4$ (G)	ATP and UTP stimulate Ca^{2+} oscillations	Bergner and Sanderson, 2002[c]
Cultured smooth muscle cells		$P2Y_2$ (B) $P2Y_4$ (B) $P2Y_6$ (B)				$P2Y_2$ (G) or $P2Y_4$ (G) $P2Y_6$ (G)	ATP and UTP increase, and UDP decreases smooth muscle proliferation	Michoud *et al.*, 2002[c]
Epithelium								
Goblet cells				$P2Y_2$ (D)		$P2Y_2$ (G)	ATP and UTP enhance mucin secretion	Kishore *et al.*, 2000[c] Wegner, 2001[c] Conway *et al.*, 2003[c]
Alveolar type II cells	$P2X_4$ (B) $P2Y_5$ (B)	$P2Y_2$ (AB)		$P2Y_2$ (D)		$P2Y_2$ (GH)	ATP enhances mucociliary clearance ATP and UTP increase Cl^- currents ATP stimulates AA release	Buell *et al.*, 1996[b] Gobran *et al.*, 1994[c] Rice *et al.*, 1995[c] Collo *et al.*, 1996[b] Taylor *et al.*, 1999[b] Kishore *et al.*, 2000[c] Laubinger *et al.*, 2001[c] Mesher *et al.*, 2003[c]
Ciliated epithelium			$P2X_4$ (D)	$P2Y_2$ (D)	$P2X_{cilia}$ (G)	P2Y (GH)	ATP potentiates surfactant release ATP accelerates ciliary beat frequency	Stutts *et al.*, 1994[c] Ma *et al.*, 1999[d] Korngreen *et al.*, 1998[b] Braiman *et al.*, 2000[c] Homolya *et al.*, 2000[c] Bo *et al.*, 2003[b] Picher and Boucher, 2003[c] Zhang and Sanderson, 2003[c]

Nonciliated epithelium (Clara cells)					$P2Y_2$ (G)	ATP and UTP stimulate Cl^- and HCO_3^- secretion	Van Scott *et al.*, 1995[c] Kishore *et al.*, 2000[c]
Epithelial cell lines							
Alveolar cell line (L2)				P2X (GH)		ATP increases $[Ca^{2+}]_i$	Dietl *et al.*, 1995[b]
HBE1 cells					$P2Y_2$ (G)	ATP decreases intracellular pH ATP activates basolateral Na^+/H^+ exchange	Walsh *et al.*, 1998[c] Sienaert *et al.*, 1998[c] Urbach *et al.*, 2002[c]
16 HBE14o cells	$P2X_4$ (B) $P2X_5$ (B)		$P2X_4$ (D)	$P2X_4$ (H)	$P2Y_4$ (G)	ATP and UTP increase Cl^- currents	Taylor *et al.*, 1999[b] Conway *et al.*, 2003[c] Zsembery *et al.*, 2003[d]
BEAS39 cells					$P2Y_2$ (H) $P2Y_6$ (G)		Lazarowski *et al.*, 1994[c] Communi *et al.*, 1999[c]
A549 cells		$P2Y_2$ (B) $P2Y_6$ (B)			$P2Y_2$ (G) $P2Y_6$ (G)	ATP and UTP regulate proliferation	Schäfer *et al.*, 2003[c]
CALU-3 serous cells	$P2X_4$ (B) $P2X_5$ (B)	$P2Y_1$ (B)			Apical $P2Y_1$ (G) Basolateral $P2Y_2$ (G)	ATP activates basolateral Na^+/H^+ exchange	Clunes *et al.*, 2002[c] Taylor *et al.*, 1999[b]
Cystic fibrosis					$P2Y_2$ (G)		Parr *et al.*, 1994[c] Clarke *et al.*, 1997[c] Weisman *et al.*, 1998b[c]
IB3-1 cells			$P2X_4$ (D)	$P2X_4$ (H)	$P2Y_2$ (H)		Paradiso, 1997[c] Paradiso *et al.*, 2001[c] Zsembery *et al.*, 2003[d]
Neuroepithelial bodies			$P2X_3$ (D)			ATP is involved in mechanosensory transduction and O_2 sensing	Brouns *et al.*, 2000[b]

(*continued*)

TABLE III (*continued*)

Cellular component	Receptor mRNA	Receptor protein	Pharmacological and biochemical profile	Function	References
Sensory nerves			P2X (G)	ATP evokes cardiorespiratory reflexes	Pelleg and Hurt, 1996[b] Katchanov *et al*., 1998[b] McQueen *et al*., 1998[b]
Pulmonary vasculature	See Table XXV				

[a]Receptor mRNA: A, Northern blot; B, RT-PCR; C, *in situ* hybridization. Receptor protein: D, immunostaining; E, Western blot; F, autoradiography/ligand binding. Pharmacological and biochemical profile: G, pharmacology/electrophysiology; H, Ca^{2+} imaging; I, biochemistry. AA, arachidonic acid; ACh, acetylcholine; Ap_4A, P^1,P^4–di-(adenosine-5′)-tetraphosphate; Ap_5A, P^1,P^4-di-(adenosine-5′)-pentaphosphate; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; AVP, arginine vasopressin; CA, catecholamine; CGRP, calcitonin gene-related peptide; DRG, dorsal root ganglion; EJP, excitatory junction potentials; GABA, γ-aminobutyric acid; EDHF, endothelium-dependent hyperpolarizing factor; EJP, excitatory junction potential; EPSC, excitatory postsynaptic current; EPSP, excitatory postsynaptic potential; IJP, inhibitory junction potential; IL, interleukin; INF, interferon; IPSC, inhibitory postsynaptic current; LH, luteinizing hormone; LPS, lipopolysaccharide; IPSC, inhibitory postsynaptic current; MAPK, mitogen-activated protein kinase; MDCK, Madin–Darby canine kidney; α,β-meATP, α,β-methylene ATP; MNDA, methyl neodecanamide; NA, noradrenaline; NANC, nonadrenergic noncholinergic; NGF, nerve growth factor; NMJ, neuromuscular junction; NO, nitric oxide; NOS, nitric oxide synthase; PG, prostaglandin; PL, phospholipase; PTH, parathyroid hormone; RB2, Reactive Blue 2; R, receptors; SCG, superior cervical ganglion; SMC, smooth muscle cell; TNF-α, tumor necrosis factor-α.

[b]References refer to P2X receptors.

[c]References refer to P2Y receptors.

[d]References refer to P2X and P2Y receptors.

[e]References refer to uncharacterized P2 receptors.

P2 receptor–mediated mucociliary clearance of airway epithelium (Picher and Boucher, 2003).

In summary, $P2Y_2$, $P2Y_4$, and $P2Y_6$ receptor mRNAs are the predominant receptor subtypes in airway smooth muscle and epithelial cells and these receptors have also been identified functionally. Several functional P2X receptor subtypes are also present. $P2X_1$ receptors constrict the pulmonary vasculature and both $P2Y_2$ and $P2Y_6$ receptors mediate vasodilation, although $P2X_2$ and $P2X_4$ receptor subtype mRNA and protein has also been identified.

2. Trachea

ATP exerted a contractile effect on guinea pig tracheal ring preparations via the production of prostanoids (Kamikawa and Shimo, 1976), and Advenier and colleagues found that ATP could both contract and relax isolated tracheal preparations depending on the initial tone of the preparation, contraction on basal tone (Advenier *et al.*, 1982; Candenas *et al.*, 1992; Mizrahi *et al.*, 1982), but relaxation on raised tone (Advenier *et al.*, 1982; Welford and Anderson, 1988). The contractile effects of ATP and that of UTP were greater when applied to the mucosal surface of the perfused trachea and the effect was diminished by removal of the epithelium or by indomethacin (Fedan *et al.*, 1993a). Conversely, the relaxant effect of ATP was greater when the ATP was applied to the serosal surface (Fedan *et al.*, 1993b).

Other effects of extracellular ATP on the trachea include increasing mucociliary activity (Lansley *et al.*, 1992; Saano *et al.*, 1990; Wong and Yeates, 1992) and the ability to stimulate mucin secretion from hamster tracheal goblet cells in culture (Kim and Lee, 1991).

Table IV summarizes the receptor subtypes present in the trachea based on mRNA, protein, and pharmacological and biochemical profiles. The functions claimed for the receptors together with key references are included.

ATP release from tracheal epithelial cells has been demonstrated in response to hypotonic shock and mechanical stimulation (Musante *et al.*, 1999; Watt *et al.*, 1998).

In summary, $P2Y_1$ and $P2Y_2$ receptor mRNA and protein are predominant in tracheal smooth muscle and epithelial cells and these receptors have been identified functionally. Functional $P2X_1$ receptors have been identified on smooth muscle and $P2X_4$ and $P2X_7$ receptor mRNA and protein are also present on epithelium.

3. Nasal Respiratory Epithelium

Early studies showed that exogenous ATP activated immotile cilia from nasal biopsy specimens from patients with immotile cilia syndrome to levels equal to or slightly greater than the spontaneous activity seen in normal

TABLE IV
Trachea[a]

Cellular components	Receptor mRNA		Receptor protein	Pharmacological and biochemical profile		Function	References
Perfused trachea					$P2Y_2$ (G)	ATP and UTP induce greater contractions when applied to the mucosal surface	Fedan *et al.*, 1994[c]
Tracheal smooth muscle				$P2X_1$ (H)	$P2Y_1$ (H) $P2Y_2$ (H)	ATP and UTP increase $[Ca^{2+}]_i$	Sawai *et al.*, 1997[d] Michoud *et al.*, 1997[c]
Epithelial cells							
Ciliated epithelium	$P2X_4$ (B) $P2X_7$ (B)	$P2Y_1$ (B) $P2Y_2$ (B)		$P2X_7$ (H)	$P2Y_1$ (H) $P2Y_2$ (GH)	ATP activates ciliary function ATP and UTP increase $[Ca^{2+}]_i$	Aksoy *et al.*, 1995[c] Satoh *et al.*, 1995[c] Hwang *et al.*, 1996[c] Kim *et al.*, 1996b[c] Korngreen and Priel, 1996[b] Iwase *et al.*, 1997[c] Kondo *et al.*, 1998[c] Korngreen *et al.*, 1998[c] Cressman *et al.*, 1999[c] Evans and Sanderson, 1999[c] Marino *et al.*, 1999[d] Uzlaner and Priel, 1999[c] Woodruff *et al.*, 1999[c] Inglis *et al.*, 2000[c] Yang *et al.*, 2000[c] Wu *et al.*, 2001[c] Lieb *et al.*, 2002[c] Nlend *et al.*, 2002[c]

Goblet cells	$P2X_4$ (B) $P2X_7$ (B)	$P2Y_1$ (B) $P2Y_2$ (AB)	$P2X_7$ (H)	$P2Y_1$ (H) $P2Y_2$ (H)	ATP and UTP stimulate mucin secretion ATP and UTP increase $[Ca^{2+}]_i$	Marino *et al.*, 1999[d] Abdullah *et al.*, 1996, 2003[c]
Goblet cell line—SPOC1 cells		$P2Y_2$ (B)		$P2Y_2$ (G)	ATP and UTP stimulate mucin secretion via an apical $P2Y_2$ R	Yamaya *et al.*, 1996[c]
Submucosal gland epithelial cells				$P2Y_2$ (GH)	ATP and UTP induce Cl^- secretion ATP and UTP increase $[Ca^{2+}]_i$	Zhang and Roomans, 1997[c]
Submucosal gland						
Acinar cells			P2 (G)		ATP increases $[Ca^{2+}]_i$	Shimura *et al.*, 1994[e]
Submucosal gland cell line—MM39 cells		$P2Y_2$ (B) $P2Y_4$ (B)		$P2Y_2$ (GH) $P2Y_4$ (GH)	ATP and UTP increase $[Ca^{2+}]_i$ ATP and UTP induce protein secretion Ap_4A induces secretary leukocyte protease secretion	Merten *et al.*, 1998[c] Saleh *et al.*, 1999[c]

[a]See footnote *a* for Table III.
[b]References refer to P2X receptors.
[c]References refer to P2Y receptors.
[d]References refer to P2X and P2Y receptors.
[e]References refer to uncharacterized P2 receptors.

subjects (Forrest *et al.*, 1979; Korngreen and Priel, 1993; Rossman *et al.*, 1980). Chemosensitivity of rat olfactory epithelium homogenate to odorant (diethyl sulfide) was not observed if ATP or GTP was absent (Vodyanoy and Vodyanoy, 1987). ATP regulated Cl^- secretion in cultured human nasal epithelial cells when applied to both basolateral and apical membranes, but not when applied to basolateral membranes of epithelial cells from cystic fibrosis patients (Clarke and Boucher, 1992).

Table V summarizes the receptor subtypes present in the nasal respiratory epithelium based on mRNA, protein, and pharmacological and biochemical profiles. The functions claimed for the receptors together with key references are included.

ATPase-stained nasal epithelial cells were associated with ciliary motility, but were not present in cells without ciliary activity (Schütz *et al.*, 2002).

In summary, $P2X_2$ and $P2Y_2$ mRNA and protein have been identified in nasal respiratory epithelial cells. Although P2X receptors have been identified functionally in nasal epithelium, the subtype has not been characterized. Functional $P2Y_2$ and $P2Y_6$ receptors are expressed in nasal epithelial cells. Bowman's glands express protein for $P2Y_2$ receptors.

B. Gastrointestinal and Related Systems

1. Gut

a. Esophagus Early papers recognized that ATP may be a cotransmitter with either vasoactive intestinal polypeptide (VIP) and/or nitric oxide (NO) in NANC inhibitory nerves supplying the lower esophageal sphincter (Castell, 1975; De Carle and Christensen, 1976; Fisher and Cohen, 1976). Epithelial cells from the esophagus respond to extracellular ATP by an increase in mucociliary activity (Ovadyahu *et al.*, 1988; Weiss *et al.*, 1992).

b. Stomach ATP was considered as a cotransmitter in NANC inhibitory nerves of the stomach (Baer and Frew, 1979; Frew and Lundy, 1982; Grider *et al.*, 1982; Heazell, 1975; Huizinga *et al.*, 1981; Lefebvre and Willems, 1979; Ohga and Taneike, 1977; Okwuasaba *et al.*, 1977), but the evidence offered was ambiguous. However, P2 receptors were later identified in gastric smooth muscle (Bitar and Makhlouf, 1982; Delbro and Fändriks, 1984; Lefebvre and Burnstock, 1990; Matharu and Hollingsworth, 1992) and P2 receptor antagonists were shown to attenuate NANC inhibitory responses (Baccari *et al.*, 1990; Beck *et al.*, 1988; Brizzi *et al.*, 1984; Ohno *et al.*, 1993; Zagorodnyuk *et al.*, 1990). It was recognized early that ATP regulates acid secretion in gastric mucosa (Gil-Rodrigo *et al.*, 1990; Kidder, 1973; Sanders *et al.*, 1976).

TABLE V

Nasal Respiratory Epithelium[a]

Cellular component	Receptor mRNA		Receptor protein		Pharmacological and biochemical profile		Function	References
Nasal epithelium								
Slice preparation	$P2X_2$ (B)	$P2Y_2$ (B)	$P2X_2$ (D)	$P2Y_2$ (D)	P2X (G)	P2Y (G)	Purinergic R modify odor sensitivity	Hegg *et al.*, 2003[d]
Cultured nasal epithelium						$P2Y_2$ (G) $P2Y_6$ (G)	ATP and UTP increase fluid transport	Benali *et al.*, 1994[c]
Cultured polarized nasal epithelium						$P2Y_2$ (G) $P2Y_6$ (G)	UDP stimulates formation of inositol phosphates	Lazarowski *et al.*, 1997[c]
Cultured ciliated nasal epithelium					P2X (G)	$P2Y_2$ (G) $P2Y_6$ (G)	ATP increases $[Ca^{2+}]_i$ Extracellular Na^+ regulates ciliary motility by inhibiting P2X R UTP, UDP, and ATP stimulate ciliary beating via $P2Y_2$ and $P2Y_6$ R	Ma *et al.*, 1999[b] Morse *et al.*, 2001[c]
Sustentacular epithelial cells				$P2Y_2$ (D)				Hegg *et al.*, 2003[c]
Bowman's gland				$P2Y_2$ (D)				Hegg *et al.*, 2003[c]
Avian nasal salt gland						$P2Y_2$ (G)	UTP activates Ca^{2+}-sensitive K^+ and Cl^- currents	Martin and Shuttleworth, 1995[c]

[a]See footnote *a* for Table III.
[b]References refer to P2X receptors.
[c]References refer to P2Y receptors.
[d]References refer to P2X and P2Y receptors.

c. Small Intestine A high level of ATP was shown to be associated with 5-hydroxytryptamine (5-HT) in dog small intestine (Prusoff, 1960), although the precise location was not determined. Rebound and/or contraction of the small intestine of guinea pig, rat, and musk shrew to ATP and relaxation to adenosine were reported (Hourani *et al.*, 1991; Iso, 1974; Kamikawa *et al.*, 1977; Nagata *et al.*, 1993; Sakai *et al.*, 1979a) and receptors for ATP and adenosine on smooth muscle recognized (Ally and Nakatsu, 1976; Kažić and Milosavljević, 1977). ATP inhibited the contractile responses to periarterial nerve stimulation of the rabbit and guinea pig intestine (Bowman and Hall, 1970; Gintzler and Musacchio, 1975), but probably via the presynaptic action of its breakdown product adenosine. ATP (via adenosine) also inhibited release of acetylcholine (ACh) from enteric neurons (Hayashi *et al.*, 1978; Sawynok and Jhamandas, 1976; Wiklund *et al.*, 1985). Evidence was presented to satisfy the view that responses of the small intestine to transmural nerve stimulation were mediated, at least, in part, by ATP in guinea pig ileum (Crist *et al.*, 1992; He and Goyal, 1993; Ohkawa, 1974) and rat duodenum (Manzini *et al.*, 1985, 1986a). ATP and ADP produced inhibitory effects on peristalsis (Okwuasaba and Hamilton, 1975). In the rabbit jejunum, inhibitory junction potentials (IJPs), that were recorded in the circular, but not the longitudinal muscle, were proposed to be due to purinergic transmission (Kitamura, 1978); ATP and α,β-methylene ATP (α,β-meATP) act on cholinergic nerves in the guinea pig ileum to release ACh (Moody and Burnstock, 1982; Northway and Burks, 1980) presumably via $P2X_1$ or $P2X_3$ receptors. NANC inhibition of smooth muscle of the human small (and large) intestine was shown to be reduced by desensitization with α,β-meATP and mimicked by ATP (Zagorodnyuk and Shuba, 1986). ATP inhibited amino acid uptake and ion and sugar transport into epithelial cells of the small intestine (Kimmich and Randles, 1980; Kohn *et al.*, 1970; Korman *et al.*, 1982; Reiser and Christiansen, 1971; Wróbel and Michalska, 1977).

d. Colon A role for ATP in NANC responses of the colon was considered during the late 1970s and 1980s (Crema *et al.*, 1982; Eaglesom and Zeitlin, 1978; Jager and van der Schaar, 1990; Tonini *et al.*, 1981). A role for ATP in parasympathetic (pelvic nerve)-mediated NANC contraction was also suggested (Hedlund *et al.*, 1986). Stimulation of lumbar sympathetic nerves evoked contraction of the cat colon circular muscle mediated by ATP and noradrenaline (NA) (Venkova and Krier, 1993). Apamin reduced responses to α,β-meATP and NANC relaxation (Costa *et al.*, 1986). P2Y receptors mediated relaxation of the longitudinal muscle of the rat colon (Bailey and Hourani, 1992) and mouse rectum (Unekwe and Savage, 1991). The first study of the purinoceptor subtypes present in the muscularis mucosae of the rat colon showed that P2Y receptors mediated contraction (Bailey and Hourani, 1990). ATP produced hyperpolarization and inhibited spontaneous

contraction of the circular smooth muscle of the human colon (Hoyle *et al.*, 1990; Keef *et al.*, 1993). Rebound contractions following relaxation responses of the colon to ATP are partly mediated by prostaglandins (Bennett *et al.*, 1977; Burnstock *et al.*, 1975; den Hertog and van den Akker, 1979).

e. Taenia and Cecum The guinea pig taenia coli was the focus of early interest in purinergic signaling following the discovery by Burnstock and his colleagues of NANC inhibitory nerves in this preparation (Burnstock *et al.*, 1964). ATP and ADP produced potent relaxation of the taenia and quinidine antagonized these actions and the responses to stimulation of NANC nerves (Burnstock *et al.*, 1970) as did high concentrations of phentolamine (Satchell *et al.*, 1973; Tomita and Watanabe, 1973), 2,2′-pyridylisatogen tosylate (Hooper *et al.*, 1974; Spedding and Weetman, 1978), apamin (Banks *et al.*, 1979; Den Hertog *et al.*, 1985; Maas and Den Hertog, 1979; Shuba and Vladimirova, 1980), Reactive Blue 2 (Manzini *et al.*, 1986b), and suramin (Den Hertog *et al.*, 1989). Stimulation of enteric nerves was shown to produce ATP release (Rutherford and Burnstock, 1978; Su *et al.*, 1971; White *et al.*, 1981).

Adenosine was taken up by NANC inhibitory nerves for conversion to ATP and subsequent reincorporation into physiological stores (Satchell *et al.*, 1972). Papers followed consistent with the hypothesis (Brown and Burnstock, 1981; Burnstock and Wong, 1978; Cocks and Burnstock, 1979; Den Hertog, 1982; Ferrero *et al.*, 1980; Foster *et al.*, 1978; Fujiwara *et al.*, 1982a; Jager and Den Hertog, 1974; Jager and Schevers, 1980; MacKenzie and Burnstock, 1980; Maguire and Satchell, 1979; Mehta and Kulkarni, 1983; Satchell, 1981; Satchell and Burnstock, 1975; Satchell and Maguire, 1975; Spedding and Weetman, 1976). Structure activity studies of analogues of ATP revealed that some compounds were more effective (Burnstock *et al.*, 1983, 1984; Cusack and Planker, 1979; Foster *et al.*, 1983; Welford *et al.*, 1986).

NANC inhibitory responses in the taenia coli were blocked by morphine or enkephalin, probably acting on sympathetic transmission in the myenteric plexus (Huizinga and Den Hertog, 1979; Shimo and Ishii, 1978). The receptor for ATP was recognized as a P2Y subtype unusually sensitive to α,β-meATP by Burnstock and Kennedy in 1985 and this was later confirmed by other groups (Hourani *et al.*, 1991).

f. Internal Anal Sphincter ATP was shown to relax the internal anal sphincter (Biancani *et al.*, 1985; Burleigh *et al.*, 1979; Crema *et al.*, 1983; Nissan *et al.*, 1984; Rattan and Shah, 1988) and mediate NANC inhibitory neural responses (Baird and Muir, 1990; Lim and Muir, 1986).

Table VI summarizes the receptor subtypes present in the gut based on mRNA, protein, and pharmacological and biochemical profiles. The functions claimed for the receptors together with key references are included (cf. Tables XXIV, XLIV, and XLV; see Fig. 2).

Evidence has been presented for ATP release from smooth muscle of guinea pig ileal longitudinal muscle upon stimulation of muscarinic receptors (Katsuragi *et al.*, 1992; Nitahara *et al.*, 1995). Strong evidence was presented that ATP mediates the apamin-sensitive fast component of IJPs via postjunctional P2 purinoceptors on circular smooth muscle of the guinea pig ileum (Crist *et al.*, 1992; King, 1994).

Release of ATP from perfused taenia coli following stimulation of NANC inhibitory nerves was demonstrated using the luciferin/luciferase technique (Burnstock *et al.*, 1978b) and more recently by high-performance liquid chromatography (HPLC) (McConalogue *et al.*, 1996). ATP was recently shown to be released from mucosal epithelial cells during distention of the rat colorectum, which stimulates sensory nerves via $P2X_3$ receptors (Wynn *et al.*, 2003).

In summary, intestinal smooth muscle expresses mRNA and protein for $P2X_7$ and $P2Y_1$ receptors, although protein for $P2X_2$ receptors has been shown. Functionally both $P2X_1$ and $P2X_2$ receptors have been identified together with $P2Y_1$ and $P2Y_2$ receptors. It has been demonstrated that endothelial cells of the intestine express mRNA for $P2Y_1$, $P2Y_2$, $P2Y_4$, and $P2Y_6$ receptors and protein for $P2X_5$, $P2X_7$, and $P2Y_6$ receptors. Functional P2Y receptors corresponding to the presence of the mRNA for P2Y receptors have been shown. Note that the enteric nervous system is included in the section devoted to the nervous system (Table XLI).

2. Liver and Biliary System

The hypoglycemic effect of ATP on the rat liver *in vivo* was first reported by Levine in 1965. ATP increased blood glucose levels and reduced the glycogen content of the liver. Later, these findings were reproduced on isolated, perfused rat liver and in rat hepatocytes (Buxton *et al.*, 1986; Clemens and Chaudry, 1983; Clemens *et al.*, 1981) and it was proposed that the stimulation of glucogenolysis by ATP was mediated by purinergic receptors located on hepatocytes that activated glycogen phosphorylase in a cAMP-independent manner (Keppens and De Wulf, 1985). These receptors were subsequently identified as of the P_{2Y} subclass of P2 purinoceptors (Keppens and De Wulf, 1986).

ATP has multiple actions on isolated hepatocytes, although the best studied is the glycogenolytic effect. Other effects are the inactivation of glycogen synthase (Keppens *et al.*, 1992) and antiglycogen effects by inhibiting the cAMP increase after glycogen by an increase in phosphodiesterase

TABLE VI
Gut[a]

Cellular component	Receptor mRNA	Receptor protein	Pharmacological and biochemical profile		Function	References
Esophagus						
Circular smooth muscle				P2Y (G)	Fast apamin-sensitive IJPs may be mediated by P2Y R	Zhang and Paterson, 2002[c]
Muscularis mucosae				P2 (G)	ATP and ADP induce contraction	Percy *et al.*, 1997[e]
Lower esophageal sphincter				P2Y (G)	Apamin-sensitive IJPs may be mediated by P2Y R ATP may be producing relaxation indirectly via nerves	Imaeda and Suzuki, 1997[c] Matsuda *et al.*, 1997[c] Yuan *et al.*, 1998[c]
Stomach						
Smooth muscle	$P2Y_1$ (B)	$P2X_7$ (D)	P2X (G)	$P2Y_1$ (G) $P2Y_2$ (G) P2Y ? (G)	ATP and UTP produce contraction of circular muscle ATP released from NANC nerves induces PGE_2 production α,β-meATP produces relaxation via unidentified P2Y R subtype Fast IJP recorded in circular muscle of gastric fundus is blocked by α,β-meATP, RB2, and apamin	Baccari *et al.*, 1996[c] Mashimo *et al.*, 1996[c] Otsuguro *et al.*, 1996, 1998[c] Rhee *et al.*, 1996[c] Currò and Preziosi, 1998[c] Murthy and Makhlouf, 1998[d] Jenkinson and Reid, 2000[c] Sergeant *et al.*, 2002[c] Menzies *et al.*, 2003[b]
Isolated myocytes				$P2Y_2$ (G)	ATP and UTP induce a transient increase in $[Ca^{2+}]_i$	Blottiére *et al.*, 1996[c]
Pyloric sphincter				P2Y (G)	ATP with NO (slower component) mediate NANC inhibitory responses	Soediono and Burnstock, 1994[c]
Pylorus			P2X (G)	P2Y (G)	Apamin blocks pylorus relaxation	Ishiguchi *et al.*, 2000a[c], 2000b[b]
Gastroduodenal junction			P2X (G)	P2Y (G)		Glasgow *et al.*, 1998[e]

(*continued*)

TABLE VI (*continued*)

Cellular component	Receptor mRNA		Receptor protein		Pharmacological and biochemical profile		Function	References
Duodenum								
Smooth muscle					P2X (G)	$P2Y_1$ (G) $P2Y_2$ (G) P2Y ? (G)	ATP acting via P2Y R produces relaxation (fully developed by Day 25) UTP acting via $P2Y_2$ R causes contraction Nicotine-induced NANC relaxation is desensitized by α,β-meATP relaxation An unidentified P2Y R mediates relaxation P2Y R mediate fast IJPs	Irie *et al.*, 1994[b] Johnson and Hourani, 1994[c] Windscheif *et al.*, 1995[c] Zagorodnyuk *et al.*, 1995[c] Brownhill *et al.*, 1997[c]
Muscularis mucosae					P2X (G)	$P2Y_2$ (G) or $P2Y_4$ (G)	ATP induces suramin-sensitive contraction ATP and UTP induce suramin-insensitive contractions P2X and $P2Y_2$ or $P2Y_4$ R mediate contraction	Johnson *et al.*, 1996[d]
Ileum								
Longitudinal muscle	$P2X_1$ (AB)	P2Y (B)	$P2X_7$ (D)	$P2Y_1$ (D)	P2X (G)	$P2Y_1$ (G) $P2Y_2$ (G) P2Y ? (G)	P2X-like R on cholinergic nerves mediate ACh release and contraction ATP and ADP via P2Y-like R mediate relaxation P2Y R on cholinergic terminals mediate inhibition ATP, 2-MeSATP, and 2-chloroATP increase apamin-sensitive whole cell outward K^+ current P2Y R mediate relaxant phase of GABA actions	Kennedy and Humphrey, 1994[d] Nitahara *et al.*, 1995[c] Longhurst *et al.*, 1996[b] Smits and Lefebvre, 1996[c] Matsuo *et al.*, 1997[c] Pencheva, 1997[c] Vogalis and Goyal, 1997[c] Fernández *et al.*, 1998[c] Sato *et al.*, 1999[b] Sawyer *et al.*, 2000[c] Storr *et al.*, 2000[d] Ivancheva *et al.*, 2001[b] Giaroni *et al.*, 2002[d]

						Kadowaki *et al.*, 2003[c] Menzies *et al.*, 2003[b]
Isolated myocytes	$P2Y_1$ (B)			$P2Y_1$ (G) $P2Y_2$ (G)	ATP and UTP induce a transient increase in $[Ca^{2+}]_i$	Blottiére *et al.*, 1996[c] Pacaud *et al.*, 1996[c] Vigne *et al.*, 1998[c]
Jejunum						
Circular muscle				$P2Y_1$ (G)	Fast IJPs mediated by ADPβS-sensitive P2Y R ATP evokes an apamin-sensitive hyperpolarization	Murr *et al.*, 1999[c] Xue *et al.*, 1999, 2000[c]
Isolated myocytes				$P2Y_2$ (G)	ATP and UTP induce a transient increase in $[Ca^{2+}]_i$	Blottiére *et al.*, 1996[c]
Sphincter of Oddi				P2Y ? (G)	ATP evokes fast IJPs as an apamin-sensitive NANC inhibitory transmitter	Imoto *et al.*, 1998[c] Woods *et al.*, 2003[c]
Colon						
Longitudinal muscle		$P2X_2$ (D) $P2X_7$ (D)	$P2X_2$ (G)	$P2Y_1$ (G) $P2Y_2$ (G)	ATP induces relaxation via suramin-sensitive P2Y R ATP increases "Ca^{2+} puffs" ATP evokes the non-NO-mediated IJPs P2Y R mediate release of $[Ca^{2+}]_i$	Briejer *et al.*, 1995[c] Qian and Jones, 1995[c] Börjesson *et al.*, 1997, 1999[c] Koh *et al.*, 1997[c] Spencer *et al.*, 1998[c] Bayguinov *et al.*, 2000[c] Rózsai *et al.*, 2001[c] Serio *et al.*, 2003[c] Menzies *et al.*, 2003[b]
Circular muscle		$P2X_2$ (D) $P2X_7$ (D)	$P2X_1$ (G)	$P2Y_1$ (G)	P2X R mediate contraction P2Y R mediate relaxation ATP is responsible for the first phase of apamin-sensitive IJPs ATP modulates Cl^- currents Purinergic NANC inhibitory neurotransmission	Venkova *et al.*, 1994[c] Zagorodnyuk and Maggi, 1994, 1998[c] Lee *et al.*, 1996a[b] Maggi and Giuliani, 1996[c] Zagorodnyuk *et al.*, 1996, 1998[c] Dick *et al.*, 1998[c] Franck *et al.*, 1999[c] Plujà *et al.*, 1999[c] Matsuyama *et al.*, 2003[c] Menzies *et al.*, 2003[b]

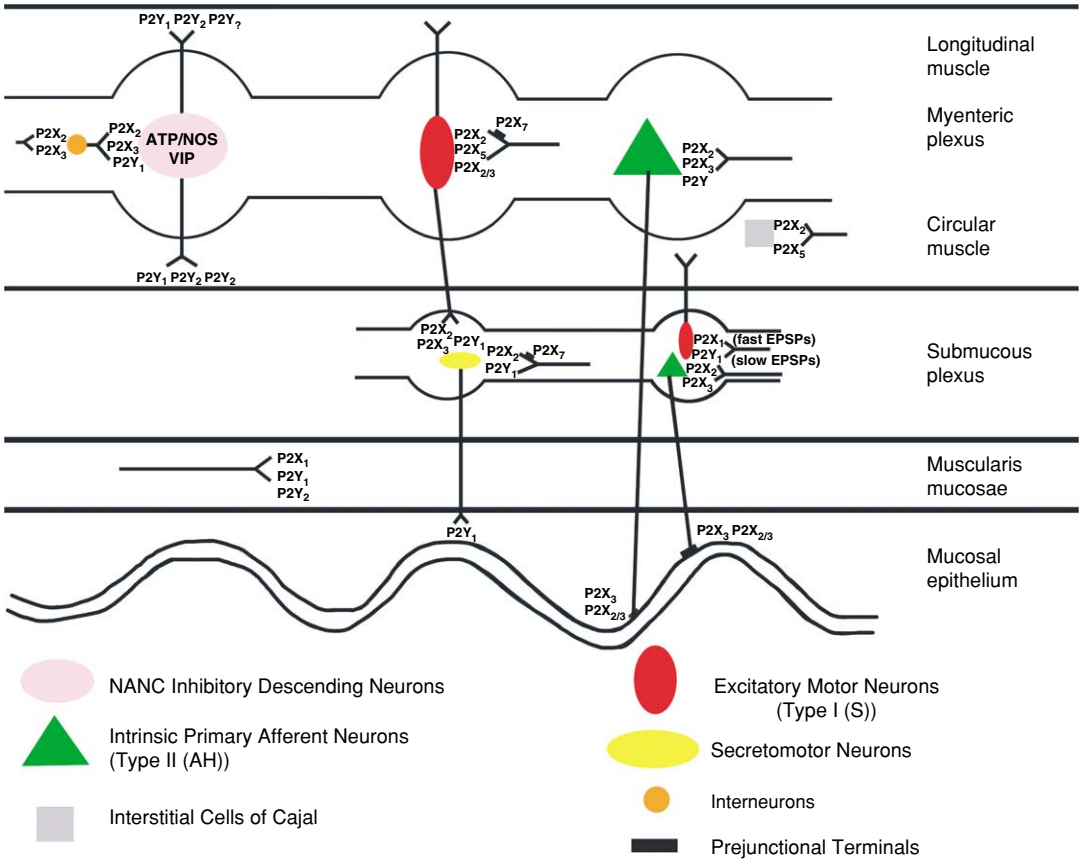
(*continued*)

TABLE VI (*continued*)

Cellular component	Receptor mRNA	Receptor protein	Pharmacological and biochemical profile	Function	References
Isolated myocytes			$P2Y_2$ (G)	ATP and UTP induce a transient increase in $[Ca^{2+}]_i$	Blottiére *et al.*, 1996[c]
Muscularis mucosae			$P2Y_1$ (G) $P2Y_2$ (G)	ATP and UTP contract the smooth muscle	Tennant *et al.*, 1999[c] Percy *et al.*, 2003[c]
Taenia coli			$P2Y_1$ (G) $P2Y_2$? (G) P2Y ? (G)	ATP is an NANC inhibitory transmitter The main P2Y R subtype involved is sensitive to α,β-meATP and has not yet been cloned	Burnstock *et al.*, 1994[c] Piper and Hollingsworth, 1995[c] Windscheif *et al.*, 1995[c] Bültmann *et al.*, 1996[c] Selemidis *et al.*, 1997[c] Barthó *et al.*, 1998[c] Hourani *et al.*, 1998[c] Kong *et al.*, 2000[c]
Cecum			$P2Y_2$ (G)	ATP and UTP induce a transient increase in $[Ca^{2+}]_i$	Blottiére *et al.*, 1996[c]
Internal anal sphincter (IAS)			P2Y (G)	ATP induces relaxation via an apamin-sensitive R	Knudsen *et al.*, 1995[c] Rae and Muir, 1996[c] De Luca *et al.*, 1999[c]
Interstitial cells of Cajal		$P2X_2$ (D) $P2X_5$ (D)		ATP may provide a feedback mechanism for pacemaker activity	Burnstock and Lavin, 2002[b]
Intestinal gland	$P2Y_2$ (B)	$P2X_5$ (D) $P2X_7$ (D)	$P2Y_2$ (G)		Kerstan *et al.*, 1998[c] Gröschel-Stewart *et al.*, 1999b[b]
Gut epithelium					
Esophagus	$P2Y_2$ (C)	$P2X_5$ (D) $P2X_7$ (D)	P2Y (G)	ATP increases ciliary beat frequency ATP modulates mucous and acid secretion	Gheber *et al.*, 1995[c] Tarasiuk *et al.*, 1995[c] Levin *et al.*, 1997[c] Gröschel-Stewart *et al.*, 1999a[b]

Stomach	$P2Y_2$ (C)			P2Y (G)	Different P2Y R mediate responses in apical and basolateral membranes	Ota *et al.*, 1994[c] Gil-Rodrigo *et al.*, 1996[c] Vallejo *et al.*, 1996[c]
Small intestine	$P2Y_2$ (BC) $P2Y_4$ (B) $P2Y_6$ (B)	$P2X_5$ (D) $P2X_7$ (D)		$P2Y_2$ (G) $P2Y_4$ (G) $P2Y_6$ (G)	ATP and UTP increase $[Ca^{2+}]_i$ and Cl^- secretion UDP increases Cl^- secretion $P2X_5$ and $P2X_7$ R modulate epithelial cell functions	Inoue *et al.*, 1997[c] Kerstan *et al.*, 1998[c] Browne and Harvey, 1999[c] Cressman *et al.*, 1999[c] Gröschel-Stewart *et al.*, 1999b[b] Satoh *et al.*, 1999[c] McAlroy *et al.*, 2000[c] Robaye *et al.*, 2003[c]
Colon	$P2Y_1$ (B) $P2Y_2$ (BC) $P2Y_6$ (B)		$P2Y_6$ (D)	$P2Y_1$ (GH) $P2Y_2$ (H) $P2Y_6$ (H)	Basolateral $P2Y_1$ R mediate NaCl secretion $P2Y_2$ R mediate K^+ secretion Luminol $P2Y_2$ R mediate electrogenic Na^+ absorption	Leipziger *et al.*, 1997[c] Browne *et al.*, 2001[c] Smitham and Barrett, 2001[c] Yamamoto and Suzuki, 2002[c] Zhang *et al.*, 2002[c] Köttgen *et al.*, 2003[c]
T84 cells				$P2Y_6$ (H)	UDP increases Cl^- secretion	Browne *et al.*, 2001[c]
Enteric nervous system	See Table XLIV					
Sensory neurons	See Table XLV					
Intestinal vasculature	See Table XXIV					

[a]See footnote *a* for Table III.
[b]References refer to P2X receptors.
[c]References refer to P2Y receptors.
[d]References refer to P2X and P2Y receptors.
[e]References refer to uncharacterized P2 receptors.


Longitudinal muscle
Myenteric plexus
Circular muscle
Submucous plexus
Muscularis mucosae
Mucosal epithelium
ATP/NOS VIP
(fast EPSPs)
(slow EPSPs)
NANC Inhibitory Descending Neurons
Intrinsic Primary Afferent Neurons (Type II (AH))
Interstitial Cells of Cajal
Excitatory Motor Neurons (Type I (S))
Secretomotor Neurons
Interneurons
Prejunctional Terminals

activity (Okajima *et al.*, 1987). Since ATP and its analogues can selectively alter these systems, it was suggested that there were at least three different receptors (Dixon *et al.*, 1990; Keppens, 1993).

Table VII summarizes the receptor subtypes present in the liver and biliary system based on mRNA, protein, and pharmacological and biochemical profiles. The functions claimed for the receptors together with key references are included (cf. Tables XXIV and LI).

ATP was present in human, pig, and rat bile (Chari *et al.*, 1996), in concentrations thought to be sufficient to activate P2Y receptors, located on the apical membrane of biliary cells (Cotton and Reuss, 1991). The bile acid, ursodeoxycholic acid, can stimulate the release of ATP into rat bile from cholangiocytes and hepatocytes (Feranchak and Fitz, 2002), which may stimulate fluid and electrolyte secretion by bile duct epithelial cells downstream (Nathanson *et al.*, 2001).

Hepatocytes also have the ability to secrete ATP (Nukina *et al.*, 1994), which may stimulate P2 receptors on adjacent hepatocytes or bile duct cells (Dranoff and Nathanson, 2000; Schlosser *et al.*, 1997). Hepatocytes also release ATP in response to osmotic stress; volume recovery following this is found to depend on the binding of the released ATP to P2Y receptors on these cells and activation of Cl^- channels (Feranchak *et al.*, 2000; Roman *et al.*, 1999).

In summary, multiple P2Y receptor mRNA has been identified on the plasma membrane of the two principal epithelial cell types (hepatocytes and cholangiocytes) and functionally, $P2Y_1$, $P2Y_2$, and $P2Y_4$ receptors have been identified that exert potent regulatory effects on both liver and biliary function.

FIG. 2 Schematic representation of the distribution of P2 receptors in mammalian intestine. ATP acting on a P2Y receptor mediates slow synaptic excitation of descending interneurons. Neuronal $P2Y_1$ receptors mediate relaxation, largely through NO and ATP acting on smooth muscle via $P2Y_1$, $P2Y_2$, and a novel P2Y receptor subtype responsive to α,β-meATP. $P2X_2$ receptors mediate contraction of the mouse colonic smooth muscle (not shown in the schematic). Descending interneurons express $P2X_2$ and $P2X_3$ receptors, whereas ascending interneurons express $P2X_3$ receptors only in the guinea pig myenteric plexus. Secretomotor neurons in submucosal ganglia receive slow excitatory synaptic input via $P2Y_1$ receptors. $P2X_7$ receptors are associated with nerve fibers in both myenteric and submucous plexuses. $P2X_2$ receptors contribute to fast EPSPs in Type I (S) neurons. Interstitial cells of Cajal express $P2X_2$ and $P2X_5$ receptors; it is speculated that release of ATP from enteric nerves, enteric glial cells, or contracting smooth muscle may provide a feedback mechanism for pacemaker activity in the gut. In the muscularis mucosae ATP and UTP induce contraction via $P2Y_1$ and $P2Y_2$ receptors, respectively, the ATP effect being indomethacin sensitive. It is thought that contraction-related prostaglandin synthesis and noncholinergic secretomotor neuron stimulation represent the physiological transduction mechanism through which muscularis mucosae motor activity is translated into mucosal secretion. The distribution of P2 receptors shown in this schematic does not show species variation.

TABLE VII
Liver and Biliary System[a]

Cellular component	Receptor mRNA		Receptor protein	Pharmacological and biochemical profile		Function	References
Hepatocytes		$P2Y_1$ (B) $P2Y_2$ (B) $P2Y_4$ (B) $P2Y_6$ (B)		P2X (G)	$P2Y_1$ (G) $P2Y_2$ (G) $P2Y_{13}$ (G)	ATP regulates gluconeogenesis, stimulates glycogen breakdown, and decreases glycolysis ATP inhibits pyruvate kinase ATP inhibits fatty acid synthesis	Guzmán *et al.*, 1996[c] Capiod, 1998[d] Dixon *et al.*, 2000, 2003a,b[c] Glavy *et al.*, 2000[c] Ichai *et al.*, 2001[c]
Hepatic stellate cells					$P2Y_2$ (H)	ATP and UTP induce contraction	Takemura *et al.*, 1994[c]
Cholangiocytes	$P2X_4$ (B)	$P2Y_1$ (B) $P2Y_2$ (AB) $P2Y_4$ (B) $P2Y_6$ (B)			$P2Y_1$ (G) $P2Y_2$ (G)	ATP is released into bile and modulates its release ATP promotes Cl^- secretion via an apical $P2Y_2$ R	McGill *et al.*, 1994[c] Roman *et al.*, 1999[c] Schlenker *et al.*, 1997[c] Zsembery *et al.*, 1998[c] Salter *et al.*, 2000[c] Dranoff *et al.*, 2001[d]
Intrahepatic biliary epithelial cell line					$P2Y_2$ (G)	ATP and UTP increase $[Ca^{2+}]_i$	Wolkoff *et al.*, 1995[c]
Liver plasma membrane					P2Y (G)	ATP stimulates PLD	Malcolm *et al.*, 1995[c] Yegutkin and Burnstock, 1999[c]
Perfused liver				P2X (G)	P2Y (G) $P2Y_2$ (G)	ATP and UTP transiently decrease perfusion pressure ATP decreases secretion of triglyceride and apoprotein B	Takemura *et al.*, 1998[c] Yamauchi *et al.*, 1998[b] Fernandes *et al.*, 2002[e]
Liver vasculature	See Table XXIV						

Endothelial cells					
Sinusoidal cells			P2Y (G)	ATP induces prostanoid secretion	Hashimoto *et al.*, 1995[c]
Kupffer cells			P2Y (G)	ATP induces prostanoid secretion	Hashimoto *et al.*, 1995[c]
Bile duct	$P2X_4$ (B)	$P2X_4$ (D)	$P2Y_2$ (G)	ATP evokes Cl^- permeability	McGill *et al.*, 1994, 1995[c]
Epithelium			$P2Y_4$ (G)	ATP and UTP increase $[Ca^{2+}]_i$	Roman *et al.*, 1999[c]
			$P2Y_6$ (G)	UTP modulates bile release	Dranoff *et al.*, 2001[d]
					Bo *et al.*, 2003[b]
Cell lines			$P2Y_2$ (H)	ATP and UTP increase $[Ca^{2+}]_i$	Wolkoff *et al.*, 1995[c]
Cancer cells	See Table LI				
Gallbladder					
Epithelium		$P2Y_1$ (B)	$P2Y_2$ (G)	UTP mediates Cl^- secretion	Clarke *et al.*, 1999[c]
		$P2Y_2$ (B)		ATP and UTP increase $[Ca^{2+}]_i$	Cressman *et al.*, 1999[c]
		$P2Y_4$ (B)		ATP and UTP induce production of inositol phosphate	
		$P2Y_6$ (B)			

[a]See footnote *a* for Table III.
[b]References refer to P2X receptors.
[c]References refer to P2Y receptors.
[d]References refer to P2X and P2Y receptors.
[e]References refer to uncharacterized P2 receptors.

C. Urinary System

1. Kidney

The effects of exogenous ATP on the kidney were first documented in the mid-1960s, when it was reported that arterial infusion of ATP caused an increase in renal blood flow but a reduction in the glomerular filtration rate (Harvey, 1964). These effects were claimed to be due to ATP-induced vasodilatation of the efferent arterioles, although the possibility of an effect on glomerular permeability was not discounted. A later study showed a similar increase in renal blood flow in the dog (Tagawa and Vander, 1970), rabbit (Needleman *et al.*, 1970), and rat kidney (Sakai *et al.*, 1979b) in response to ATP.

Periarterial nerve stimulation of the isolated rat kidney induced a vasoconstrictor response that was mediated by the co-release of NA, acting on α_1-adrenoceptors and ATP acting on P2X receptors (Rump *et al.*, 1992; Schwartz and Malik, 1989). The neurally released ATP, in addition to activating P2X receptors, was thought to also induce vasodilatation via a P2Y receptor (Churchill and Ellis, 1993). Exogenous ATP increased preglomerular vascular resistance via P2 receptors and a role in the regulation of tubuloglomerular feedback responsiveness was postulated (Mitchell and Navar, 1993).

The perfused rabbit kidney is known to generate prostanoids in response to different stimuli. One of these stimuli is ATP. Both ATP and ADP induced the hydrolysis of arachidonic acid (AA) and linoleic acid by biochemical pathways distinct from other stimuli such as bradykinin and angiotensin II, although the receptor subtype responsible for this effect was not characterized (Schwartzman and Raz, 1982; Schwartzman *et al.*, 1981). Basolateral membranes of the thick ascending limb of the loop of Henle from the mouse contain cation channels that are inhibited by exogenous ATP via a P2X subtype (Paulais and Teulon, 1989). Rat renal cortex and glomerular mesangial cells expressed P2Y receptors, stimulation of which induced the formation of inositol phosphates (Nanoff *et al.*, 1990; Pfeilschifter, 1990a). Further examination of the mesangial cells showed that both ATP and UTP were acting at the same receptor (Pfeilschifter, 1990b).

The effect of exogenous ATP on intracellular calcium concentrations in primary cultured rabbit proximal convoluted tubules was to induce transient increases by releasing cytoplasmic stores. This effect was inhibited by suramin and was G protein coupled, therefore of the P2Y subtype of receptor (Cejka *et al.*, 1993).

Several cell lines have been raised from different renal tissues. One such cell line is MDCK, renal epithelial cells derived from collecting ducts of Madin–Darby canine kidneys. The application of ATP to a monolayer of these cells

resulted in an acute and sustained stimulation of short-circuit current as a result of basal to apical Cl^- secretion (Simmons, 1979, 1981). Another cell line is a renal epithelial cell line of proximal tubules, LLC-PK_1, which responded to ATP by a rapid and large release of intracellular calcium transients (Harada *et al.*, 1991; Weinberg *et al.*, 1989). ATP also inhibited arginine vasopressin (AVP)-stimulated adenylate cyclase formation, identified as a P2Y receptor based on agonist potency orders (Anderson *et al.*, 1991).

Table VIII summarizes the receptor subtypes present in the kidney based on mRNA, protein, and pharmacological and biochemical profiles. The functions claimed for the receptors together with key references are included (cf. Table XXIV; see Fig. 3).

Kidney macula densa cells, located within the thick ascending limb, are unique biosensors that detect changes in luminal NaCl concentration and transmit signals to the mesangial cell/afferent arteriole complex, causing alterations in both vascular tone of the afferent arterioles (tubuloglomerular feedback, TGF), and in renin secretion from juxtaglomerular cells of the afferent arterioles (Nishiyama and Navar, 2002; Yao *et al.*, 2003a). These cells are known to produce and release ATP (Bell *et al.*, 2001; Schnermann and Marver, 1986) and are thought to modulate the sensitivity of the TGF mechanism.

Epithelial cells obtained from autosomal dominant polycystic kidney disease (ADPKD) released significant amounts of ATP under isotonic conditions; the amount of ATP released was significantly higher when challenged with hypotonic conditions (Wilson *et al.*, 1999a). It was thought that ATP released into the lumen of an ADPKD cyst becomes trapped since it has a negative charge. ATP then becomes concentrated to such as extent that autocrine and/or paracrine stimulation of purinergic receptors occurs.

In summary, P2 receptors are widely expressed within the kidney. mRNA and protein for multiple P2X and P2Y receptor subtypes are expressed in structures of the kidney. Functional $P2X_4$ and $P2X_7$ receptors have been demonstrated, together with several P2Y receptor subtypes.

2. Bladder and Urethra

a. Urinary Bladder ATP contracted the smooth muscle of the dog, cat, rabbit, rat, guinea pig, ferret, and marmoset urinary bladder (Ambache and Zar, 1970; Buchthal and Kahlson, 1944; Burnstock *et al.*, 1972a,b; Dean and Downie, 1978; Downie and Dean, 1977; Matsumura *et al.*, 1968; Moss and Burnstock, 1985) thus ATP was suggested as the transmitter substance producing the atropine-resistant contraction of the mammalian bladder. Further studies examined the criteria for acceptance of ATP as a

TABLE VIII
Kidney[a]

Cellular component	Receptor mRNA		Receptor protein		Pharmacological and biochemical profile		Function	References
Whole kidney			$P2X_4$ (E)					Bo *et al.*, 2003[b]
Glomerulus								
Mesangial cells	$P2X_4$ (B) $P2X_5$ (B) $P2X_7$ (A)	$P2Y_1$ (B) $P2Y_2$ (B) $P2Y_4$ (B) $P2Y_6$ (B) $P2Y_{11}$ (B) $P2Y_{12}$ (B)		$P2Y_1$ (D)	$P2X_7$ (G)	$P2Y_2$ (G) or $P2Y_4$ (G)	ATP induces apoptosis and necrosis via $P2X_7$ R ATP and UTP increase $[Ca^{2+}]_i$ ATP and UTP activate p38-MAPK pathway $P2X_7$ R stimulation induces reactive oxygen species generation	Ishikawa *et al.*, 1994[c] Takeda *et al.*, 1996[c] Schulze-Lohoff *et al.*, 1998[b] Gutierrez *et al.*, 2000[c] Harada *et al.*, 2000,[d] 2003[b] Huwiler *et al.*, 2000[c] Schwiebert and Kishore, 2001[b] Turner *et al.*, 2003[c] Vonend *et al.*, 2003[c]
Podocytes	$P2X_7$ (B)	$P2Y_1$ (B) $P2Y_2$ (B) $P2Y_6$ (B)		$P2Y_2$ (D)		$P2Y_2$ (GH) $P2Y_6$ (GH)	ATP increases $[Ca^{2+}]_i$	Fischer *et al.*, 2001[d] Turner *et al.*, 2003[c]
Endothelial cells				$P2Y_1$ (D)		$P2Y_2$ (G)	$P2Y_2$ R mediate Ca^{2+} mobilization	Briner and Kern, 1994[c] Huwiler *et al.*, 1997[c] Turner *et al.*, 2003[c]
Epithelial cells	$P2X_4$ (B) $P2X_5$ (B) $P2X_6$ (B) $P2X_7$ (B)	$P2Y_1$ (B) $P2Y_2$ (B) $P2Y_4$ (B) $P2Y_6$ (B) $P2Y_{11}$ (B)				$P2Y_1$ (G)	ATP increases $[Ca^{2+}]_i$ ATP has mitogenic effects Adrenergic stimulation of renal cortex releases ATP from epithelial cells	Schwiebert *et al.*, 2002b[c] Vonend *et al.*, 2002[d]
Polycystic kidney Epithelial cells	$P2X_4$ (B) $P2X_5$ (B)	$P2Y_2$ (B) $P2Y_6$ (B)			P2X (G)	P2Y (G)	P2 R modulate Cl^- secretion	Schwiebert and Kishore, 2001[b] Schwiebert *et al.*, 2002a[d]
Nephron cell lines								
MDCK cells		$P2Y_1$ (B) $P2Y_2$ (B) $P2Y_6$ (B)				$P2Y_1$ (G) $P2Y_2$ (G) $P2Y_{11}$ (G)	ATP and UTP stimulate AA formation ATP increases $[Ca^{2+}]_i$	Zegarra-Moran *et al.*, 1995[c] Gordjani *et al.*, 1997[c] Post *et al.*, 1998[c]

		$P2Y_{11}$ (B)					ATP and UTP stimulate AA formation	Zambon *et al.*, 2000, 2001[c] Dai *et al.*, 2001[c] Insel *et al.*, 2001[c] Ostrom *et al.*, 2001[c] Torres *et al.*, 2002[c] Hughes *et al.*, 2003[c]
A6 cells						$P2Y_1$ (GH) $P2Y_2$ (G)	ATP increases $[Ca^{2+}]_i$ P2Y R modulate Cl^- secretion	Mori *et al.*, 1996[c] Banderali *et al.*, 1999[c]
Loop of Henle								
Descending limb		$P2Y_1$ (B) $P2Y_2$ (B) $P2Y_6$ (B)					ATP increases $[Ca^{2+}]_i$	Bailey *et al.*, 2000, 2001[c]
Ascending limb		$P2Y_1$ (B) $P2Y_2$ (B) $P2Y_6$ (B)		$P2Y_2$ (D)		$P2Y_2$ (H)		Paulais *et al.*, 1995[c] Bailey *et al.*, 2000, 2001[c] Turner *et al.*, 2003[c]
Collecting ducts								
Proximal convoluted tubule	$P2X_4$ (B) $P2X_5$ (B)	$P2Y_1$ (B) $P2Y_2$ (B) $P2Y_6$ (B)	$P2X_4$ (D) $P2X_4$ (D)	$P2Y_1$ (D) $P2Y_4$ (D)		$P2Y_1$ (G) $P2Y_2$ (G) $P2Y_6$ (H)	ATP and UDP increase $[Ca^{2+}]_i$	Bailey *et al.*, 2000, 2001[c] Dockrell *et al.*, 2001[c] Schwiebert and Kishore, 2001[b] Turner *et al.*, 2003[d]
LLC-PK1 cells	$P2X_1$ (B)				$P2X_1$ (H)			Filipovic *et al.*, 1998[b]
Distal convoluted tubule	$P2X_1$ (B) $P2X_2$ (B) $P2X_3$ (B) $P2X_4$ (B) $P2X_5$ (B)	$P2Y_4$ (B)	$P2X_4$ (D) $P2X_6$ (D)				ATP increases $[Ca^{2+}]_i$ P2X R stimulation inhibits AVP- and PTH-mediated Mg^{2+} uptake	Dai *et al.*, 2001[c] Turner *et al.*, 2003[b]
DC1 cell line						$P2Y_2$ (GH)	ATP and UTP increase $[Ca^{2+}]_i$	Bidet *et al.*, 2000[c] Rubera *et al.*, 2000[c]
Cortical collecting duct	$P2X_3$ (B) $P2X_4$ (B)	$P2Y_1$ (B) $P2Y_2$ (B)	$P2X_4$ (D) $P2X_6$ (D)		$P2X_4$ (H)	$P2Y_2$ (GH)	ATP and UTP increase $[Ca^{2+}]_i$	Deetjen *et al.*, 2000[c] Lu *et al.*, 2000[c]

(*continued*)

TABLE VIII (*continued*)

Cellular component	Receptor mRNA		Receptor protein		Pharmacological and biochemical profile		Function	References
		$P2Y_6$ (B)						Bailey *et al.*, 2001[c] Schwiebert and Kishore, 2001[b] Lehrmann *et al.*, 2002[c] Tschop *et al.*, 2002[d]
M1 cells	$P2X_3$ (B) $P2X_5$ (B)	$P2Y_1$ (B)	$P2X_5$ (D)			$P2Y_2$ (GH)	ATP inhibits Na^+ absorption ATP stimulates Cl^- secretion ATP increases $[Ca^{2+}]_i$	Cuffe *et al.*, 2000[c] Parker *et al.*, 2001[c] Thomas *et al.*, 2001[c]
Inner medullary collecting duct		$P2Y_2$ (B)	$P2X_5$ (D)	$P2Y_2$ (E)		$P2Y_1$ (G) $P2Y_2$ (G)	ATP and UTP promote cell proliferation	Ishikawa *et al.*, 1997[c] Kishore *et al.*, 2000[c]
IMCD-K2 cells	$P2X_3$ (B) $P2X_4$ (B)	$P2Y_1$ (B) $P2Y_2$ (B)			P2X (G)	$P2Y_1$ (G) $P2Y_2$ (G)	ATP regulates K^+ secretion	McCoy *et al.*, 1999[c] Schwiebert and Kishore, 2001[b]
Outer medullary collecting duct		$P2Y_1$ (B) $P2Y_2$ (B) $P2Y_4$ (B) $P2Y_6$ (B)	$P2X_5$ (D)	$P2Y_1$ (D)		$P2Y_1$ (G) $P2Y_2$ (G) or $P2Y_4$ (G)	ATP modulates water permeability	Bailey *et al.*, 1999, 2000, 2001[c] Turner *et al.*, 2003[b]
Cell lines								
HEK 293 cells		$P2Y_1$ (B) $P2Y_4$ (B) $P2Y_{11}$ (B)				$P2Y_1$ (GH) $P2Y_2$ (GH) $P2Y_4$ (GH)	ATP and UTP stimulate MAPK cascade ATP increases $[Ca^{2+}]_i$	Gao *et al.*, 1999b[c] Van der Weyden *et al.*, 2000a[c] Werry *et al.*, 2001[c] Fischer *et al.*, 2003[c]
Juxtaglomerular cells of afferent arterioles						P2 (G)	ATP is a mediator in the propagation of Ca^{2+} waves	Yao *et al.*, 2003a[e]
Renal vasculature	See Table XXIV							

[a]See footnote *a* for Table III.
[b]References refer to P2X receptors.
[c]References refer to P2Y receptors.
[d]References refer to P2X and P2Y receptors.
[e]References refer to uncharacterized P2 receptors.

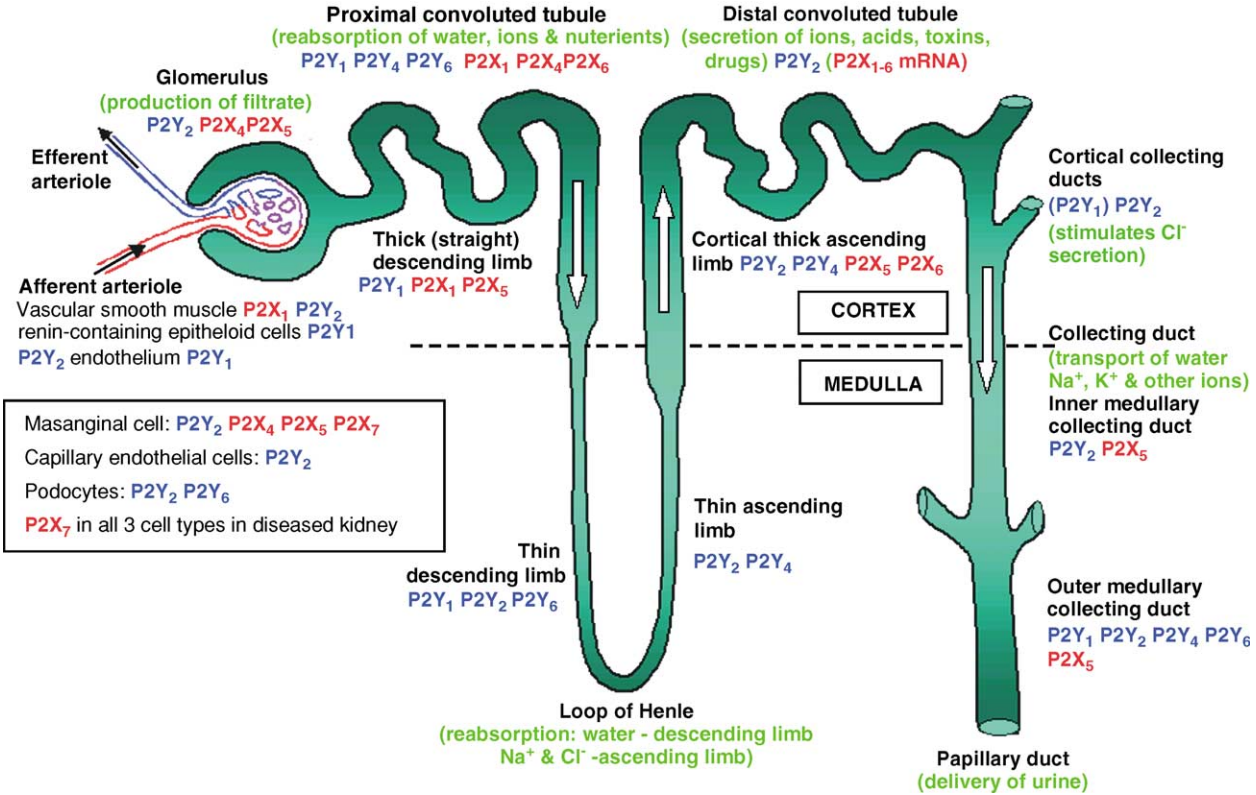


FIG. 3 Summary of the nephron segments and the distribution of P2 receptor subtypes. (Based on a figure by Turner *et al.*, 2003.)

neurotransmitter in the bladder; the results supported the view that ATP was a neurotransmitter with ACh of mammalian detrusor (Burnstock, 2000b; Burnstock *et al.*, 1978a,b) acting on P2X receptors (Burnstock and Kennedy, 1985; Howson *et al.*, 1988). A postjunctional inhibitory P2 receptor of the rat bladder was identified (Dahlén and Hedqvist, 1980) and ATP-induced inhibition of pelvic nerve-evoked bladder contractions of the cat noted (Theobald and De Groat, 1989) probably acting on P2Y receptors (Theobald, 1992). ATP relaxed the bladder smooth muscle via a P2Y receptor in the mouse (Boland *et al.*, 1993).

b. Urethra Isolated strips of precontracted guinea pig urethra relaxed in the presence of exogenous ATP, and ATP also inhibited spontaneous bursts of electrical activity of the urethra (Callahan and Creed, 1981). The urethra of rabbits, pigs, cats, and humans also relaxed in response to ATP (Andersson *et al.*, 1983; Hills *et al.*, 1984; Klarskov, 1988; Persson, 1976), although the receptor subtype was not identified.

Table IX summarizes the receptor subtypes present in the bladder and urethra based on mRNA, protein, and pharmacological and biochemical profiles. The functions claimed for the receptors together with key references are included (cf. Tables XXIV and XLV).

The antimalarial drug quinacrine is known to bind to adenine nucleotides, in particular ATP (Irvin and Irvin, 1954), and has been used to visualize nerves that contain and release ATP (Crowe and Burnstock, 1981a). Quinacrine was used to visualize ATP in a subpopulation of nerve fibers, ganglion cells, and nerve cell bodies of the bladder (Burnstock *et al.*, 1978a) and the luciferin-luciferase assay demonstrated the direct release of ATP from parasympathetic neurons of the guinea pig bladder (Burnstock *et al.*, 1978b). In the rat bladder, the release of ATP by electrical field stimulation (EFS) was detected by HPLC (Tong *et al.*, 1997b). In the rabbit bladder, the results from luciferin-luciferase assays suggested that ATP was being released from the smooth muscle in response to transmural stimulation (Chaudhry *et al.*, 1984). ATP was released from rabbit and mouse bladder urothelium in response to distention (Ferguson *et al.*, 1997; Vlaskovska *et al.*, 2001) mediating mechanosensory transduction (de Groat and Yoshimura, 2001).

In summary, the expression of protein for multiple P2X receptor subtypes has been shown in smooth muscle and urothelium of the bladder although functionally $P2X_1$ receptors are the main subtype causing contraction. The bladder smooth muscle also contains a functional P2Y receptor although this has not been fully characterized. Urethra smooth muscle has a functional P2X and a P2Y receptor although further characterization is required. Urethral epithelial cells are known to contain protein for $P2X_5$, $P2X_6$, and $P2X_7$ receptors.

TABLE IX

Bladder and Urethra[a]

Cellular component	Receptor mRNA	Receptor protein	Pharmacological and biochemical profile	Function	References
Bladder smooth muscle	$P2X_1$ (B) $P2Y_1$ (BC) $P2X_4$ (A)	$P2X_1$ (DF) $P2X_2$ (D) $P2X_4$ (DE) $P2X_5$ (D) $P2X_6$ (D) $P2X_7$ (D)	$P2X_1$ (G) P2Y (G)	ATP and ACh are parasympathetic cotransmitters ATP induces contraction via P2X R and relaxation via P2Y R ATP involved in micturition reflex	Bo *et al.*, 1994, 1995, 2003[b] Suzuki and Kokubun, 1994[b] Bolego *et al.*, 1995[d] Evans *et al.*, 1995[b] Michel *et al.*, 1996a[b] Zhao *et al.*, 1996[b] Naramatsu *et al.*, 1997[b] Tong *et al.*, 1997a,b[c] Obara *et al.*, 1998[c] McMurray *et al.*, 1998[d] Hansen *et al.*, 1998[b] Cockayne *et al.*, 2000[b] Lee *et al.*, 2000b[b] Vial and Evans, 2000, 2001[b] Elneil *et al.*, 2001[b] O'Reilly *et al.*, 2001b[b] Menzies *et al.*, 2003[b]
Bladder urothelium		$P2X_3$ (D) $P2X_5$ (D) $P2X_6$ (D) $P2X_7$ (D)			Cockayne *et al.*, 2000[b] Lee *et al.*, 2000b[b] Elneil *et al.*, 2001[b]
Bladder sensory nerves	See Table XLV				

(*continued*)

TABLE IX (*continued*)

Cellular component	Receptor mRNA	Receptor protein	Pharmacological and biochemical profile		Function	References
Urethra smooth muscle			P2X (G)	P2Y (G)	ATP and NO are NANC transmitters ATP induces relaxation via P2Y R ATP initiates EJPs	Pinna *et al.*, 1996, 1998[c] Ohnishi *et al.*, 1997[c] Werkström *et al.*, 1997[c] Hashitani and Edwards, 1999[b] Andersson, 2001[c]
Urethra epithelium		$P2X_5$ (D) $P2X_6$ (D) $P2X_7$ (D)				Lee *et al.*, 2000a[b]
Bladder and urethral vasculature	See Table XXIV					

[a]See footnote *a* for Table III.
[b]References refer to P2X receptors.
[c]References refer to P2Y receptors.
[d]References refer to P2X and P2Y receptors.

3. Ureter

Table X summarizes the receptor subtypes present in the ureter based on mRNA, protein, and pharmacological and biochemical profiles. The functions claimed for the receptors together with key references are included (cf. Tables XXIV and XLV).

ATP is released from guinea pig ureter urothelium in response to distention (Knight *et al.*, 2002) mediating mechanosensory transduction (de Groat and Yoshimura, 2001).

In summary, protein for multiple P2X receptor subtypes has been demonstrated in structures of the ureter. A functional P2 receptor has been described but has not been characterized.

D. Genital System: Males

1. Penis

ATP contracted isolated strips of canine retractor penis acting on a P2 receptor, while adenosine was without effect (Luduena and Grigas, 1972). A later comparative study found that ATP contracted the retractor penis of the rat, boar, and bull. In contrast, ATP relaxed the retractor penis of the cat. Corpus cavernosal tissue of the cat and horse contracted in response to ATP, while that of the macaque, dog, and rabbit relaxed (Klinge and Sjöstrand, 1977; Tong *et al.*, 1992; Wu *et al.*, 1993), although the receptors responsible were not identified.

Table XI summarizes the receptor subtypes present in the penis based on mRNA, protein, and pharmacological and biochemical profiles. The functions claimed for the receptors together with key references are included (cf. Table XXIV).

In summary, it has been demonstrated that functional $P2Y_1$ and $P2Y_2$ receptors mediate dilation of the corpus cavernosum, and protein for $P2X_1$ and $P2X_2$ has been shown. Endothelial cells lining the lacunar space express mRNA for $P2Y_1$ receptors.

2. Testis and Sperm

Steroid production from immature or mature mouse and rat testis leydig cells was stimulated by both adenosine and ATP following 24-h incubation in these purine compounds (Rommerts *et al.*, 1984). However, the authors were unable to conclude whether adenosine and ATP were acting at the same or independent receptors.

High concentrations of exogenous ATP had inhibitory actions against sperm motility of the hamster (Yeung, 1986) and ATP has also been used to

TABLE X
Ureter[a]

Cellular component	Receptor mRNA	Receptor protein	Pharmacological and biochemical profile	Function	References
Ureter smooth muscle		$P2X_1$ (D) $P2X_2$ (D) $P2X_5$ (D) $P2X_6$ (D)	P2 (G)	ATP induces contraction	Hernandez *et al.*, 1999[e] Lee *et al.*, 2000b[b]
Ureter epithelium		$P2X_4$ (D) $P2X_5$ (D) $P2X_6$ (D) $P2X_7$ (D)			Lee *et al.*, 2000b[b]
Sensory nerves	See Table XLV				
Ureter vasculature	See Table XXIV				

[a]See footnote *a* for Table III.
[b]References refer to P2X receptors.
[e]References refer to uncharacterized P2 receptors.

TABLE XI
Penis[a]

Cellular component	Receptor mRNA	Receptor protein	Pharmacological and biochemical profile	Function	References
Corpus cavernosum		$P2X_1$(D) $P2X_2$ (D)	$P2Y_1$(G) $P2Y_2$ (G)	ATP induces relaxation via an No-independent pathway in laboratory animals, but via an endothelial NO in humans	Broderick *et al.*, 1994, 1998[c] Levin *et al.*, 1995[c] Ragazzi *et al.*, 1996[c] Kaya *et al.*, 1998[c] Filippi *et al.*, 1999[c] Shalev *et al.*, 1999[c] Lee *et al.*, 2000a[b]
Endothelial cells lining lacunar space	$P2Y_1$ (BC)				Obara *et al.*, 1998[c]
Penile vasculature	See Table XXIV				

[a]See footnote *a* for Table III.
[b]References refer to P2X receptors.
[c]References refer to P2Y receptors.

supplement the artificial medium used for storing human sperm (Diaz *et al.*, 1992). ATP is a trigger for the acrosome reaction in sperm (Foresta *et al.*, 1992) thought to be acting via a P2X receptor.

Table XII summarizes the receptor subtypes present in the testis and sperm based on mRNA, protein, and pharmacological and biochemical profiles. The functions claimed for the receptors together with key references are included (cf. Table XXIV; see Fig. 4).

ATP from *Xenopus* sperm is thought to activate P2X receptors on oocytes possibly acting as the initial sperm to egg signal preceding fertilization (Kupitz and Atlas, 1993). The release of ATP from rat Sertoli cells into the extracellular medium was demonstrated and it was postulated that ATP might be involved in the paracrine regulation of Sertoli cell maturation (Gelain *et al.*, 2003).

In summary, functional $P2Y_2$ receptors are present in Sertoli cells and seminiferous tubule myoid cells; however, protein for multiple P2X receptor subtypes has been identified. Similarly protein for multiple P2X receptor subtypes has been identified on sperm, and although functional P2X and P2Y receptors have been demonstrated, these remain uncharacterized as yet.

3. Vas Deferens and Epididymis

a. Vas Deferens Early studies showed that ATP depressed postsynaptic α-adrenoreceptor responses to adrenergic nerve stimulation of the vas deferens and induced concentration-dependent contractions (Holck and Marks, 1978; Sakai *et al.*, 1979c). In addition, ATP was released from the guinea pig vas deferens upon transmural stimulation (Westfall *et al.*, 1978). The involvement of ATP in sympathetic transmission was confirmed by the use of the photoaffinity label arylazido aminopropionyl ATP ($ANAPP_3$) (Fedan *et al.*, 1981; Hogaboom *et al.*, 1980; Meldrum and Burnstock, 1983). The receptor was classified as belonging to the P2X subtype (Burnstock and Kennedy, 1985). Additional subtypes of P2 receptors have been identified on the vas deferens. A suramin-insensitive P2 receptor (von Kügelgen *et al.*, 1990) mediating contraction of the smooth muscle in addition to an inhibitory P2Y receptor has been identified on the mouse vas deferens (Boland *et al.*, 1992; Gailly *et al.*, 1993). A prejunctional P2 receptor, activated by β,γ-methylene ATP (β,γ-meATP), inhibited NA release in both the rat and mouse vas deferens (Kurz *et al.*, 1993).

b. Epididymis Exogenous ATP stimulated short circuit currents in a primary culture of rat epididymal cells, an effect that was specific to addition of ATP to the apical but not the basolateral side of the monolayer of cells (Wong, 1988). It was suggested that since sperm contains a high ATP concentration, it is released and may affect anion and fluid secretion by

TABLE XII

Testis and Sperm[a]

Cellular component	Receptor mRNA		Receptor protein	Pharmacological and biochemical profile		Function	References
Whole testis	$P2X_1$ (A)		$P2X_4$ (E)				Longhurst *et al.*, 1996[b] Bo *et al.*, 2003[b]
Sertoli cells	$P2X_4$ (B) $P2X_7$ (B)	$P2Y_1$ (B) $P2Y_2$ (B)	$P2X_2$ (D) $P2X_3$ (D) $P2X_7$ (D)		$P2Y_2$ (GH)	ATP increases $[Ca^{2+}]_i$ ATP increases aromatase activity ATP regulates fluid secretion ATP stimulates estradiol secretion	Filippini *et al.*, 1994[c] Foresta *et al.*, 1995[c] Rudge *et al.*, 1995[c] Meroni *et al.*, 1998[c] Ko *et al.*, 1998, 2003[c] Lalevée *et al.*, 1999[c] Glass *et al.*, 2001[b] Rossato *et al.*, 2001[d]
Seminiferous tubules	$P2X_4$ (C)		$P2X_2$ (D) $P2X_3$ (D) $P2X_7$ (D) $P2X_7$ (D)				Tanaka *et al.*, 1996[b] Glass *et al.*, 2001[b]
Myoid cells			$P2X_2$ (D)		$P2Y_2$ (G)	ATP and UTP increase $[Ca^{2+}]_i$	Rudge *et al.*, 1995[c] Glass *et al.*, 2001[b]
Leydig cells				$P2X_7$ (H)	$P2Y_2$ (H)	ATP and UTP increase $[Ca^{2+}]_i$ ATP stimulates testosterone secretion via P2X R	Foresta *et al.*, 1996a[d]
Testis vasculature	See Table XXIV						

(*continued*)

TABLE XII (*continued*)

Cellular component	Receptor mRNA	Receptor protein	Pharmacological and biochemical profile		Function	References
Sperm						
Developing—mammalian		$P2X_2$ (D) $P2X_3$ (D) $P2X_5$ (D)				Glass *et al.*, 2001[b]
Developing—fish				P2 (G)	ATP modulates spermatogenesis	Loir, 1999[e]
Mature—mammalian		$P2X_2$ (D) $P2X_3$ (D) $P2X_7$ (D)	P2X (G)	P2Y (GH)	ATP and UTP stimulate acrosomal exocytosis	Tomiyama *et al.*, 1995[e] Foresta *et al.*, 1996b[b] Rossato *et al.*, 1999[e] Glass *et al.*, 2001[b] Luria *et al.*, 2002[c]

[a]See footnote *a* for Table III.
[b]References refer to P2X receptors.
[c]References refer to P2Y receptors.
[d]References refer to P2X and P2Y receptors.
[e]References refer to uncharacterized P2 receptors.

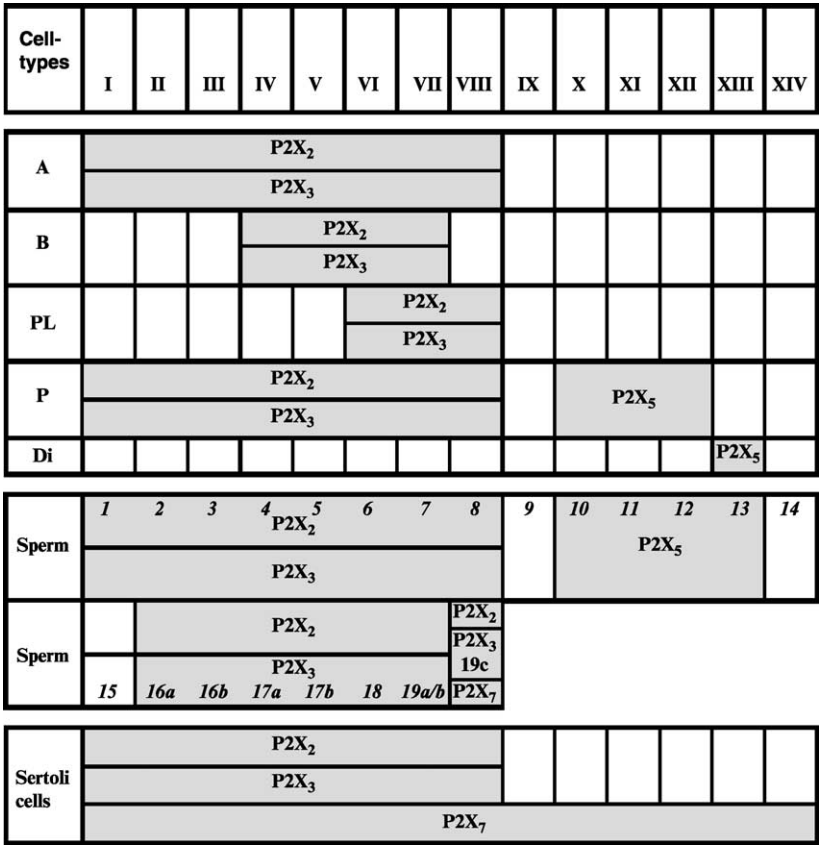


FIG. 4 Summary of P2X-immunopositive cells in the seminiferous tubules throughout the 14 stages of seminiferous epithelium. The stages of the cycle of the seminiferous epithelium are given in Roman numerals. Shaded boxes indicate the presence of immunopositive cells for a single P2X receptor subtype throughout the respective stages of the cycle. Italic numerals indicate the developmental steps of spermatid maturation. Throughout stages I to VIII younger (1–8) and older (16a–19c) generations of spermatids coexist, whereas through stages IX to XIV only one generation of developing spermatids is present. A, type A spermatogonis; B, type B spermatogonia; P, pachytene spermatocytes; Di, diplotene spermatocytes; PL, preleptotene spermatocytes; Sperm, spermatids. (Reproduced with permission from Glass *et al.*, 2001.)

the epididymis. The smooth muscle of the epididymis contracted in response to EFS; a part of the response was inhibited by α,β-meATP. Based on a rank order of potency of different P2 agonists, the receptor was characterized as a P_{2X} receptor (Ventura and Pennefather, 1991). In addition, a prejunctional P_{2Y}-like receptor, sensitive to both adenosine and ATP that inhibited transmitter release, was identified (Ventura and Pennefather, 1992).

Table XIII summarizes the receptor subtypes present in the vas deferens and epididymis based on mRNA, protein, and pharmacological and biochemical profiles. The functions claimed for the receptors together with key references are included (cf. Table XLII).

Guinea pig vas deferens preincubated in [^{3}H]adenosine released significant amounts of tritium upon transmural stimulation (Westfall *et al.*, 1978), and the direct release of ATP was measured by the luciferin-luciferase assay (Kasakov *et al.*, 1988; Kirkpatrick and Burnstock, 1987). It has also been suggested that direct nerve stimulation and stimulation by P2 agonists such as α,β-meATP and α-adrenoceptor stimulation can stimulate ATP release from extraneural sites, probably smooth muscle cells (Katsuragi *et al.*, 1991; Von Kügelgen and Starke, 1991; White *et al.*, 1981). ATP is also released form cultured guinea pig vas deferens smooth muscle cells in response to stimuli including histamine, bradykinin, and substance P (Tamesue *et al.*, 1998). Neural release of ATP in response to sympathetic stimulation has been shown in the mouse and rat (Drake and Petersen, 1992; Kurz *et al.*, 1994) and secretion of ATP from varicosities on the surface of mouse vas deferens was visualized with $DiOC_2$, and that secretion could be inhibited by suramin (Karunanithi *et al.*, 1993).

In summary, multiple P2X receptor subtype mRNA and protein has been identified in vas deferens smooth muscle and epididymal epithelium and smooth muscle. Functionally, the vas deferens smooth muscle receptor has been identified as being of the $P2X_1$ subtype, although the presence of a P2Y receptor probably of the $P2Y_2$ subtype has also been identified. In the epididymis, functional P2X and P2Y receptors as yet uncharacterized have been identified on the epithelium and mRNA and protein for $P2Y_1$ and $P2Y_2$ have been found.

4. Seminal Vesicle

ATP induced contractions in the isolated seminal vesicle of the guinea pig and was thought to act as an excitatory transmitter (Nakanishi and Takeda, 1972, 1973). Later, ATP and NA were shown to be contransmitters from the hypogastric nerve supplying the guinea pig seminal vesicle (Meldrum and Burnstock, 1985); the initial twitch-like response of the biphasic contraction mediated by EFS was greatly reduced by α,β-meATP (Wali and Greenidge, 1989).

Table XIV summarizes the receptor subtypes present in the seminal vesicles based on mRNA, protein, and pharmacological and biochemical profiles. The functions claimed for the receptors together with key references are included.

In summary, protein for $P2X_1$ and $P2X_2$ receptor subtypes has been demonstrated, although, functionally, the receptor mediating contraction has been characterized as a $P2X_1$ receptor.

TABLE XIII

Vas Deferens and Epididymis[a]

Cellular component	Receptor mRNA		Receptor protein		Pharmacological and biochemical profile		Function	References
Vas deferens smooth muscle	$P2X_1$ (B) $P2X_2$ (BC) $P2X_4$ (A)		$P2X_1$ (DF) $P2X_2$ (D) $P2X_4$ (DE) $P2X_7$ (D)		$P2X_1$ (GH)	P2Y (G) $P2Y_2$ (G)	ATP and NA are sympathetic cotransmitters ATP and Ap_4A induce contraction via P2X R ATP and UTP relax raised tone of vas deferens UTP induces contraction via $P2Y_2$ R	Michel and Humphrey, 1994[b] Bültmann and Starke, 1994[d] Bo *et al.*, 1995, 2003[b] Westfall *et al.*, 1997[b] Damer *et al.*, 1998[b] Bültmann *et al.*, 1999a,b, 2002[d] Burton *et al.*, 2000[b] Lee *et al.*, 2000a[b] Liang *et al.*, 2000[b] Mulryan *et al.*, 2000[b] Vial and Evans, 2001[b] Brain *et al.*, 2002[b] Menzies and Kennedy, 2002[b] Knight *et al.*, 2003[b] Menzies *et al.*, 2003[b]
Vas deferens sympathetic nerve terminals	See Table XLII							
Epididymis								
Smooth muscle			$P2X_1$ (D) $P2X_2$ (D)					Lee *et al.*, 2000a[b] Vial and Evans, 2001[b]
Epithelial cells	$P2X_1$ (B) $P2X_2$ (B) $P2X_4$ (B) $P2X_7$ (B)	$P2Y_1$ (B) $P2Y_2$ (B)	$P2X_1$ (D) $P2X_2$ (D) $P2X_4$ (D) $P2X_7$ (D)	$P2Y_1$ (D) $P2Y_2$ (D)	P2X (H)	P2Y (H)	ATP increases $[Ca^{2+}]_i$ ATP stimulates Cl^- secretion	Chan *et al.*, 1995[d] Shariatmadari *et al.*, 2003[d]
Interstitial cells of Cajal	$P2X_2$ (BC)		$P2X_2$ (D)				ATP may regulate smooth muscle activity and mucosal secretion	Burton *et al.*, 2000[b]

[a]See footnote *a* for Table III.
[b]References refer to P2X receptors.
[d]References refer to P2X and P2Y receptors.

TABLE XIV
Seminal Vesicle[a]

Cellular component	Receptor mRNA	Receptor protein	Pharmacological and biochemical profile	Function	References
Smooth muscle		$P2X_1$ (D) $P2X_2$ (D)	$P2X_1$ (G)	ATP and NA are sympathetic cotransmitters ATP and α,β-meATP induce contractions	Luciano *et al.*, 1995, 1998[b] Pinna *et al.*, 1997[b] Lee *et al.*, 2000a[b] Vial and Evans, 2001[b] Kubota *et al.*, 2003[b]

[a]See footnote *a* for Table III.
[b]References refer to P2X receptors.

5. Prostate Gland

Table XV summarizes the receptor subtypes present in the prostate gland based on mRNA, protein, and pharmacological and biochemical profiles. The functions claimed for the receptors together with key references are included.

In summary, protein for $P2X_1$ receptors has been shown in smooth muscle, $P2X_7$ receptors in epithelial cells, and $P2X_3$ receptors in interstitial connective tissue, probably associated with sensory nerves, Functionally, a $P2X_1$ receptor has been characterized in the smooth muscle. Although mRNA for P2X receptors has not been shown as yet, the prostate has been shown to express mRNA for $P2Y_1$ receptors.

E. Genital System: Females

1. Uterus

A progesterone–receptor complex prepared from hen oviduct cytosol was activated in the presence of ATP at low temperatures; the rate of activation was also increased by ATP (Moudgil *et al.*, 1981). This effect was also induced by other nucleotide triphosphates (Moudgil *et al.*, 1985). Estradiol–receptor binding in cytosol from immature lamb uterus increased in the presence of ATP (Lahooti *et al.*, 1990).

The effect of ATP on electrical responses following intracellular recordings of mouse uterine longitudinal smooth muscle was biphasic, an initial hyperpolarization followed by a depolarization, spike potential being suppressed and enhanced, respectively (Ninomiya and Suzuki, 1983). Isolated strips of guinea pig myometrium responded to ATP by going into spasm, possibly via the formation of prostanoids (Dozi-Vassiliades *et al.*, 1976; Moritoki *et al.*, 1979), an action that was selective for the longitudinal muscle (Pennefather and Storey, 1987). A later study showed that β,γ-meATP also induced contractions, suggestive of a P2X receptor (Smith *et al.*, 1988). ATP induced contractile responses and inward currents in smooth muscle cells from pregnant rat myometrium, which were mimicked by α,β-meATP, again suggestive of a P2X receptor (Honoré *et al.*, 1989; Osa and Maruta, 1987). Contractions of rabbit myometrial strips to ATP were enhanced in pregnant compared to nonpregnant animals (Suzuki, 1991).

Table XVI summarizes the receptor subtypes present in the uterus based on mRNA, protein, and pharmacological and biochemical profiles. The functions claimed for the receptors together with key references are included (cf. Table XXIV).

In summary, functional $P2X_1$, $P2Y_1$, and $P2Y_2$ receptors induce contractions of uterine smooth muscle, although $P2X_2$ receptor protein has also been identified on smooth muscle and multiple P2X receptor protein has

TABLE XV
Prostate Gland[a]

Cellular component	Receptor mRNA	Receptor protein	Pharmacological and biochemical profile	Function	References
Whole prostate	$P2Y_1$ (A) $P2X_1$ (A)				Janssens *et al.*, 1996[c] Longhurst *et al.*, 1996[b]
Smooth muscle		$P2X_1$ (D)	$P2X_1$ (G)	ATP and NA are sympathetic cotransmitters	Lee *et al.*, 2000a[b] Ventura *et al.*, 2003[b]
Epithelial cells		$P2X_7$ (D)	P2 (G)	ATP increases outward current and hyperpolarizes the cell membrane	Lee *et al.*, 2000a[b] Kim *et al.*, 2002a[e]
Interstitial connective tissue		$P2X_3$ (D)			Lee *et al.*, 2000a[b]

[a]See footnote *a* for Table III.
[b]References refer to P2X receptors.
[c]References refer to P2Y receptors.
[e]References refer to uncharacterized P2 receptors.

TABLE XVI
Uterus[a]

Cellular component	Receptor mRNA	Receptor protein		Pharmacological and biochemical profile		Function	References
Smooth muscle Nonpregnant		$P2X_2$ (D)	$P2Y_2$ (D)	$P2X_1$ (G)	$P2Y_1$ (G) $P2Y_2$ (G)	ATP produces spasm of uterus via both P2X and P2Y R ATP and UTP increase $PGF_{2\alpha}$ production ATP increases $[Ca^{2+}]_i$	Kelley and Hollingsworth, 1994[c] Piper and Hollingsworth, 1996[c] Gillman and Pennefather, 1998[b] Bardini *et al.*, 2000[b] Aitken *et al.*, 2001[c] Ziganshin *et al.*, 2002a,[d] 2002b[b]
Pregnant (early)		$P2X_1$ (D) $P2X_2$ (D)		P2X (G)	$P2Y_2$ (G) or $P2Y_4$ (G)	ATP induces contraction ATP increases $[Ca^{2+}]_i$	Shmigol *et al.*, 2001[c] Ziganshin *et al.*, 2002a,[d] 2002b[b]
Endometrial epithelium Nonpregnant		$P2X_5$ (D) $P2X_7$ (D)			$P2Y_2$ (G) $P2Y_6$ (G)	ATP and UTP regulate Na^+ across endometrial epithelial cells	Deachapunya and O'Grady, 1999[c] Bardini *et al.*, 2000[b] Wang and Chan, 2000[c]
Pregnant - early		$P2X_1$ (D) $P2X_2$ (D) $P2X_3$ (D) $P2X_4$ (D) $P2X_5$ (D) $P2X_6$ (D) $P2X_7$ (D)	$P2Y_1$ (D) $P2Y_2$ (D)				Slater *et al.*, 2000,[b] 2002[d] Tassell *et al.*, 2000[b]
Endometrial glands		$P2X_4$ (D)					Bo *et al.*, 2003[b]
Myometrial vasculature	See Table XXIV						

[a]See footnote *a* for Table III.
[b]References refer to P2X receptors.
[c]References refer to P2Y receptors.
[d]References refer to P2X and P2Y receptors.

been identified on endometrial epithelium. The epithelium lining the uterus and cervix possesses functional $P2Y_2$ receptors regulating ciliary activity and the movement of salt and water.

2. Ovary

Rabbit ciliated oviduct epithelial cells respond to ATP by an increase in mucociliary activity (Villalon *et al.*, 1989). ATP increased intracellular calcium in cultured Chinese hamster ovary cells via activation of an endogenous P2 purinoceptor (Iredale and Hill, 1993).

Table XVII summarizes the receptor subtypes present in the ovary and fallopian tubes based on mRNA, protein, and pharmacological and biochemical profiles. The functions claimed for the receptors together with key references are included (cf. Table XXIV).

ATP is co-stored with NA in vesicles from sympathetic nerves supplying the cat ovary. ATP is released with NA from vesicles during ovulation and is thought to modulate ovarian function (Lara and Belmar, 1991). The perfused human ovary releases ATP from vascular endothelium during increased flow (Stones *et al.*, 1996).

In summary, the whole ovary expresses mRNA for $P2X_1$ and $P2Y_1$ receptor subtypes, although protein for smooth muscle $P2X_2$ receptors has been shown. Oviduct and fallopian tube epithelial cells have functional $P2Y_2$ receptors.

3. Placenta

ATP induced reversible constrictor responses in isolated, perfused cotyledon from human placenta (Maguire *et al.*, 1990). A study of the fetal circulation of the human placenta revealed that ATP induced endothelium-dependent vasodilatation in the fetal vessels via activation of P2Y receptors and the formation of NO. This response masked a vasoconstrictor action of ATP via P2X receptors (Read *et al.*, 1993).

Table XVIII summarizes the receptor subtypes present in the placenta based on mRNA, protein, and pharmacological and biochemical profiles. The functions claimed for the receptors together with key references are included (cf. Table XXIV).

In summary, a functional $P2Y_2$ receptor has been characterized although the presence of mRNA for multiple P2X receptor subtypes together with mRNA for $P2Y_6$ receptors has also been shown.

4. Vagina and Cervix

Table XIX summarizes the receptor subtypes present in the vagina and cervix based on mRNA, protein, and pharmacological and biochemical profiles.

TABLE XVII
Ovary and Fallopian Tube[a]

Cellular component	Receptor mRNA	Receptor protein	Pharmacological and biochemical profile	Function	References
Whole ovary	$P2X_1$ (A) $P2Y_1$ (A)				Longhurst *et al.*, 1996[b] Janssens *et al.*, 1996[c]
Ovarian smooth muscle		$P2X_2$ (D)			Bardini *et al.*, 2000[b]
Ovarian vasculature	See Table XXIV				
Oviduct ciliated epithelial cells			$P2Y_2$ (GH)	ATP and UTP increase $[Ca^{2+}]_i$ ATP and UTP increase ciliary beat frequency	Cox and Leese, 1995[c] Leung *et al.*, 1995[c] Villalon *et al.*, 1995[c] Morales *et al.*, 2000[c]
Fallopian tube epithelial cells			$P2Y_2$ (GH)	ATP and UTP increase $[Ca^{2+}]_i$ ATP regulates fluid formation	Squires *et al.*, 1995[c] Dickens *et al.*, 1996[c]

[a]See footnote *a* for Table III.
[b]References refer to P2X receptors.
[c]References refer to P2Y receptors.

TABLE XVIII
Placenta[a]

Cellular component	Receptor mRNA		Receptor protein	Pharmacological and biochemical profile		Function	References
Whole placenta	$P2X_4$ (B)	$P2Y_{11}$ (B)	$P2Y_{11}$ (E)				Clarson and Glazier, 2000[b] Communi *et al.*, 2001b[c]
Trophoblasts	$P2X_1$ (B) $P2X_2$ (B) $P2X_4$ (B) $P2X_7$ (B)	$P2Y_6$ (A)	$P2X_7$ (D)	P2X (H) $P2X_7$ (H)	$P2Y_2$ (H)	ATP stimulates inositol phosphate production ATP via $P2X_7$ R activates PLD	Petit and Bélisle, 1995[c] Karl *et al.*, 1997[c] Somers *et al.*, 1999[c] Clarson and Glazier, 2000[b] Clarson *et al.*, 2002[b] Divald *et al.*, 2002[b] Roberts and Clarson, 2002[b]
Placental blood vessels	See Table XXIV						

[a]See footnote *a* for Table III.
[b]References refer to P2X receptors.
[c]References refer to P2Y receptors.

TABLE XIX
Vagina and Cervix[a]

Cellular component	Receptor mRNA		Receptor protein	Pharmacological and biochemical profile		Function	References
Vaginal smooth muscle			$P2X_2$ (D)		P2Y (G)	ATP induces relaxation via a P2Y R	Bardini *et al.*, 2000[b] Ziessen and Cellek, 2002[c]
Vaginal epithelium							
Stratified epithelial cells		$P2Y_2$ (C)	$P2X_5$ (D) $P2X_7$ (D)		$P2Y_2$ (G)	$P2X_5$ and $P2X_7$ R involved in cell turnover	Gröschel-Stewart *et al.*, 1999a[b] Bardini *et al.*, 2000[b] Min *et al.*, 2003[c]
Endocervical epithelial cells		$P2Y_2$ (C)			$P2Y_2$ (G)	ATP and UTP stimulate Cl^- and mucus secretion	Cowlen *et al.*, 2002[c] Min *et al.*, 2003[c]
Cervical epithelial cells	$P2X_4$ (A)	$P2Y_2$ (ABC)	$P2X_7$ (D)	$P2X_4$ (D)	$P2Y_2$ (G)	ATP stimulates biphasic changes in transepithelial electrical conductance	Gorodeski and Hopfer, 1995[c] Gorodeski *et al.*, 1996, 1998a,b[c] Gorodeski and Goldfarb, 1997[c] Bardini *et al.*, 2000[b] Cowlen *et al.*, 2002[c] Gorodeski, 2002[b]

[a]See footnote *a* for Table III.
[b]References refer to P2X receptors.
[c]References refer to P2Y receptors.

The functions claimed for the receptors together with key references are included.

In summary, vaginal smooth muscle contains protein for $P2X_2$ receptors; a functional P2Y receptor has been demonstrated but this has not been fully characterized. Vaginal and cervical epithelial cells both express mRNA for $P2Y_2$ receptors and functional $P2Y_2$ receptors have been demonstrated. Protein for $P2X_7$ has been shown for both types of epithelium in addition to $P2X_5$ receptor protein in vaginal epithelium.

F. Immune System

1. Thymus

DNA synthesis was markedly increased in cells from mouse and calf thymus when cultured in the presence of adenine nucleotides (Gregory and Kern, 1978; Ikehara *et al.*, 1981; Wierowski *et al.*, 1983). In addition, exogenous ATP increased Ca^{2+} uptake in mouse thymocytes, Ca^{2+} being thought to have an important mitogenic role on thymocytes (el-Moatassim *et al.*, 1987, 1989; Lin *et al.*, 1985) and induce apoptosis (el-Moatassim *et al.*, 1990; Zheng *et al.*, 1991) via the entry of cations. ATP stimulated prostaglandin E_2 (PGE_2) production in the thymic endothelial cell line TEA3α_1, classified as a P_{2U} receptor since both ATP and UTP were equipotent (Liu *et al.*, 1993).

Table XX summarizes the receptor subtypes present in the thymus based on mRNA, protein, and pharmacological and biochemical profiles. The functions claimed for the receptors together with key references are included (cf. Table XXIV).

ATP may be released from thymocytes via a nonlytic process in addition to the ATP that would be released following cell injury or loss of cell viability (Alves *et al.*, 1999).

In summary, multiple mRNA and protein have been demonstrated for thymocytes, although functionally $P2X_1$, $P2X_2$, $P2X_7$ and $P2Y_2$ receptors are present. Protein for multiple P2X receptor subtypes is present on epithelial cells, although, functionally, it appears that $P2Y_2$ receptors predominate.

2. Spleen

DNA synthesis decreased in cells cultured from mouse spleen in the presence of adenine nucleotides (Gregory and Kern, 1978; Ikehara *et al.*, 1981, 1983).

Table XXI summarizes the receptor subtypes present in the spleen based on mRNA, protein, and pharmacological and biochemical profiles. The functions claimed for the receptors together with key references are included (cf. Table XXIV).

TABLE XX
Thymus[a]

Cellular component	Receptor mRNA		Receptor protein	Pharmacological and biochemical profile		Function	References
Whole thymus	$P2X_4$ (A)		$P2X_4$ (E)				Bo *et al.*, 1995, 2003[b]
Thymocytes	$P2X_1$ (AB) $P2X_2$ (B) $P2X_6$ (B) $P2X_7$ (B)	$P2Y_1$ (B) $P2Y_2$ (BC)	$P2X_1$ (D) $P2X_4$ (D)	$P2X_1$ (G) $P2X_2$ (G) $P2X_7$ (GH)	$P2Y_2$ (H)	ATP has mitogenic actions ATP induces thymocytic apoptosis via $P2X_7$ R	Chused *et al.*, 1996[b] Chvatchko *et al.*, 1996[b] Apasov *et al.*, 1997[d] Koshiba *et al.*, 1997[d] Ross *et al.*, 1997[b] Alves *et al.*, 1999[e] Freedman *et al.*, 1999[b] Glass *et al.*, 2000[d] Nagy *et al.*, 2000[b] Loesch and Burnstock, 2002[c]
Epithelial cells							
Thymic epithelia			$P2X_2$ (D) $P2X_6$ (D)		P2Y (G)	ATP stimulates IL-6 production	von Patay *et al.*, 1999[c] Glass *et al.*, 2000[b]
Medullary epithelia			$P2X_2$ (D) $P2X_3$ (D)				Glass *et al.*, 2000[b]
Subcapsular epithelia			$P2X_2$ (D)				Glass *et al.*, 2000[b]
Perivascular epithelia		$P2Y_2$ (C)	$P2X_2$ (D)				Glass *et al.*, 2000[b] Loesch and Burnstock, 2002[c]
Thymic septal epithelia			$P2X_2$ (D) $P2X_6$ (D) $P2X_7$ (D)				Glass *et al.*, 2000[b]
Hassalls' corpuscles			$P2X_6$ (D)				Glass *et al.*, 2000[b]

(*continued*)

TABLE XX (*continued*)

Cellular component	Receptor mRNA		Receptor protein	Pharmacological and biochemical profile		Function	References
Epithelial cell lines							
TEA3A1 cells					$P2Y_2$ (G)	ATP and UTP stimulate PGE_2 production	Liu *et al.*, 1995, 1998[c]
2BH4 cells	$P2X_7$ (B)	$P2Y_2$ (B)		$P2X_7$ (H)	$P2Y_2$ (H)		Bisaggio *et al.*, 2001[d]
IT45-R1 cells		$P2Y_2$ (B)			$P2Y_2$ (H)	ATP increases $[Ca^{2+}]_i$	Bisaggio *et al.*, 2001[c]
						ATP increases $[Ca^{2+}]_i$	
Thymus vasculature	See Table XXIV						
Thymic reticulum							
Phagocytic cells				$P2X_7$ (G)			Coutinho-Silva *et al.*, 1996a,b[b]

[a]See footnote *a* for Table III.
[b]References refer to P2X receptors.
[c]References refer to P2Y receptors.
[d]References refer to P2X and P2Y receptors.
[e]References refer to uncharacterized P2 receptors.

TABLE XXI
Spleen[a]

Cellular component	Receptor mRNA		Receptor protein	Pharmacological and biochemical profile		Function	References
Whole spleen	$P2X_1$ (A)	$P2Y_2$ (B) $P2Y_6$ (A) $P2Y_{11}$ (B) $P2Y_{13}$ (B)	$P2X_4$ (E)	P2 (G)		ATP suppresses IFN-γ production from spleen cells stimulated with LPS	Communi *et al.*, 1996[c] Longhurst *et al.*, 1996[b] Haskó *et al.*, 2000[c] Van der Weyden *et al.*, 2000c[c] Zambon *et al.*, 2000[c] Communi *et al.*, 2001a[c] Bo *et al.*, 2003[b]
Superfused spleen slice				$P2X_1$ (G)	$P2Y_1$ (G)	ATP released as a sympathetic cotransmitter regulates secretion of IL-6	Straub *et al.*, 2002[d]
Spleen vasculature	See Table XXIV						

[a]See footnote *a* for Table III.
[b]References refer to P2X receptors.
[c]References refer to P2Y receptors.
[d]References refer to P2X and P2Y receptors.

ATP is released from the endothelium of the canine splenic artery, where it is postulated that it modulates sympathetic transmission, contributing to the purinergic vasoconstriction component of nerve-mediated responses (Yang and Chiba, 1998).

In summary, the presence of multiple P2Y receptor subtype mRNA has been shown in the spleen but only mRNA for $P2X_1$ receptors, although protein for $P2X_4$ receptors has been demonstrated. Functional $P2X_1$ and $P2Y_1$ receptors of the spleen have been characterized.

3. Immune Cells

a. Macrophage Exogenous ATP inhibited macrophage-mediated cytotoxicity of human tumor cells (Cameron, 1984). In mouse peritoneal macrophages, agonist-stimulated β-galactosidase secretion was inhibited by ATP and ADP (Riches *et al.*, 1985). Subsequently, several studies showed that ATP induced large nonselective conductance changes in macrophage plasma membranes (Buisman *et al.*, 1988; Greenberg *et al.*, 1988; Hara *et al.*, 1990; Steinberg *et al.*, 1987; Sung *et al.*, 1985) anticipating the presence of a $P2X_7$ receptor (el-Moatassim and Dubyak, 1993; Murgia *et al.*, 1993). Some studies also reported ADP-mediated death of macrophages (Blanchard *et al.*, 1991; Murgia *et al.*, 1992). In mouse peritoneal macrophages ATP stimulated eicosanoid synthesis (Pfeilschifter *et al.*, 1989) and in guinea pig peritoneal and rat alveolar macrophages, extracellular ATP elicited superoxide generation (Murphy *et al.*, 1993; Nakanishi *et al.*, 1991).

b. Neutrophils ATP and UTP were shown in early studies to cause a rapid, partially reversible, aggregation of neutrophils (Ford-Hutchinson, 1982). ATP was also shown to inhibit neutrophil-mediated cytotoxicity (Cameron, 1985) and chemotaxis (Elferink *et al.*, 1992) and to induce transient elevations of $[Ca^{2+}]_i$ (Cockcroft and Stutchfield, 1989; Cowen *et al.*, 1989; Kuroki *et al.*, 1989; Walker *et al.*, 1991) and to have regulatory effects on oxygen radical responses of stimulated neutrophils (Axtell *et al.*, 1990; Krautwurst *et al.*, 1992; Kuhns *et al.*, 1988; Ward *et al.*, 1988; Yu *et al.*, 1991). Extracellular ATP stimulated elastase secretion from human neutrophils (Flezar *et al.*, 1992), adhesion of neutrophils to cell surfaces (Freyer *et al.*, 1988), and AA release (Xing *et al.*, 1992), increased degranulation (Melloni *et al.*, 1986; Seifert *et al.*, 1989b), and triggered superoxide formation (McGarrity *et al.*, 1989; Naum *et al.*, 1991).

c. Basophils In permeabilized RBL-2H3 cells, ATP alone induced a low level secretory response (Ali *et al.*, 1989; Ludowyke *et al.*, 1989) that was thought to involve G protein activation (De Matteis *et al.*, 1991).

d. Eosinophils It has been reported that extracellular ATP increased $[Ca^{2+}]_i$ in cultured eosinophils derived from human umbilical cord blood (Saito *et al.*, 1991) resulting in a strong chemotactic response (Burgers *et al.*, 1993).

e. Lymphocytes ATP stimulated DNA synthesis in lymphocytes from bone marrow and thymus, but inhibited DNA synthesis in lymphocytes from spleen, lymph nodes, and peripheral blood (Ikehara *et al.*, 1981). However, most early studies suggest that ATP inhibited lymphocyte proliferation and T cell-mediated cytotoxicity via the generation of adenosine (DosReis *et al.*, 1986; Fishman *et al.*, 1980; Wolberg *et al.*, 1975), although the involvement of a P2 receptor in this event was not excluded (Henriksson, 1983; Schmidt *et al.*, 1984). Later ATP was shown to act on P2 receptors to increase cation permeability (Padeh *et al.*, 1991; Wiley and Dubyak, 1989; Wiley *et al.*, 1990) and to trigger cell death (Di Virgilio *et al.*, 1989; Filippini *et al.*, 1990; Zanovello *et al.*, 1990).

f. Hematopoietic Cells ATP increased plasma membrane permeability in hemopoietic stem cell lines and therefore increased survival (Whetton *et al.*, 1988). In HL-60 cells (promyelocytic leukemia cells) ATP and ADP increased $[Ca^{2+}]_i$ (Nonotte *et al.*, 1989) and ATP and UTP stimulated the inositol phospholipid signaling system via a P2Y receptor (Cowen *et al.*, 1990a,b), whereas in K562 cells, ADP increased $[Ca^{2+}]_i$ (Kalambakas *et al.*, 1993; Murgo and Sistare, 1992).

g. Monocytes ATP and ADP produced dose-dependent increases in $[Ca^{2+}]_i$ through mobilization of intracellular stores in the monocyte cell line THP-1 (Altieri *et al.*, 1990). ATP also induced cell lysis in THP-1 cells via a P2Z receptor (Spranzi *et al.*, 1993). In the cell line U937, the effect was found to be due to activation of P2Y receptors (Pleass *et al.*, 1990; Sipka *et al.*, 1991).

h. Mast Cells It has been known for many years that ATP causes release of histamine and subsequently degranulation of mast cells (Bloom *et al.*, 1970; Cockcroft and Gomperts, 1979a,b; Dahlquist and Diamant, 1970; Dahlquist *et al.*, 1974; Diamant and Kruger, 1967; Ennis and Pearce, 1980; Keller, 1966; Kiernan, 1972; Sugiyama, 1971; Sugiyama and Yamasaki, 1969; Tatham and Lindau, 1990). Ecto ATPases were present that influenced the effects of ATP (Chakravarty, 1980; Chakravarty and Echetebu, 1978; Magro, 1977; Takei *et al.*, 1993) and ATP was shown to release leukotriene C_4 (Saito *et al.*, 1991). In the early study of Cockcroft and Gomperts, it was suggested that an ATP^{4-} receptor was involved (Bennett *et al.*, 1981; Cockcroft and Gomperts, 1980; Gomperts, 1983; Tatham *et al.*, 1988). Cell-to-cell spread of calcium signals mediated by ATP P2 receptors on mast cells was

demonstrated in 1992 (Osipchuk and Cahalan, 1992). However, following the cloning and later subclassification of P2 receptors into P2X ion channels and P2Y G protein-coupled receptors in the early 1990s (Abbracchio and Burnstock, 1994), classification of the P2 receptors present in mast cells was possible.

Table XXII summarizes the receptor subtypes present in immune cells based on mRNA, protein, and pharmacological and biochemical profiles. The functions claimed for the receptors together with key references are included (Fig. 5).

During an immune response many situations arise that result in membrane damage and cytotoxicity and the subsequent release of cellular ATP. In addition to the nonspecific mechanisms, other systems for ATP release may occur. Filippini and colleagues reported ATP release by cytotoxic T cell clones stimulated with anti-CD3 antibodies (Filippini *et al.*, 1990). Macrophages, mast cells, microglial cells, and monocytes have been shown to release ATP under either physiological or pathological conditions (Day and Wade, 1978; Ferrari *et al.*, 1997; Gardella *et al.*, 2002; Imai *et al.*, 2000; Loomis *et al.*, 2003; Marino *et al.*, 1984; Mizumoto *et al.*, 2002).

In summary, mRNA for multiple P2X and P2Y receptor subtypes is expressed in macrophages, neutrophils, eosinophils, dendritic cells, monocytes, and hematopoietic cells, whereas lymphocytes are shown to express mRNA for P2Y receptor subtypes. In the majority of immune cell types, protein and functional $P2X_7$ receptors have been demonstrated. Several functional P2Y receptors have been characterized, although most immune cell types have been shown to have functional $P2Y_2$ receptors.

G. Cardiovascular System

1. Heart

The heart was the subject of early studies of the extracellular actions of ATP (Drury and Szent-Györgyi, 1929) and Drury (1936) later showed that different regions of the heart responded in different ways to ATP. Its chronotropic and inotropic effects were predominantly negative on mammalian atria (dog: Emmelin and Feldberg, 1948; James, 1965; Kontos *et al.*, 1968; cat: Acierno *et al.*, 1952; Bertelli *et al.*, 1972; Green and Stoner, 1950; rabbit: Bertelli *et al.*, 1972; Bielschowsky *et al.*, 1946; Emmelin and Feldberg, 1948; rat: Bertelli *et al.*, 1972; Hollander and Webb, 1957; Meinertz *et al.*, 1973), but positive on both mammalian (rabbit: Green and Stoner, 1950; rat: Burnstock and Meghji, 1983; Legssyer *et al.*, 1988) and amphibian (Boyd and Forrester, 1968; Burnstock and Meghji, 1981; Kanda *et al.*, 1954; Lichtneckert and Straub, 1949; Linder and Rigler, 1931; Loewi, 1949; Marshall and

TABLE XXII

Immune Cells[a]

Cellular component	Receptor mRNA	Receptor protein		Pharmacological and biochemical profile		Function	References
Macrophage							
BAC1.2F5				$P2X_7$ (G)		ATP elevates cytosolic Ca^{2+}	Nuttle and Dubyak, 1994[b]
RAW 264.7				$P2X_7$ (G)	$P2Y_2$ (G)	ATP potentiates NOS expression induced by LPS	Tonetti *et al.*, 1994, 1995[c]
							Denlinger *et al.*, 1996[c]
						ATP and Bz-ATP activate $P2X_7$ R to form pores	Lin and Lee, 1996[c]
							Lin, 1997[c]
						ATP and UTP induce AA release	Hu *et al.*, 1998[b]
						ATP inhibits macrophage-mediated toxicity	Lin and Chen, 1998[c]
							Sperlágh *et al.*, 1998c[b]
						ATP inhibits lysosomal enzyme secretion	Sommer *et al.*, 1999[c]
J774 (mouse macrophage cell line)	$P2X_7$ (C)	$P2X_7$ (E)	$P2Y_6$ (E)	$P2X_7$ (G)	$P2Y_2$ (G)		Zambon *et al.*, 1994[b]
					$P2Y_6$? (G)	ATP induces large nonselective conductances in plasma membranes	Chiozzi *et al.*, 1996, 1997[b]
							Coutinho-Silva and Persechini, 1997[b]
						ATP kills macrophages	Lin and Chen, 1997[c]
						ATP synergizes with tenidap in activation of $P2X_7$ R	Chen *et al.*, 1998[c]
							Sanz *et al.*, 1998[c]
						UTP potentiates PGE_2 release	Chen and Lin, 2000[c]
Peritoneal macrophages		$P2X_7$ (E)		$P2X_7$ (GI)	$P2Y_2$ (GI)	ATP suppresses TNF-α and IL-12 release	Perregaux and Gabe, 1994, 1998[d]
							Ichinose, 1995[d]
						ATP elicits superoxide generation	Naumov *et al.*, 1995[b]
						ATP releases IL-1β accompanied by cell death	Alonso-Torre and Trautmann, 1995[c]
						ATP causes giant cell formations	Coutinho-Silva *et al.*, 1996a[b]
						ATP and UTP control the generation of reactive O_2	Haskó *et al.*, 2000[c]
							Le Feuvre *et al.*, 2002[b]
							Brough *et al.*, 2003[b]

(*continued*)

TABLE XXII (*continued*)

Cellular component	Receptor mRNA		Receptor protein	Pharmacological and biochemical profile		Function	References
Alveolar macrophages	$P2X_1$ (B) $P2X_4$ (B) $P2X_7$ (B)	$P2Y_1$ (B) $P2Y_2$ (B) $P2Y_4$ (B) $P2Y_{12}$ (B)	$P2X_7$ (D)	$P2X_4$ (G) $P2X_7$ (G)	$P2Y_1$ (G) $P2Y_2$ (G)		Messeri *et al.*, 1999[c] Smith *et al.*, 2001b[b] Bowler *et al.*, 2003[d] Lemaire and Leduc, 2003[b]
Human monocyte-derived macrophages	$P2X_1$ (B) $P2X_7$ (B)	$P2Y_2$ (B) $P2Y_{11}$ (B)		$P2X_7$ (G)	$P2Y_2$ (G) or $P2Y_4$ (G) $P2Y_{14}$ (H)		Hickman *et al.*, 1994[b] Blanchard *et al.*, 1995[b] Falzoni *et al.*, 1995[c] Schmid-Antomarchi *et al.*, 1997[c] Oshimi *et al.*, 1999[c] Di Virgilio *et al.*, 1999[b] Eschke *et al.*, 2002[b] Into *et al.*, 2002[b] Li *et al.*, 2002[b] Skelton *et al.*, 2003[c] Wiegang, 2003[d]
LPS-primed macrophages			$P2X_7$ (D)	$P2X_7$ (G)	P2Y (G)	ATP induces IL-1 release from LPS-primed macrophages	Griffiths *et al.*, 1995[c] Ferrari *et al.*, 1997[b]
Mycobacterium-infected human macrophages		$P2Y_{11}$ (B)		$P2X_7$ (GH)	$P2Y_2$ (G) $P2Y_{11}$ (G)	ATP kills the mycobacteria and macrophage	Lammas *et al.*, 1997[b] Sikora *et al.*, 1999[b] Zaborina *et al.*, 1999, 2000[b] Koshlukova *et al.*, 2000[b] Melnikov *et al.*, 2000[b] Coutinho-Silva *et al.*, 2001b[b] Fairbairn *et al.*, 2001[b] Kusner and Barton, 2001[b] Stober *et al.*, 2001[c] Canaday *et al.*, 2002[b]

Human colonic macrophages	$P2X_7$ (B)		$P2X_7$ (G)			Li *et al.*, 2000b[b]
Neutrophils	$P2X_1$ (B) $P2X_4$ (B) $P2X_5$ (B) $P2X_7$ (AB)	$P2Y_1$ (B) $P2Y_2$ (B)	$P2X_7$ (G)	$P2Y_2$ (GH) or $P2Y_4$ (GH)	ATP and UTP promote adhesion to endothelial cells ATP increases $[Ca^{2+}]_i$ ATP induces actin polymerization ATP modulates Fcγ receptor-triggered phagocytosis ATP produces respiratory bursts as part of the defense mechanism ATP releases elastase ATP enhances the oxidative burst induced by chemokines	O'Flaherty and Cordes, 1994[c] Dawicki *et al.*, 1995[c] Suszták *et al.*, 1995[c] Zhang *et al.*, 1996b[c] Zalavary *et al.*, 1996[c] Chen and Jan, 2000[c] Suh *et al.*, 2001a[b] Tamura *et al.*, 2001[c]
Basophils				P2 (G)	Secretion of allergic and inflammatory mediators	Ludowyke and Scurr, 1994[e]
Eosinophils	$P2X_1$ (B) $P2X_4$ (B) $P2X_5$ (B) $P2X_7$ (B)	$P2Y_1$ (B) $P2Y_2$ (B) $P2Y_4$ (B) $P2Y_6$ (B) $P2Y_{11}$ (B)	$P2X_1$ (G) $P2X_7$ (G)	$P2Y_2$ (G) $P2Y_6$ (G)	ATP induces O_2 radicals ATP induces actin regeneration ATP increases $[Ca^{2+}]_i$ Nucleotides induce release of IL-8 and eosinophil cationic protein via $P2Y_6$, $P2X_1$, and $P2X_3$ R	Dichmann *et al.*, 2000[c] Ferrari *et al.*, 2000a[d] Idzko *et al.*, 2002, 2003[d] Mohanty *et al.*, 2001[b]
Lymphocytes		$P2Y_1$ (B) $P2Y_2$ (B) $P2Y_4$ (B) $P2Y_6$ (B) $P2Y_{11}$ (B) $P2X_1$ (D) $P2X_2$ (D) $P2X_4$ (D) $P2X_7$ (D)	$P2X_7$ (GI)	$P2Y_{11}$ (G)	ATP regulates differentiation and cell death ATP causes loss of L-selectin ATP involved in mitogenic stimulation ATP increases proliferation rate of lymphoid cells transfected with $P2X_7$ R	Wiley *et al.*, 1994[b] Bretschneider *et al.*, 1995[b] Baricordi *et al.*, 1996, 1999[b] Chused *et al.*, 1996[b] Jamieson *et al.*, 1996[b] Macino *et al.*, 1996[b] Gargett *et al.*, 1997[b] Markwardt *et al.*, 1997[b]

(*continued*)

TABLE XXII (*continued*)

Cellular component	Receptor mRNA		Receptor protein	Pharmacological and biochemical profile		Function	References
						$P2Y_{11}$ R may mediate developmental fate of B-lymphocytes Secretion of IL-2 and IFN-γ requires extracellular ATP	Jin *et al.*, 1998[c] Persechini *et al.*, 1998[b] Smith *et al.*, 1998[b] Conigrave *et al.*, 2001[c] Sluyter *et al.*, 2001[b] Adinolfi *et al.*, 2002[b] Duhant *et al.*, 2002[c] Budagian *et al.*, 2003[b] Langston *et al.*, 2003[e] Loomis *et al.*, 2003[b]
Dendritic cells	$P2X_1$ (B) $P2X_4$ (B) $P2X_5$ (B) $P2X_7$ (B)	$P2Y_1$ (B) $P2Y_2$ (B) $P2Y_4$ (B) $P2Y_5$ (B) $P2Y_6$ (B) $P2Y_{10}$ (B) $P2Y_{11}$ (B) $P2Y_{12}$ (B)	$P2X_7$ (E)	$P2X_7$ (G)	$P2Y_2$ (GH) or $P2Y_4$ (GH) $P2Y_6$ (GH) $P2Y_{11}$ (G)	ATP increases migration ATP increases $[Ca^{2+}]_i$ $P2X_7$ R participate in apoptosis and mediate loss of CD23 associated with inflammation ATP and TNF-α synergize to increase cell maturation ATP induces cytokine release P2Y R mediate chemotaxis and actin polymerization	Berchtold *et al.*, 1999[d] Liu *et al.*, 1999b[c] Marriott *et al.*, 1999[c] Mutini *et al.*, 1999[b] Coutinho-Silva *et al.*, 1999[b] Ferrari *et al.*, 2000b[d] Nihei *et al.*, 2000[b] Schnurr *et al.*, 2000, 2003[c] Idzko *et al.*, 2002[d] la Sala *et al.*, 2002[c] Sluyter and Wiley, 2002[b] Wilkin *et al.*, 2002[c] Stuplich *et al.*, 2003[c]

Monocytes							
Freshly isolated	$P2X_7$ (B)	$P2Y_1$ (B) $P2Y_2$ (B) $P2Y_4$ (B) $P2Y_6$ (B)	$P2X_7$ (DE)	$P2X_7$ (G)	$P2Y_1$ (G) $P2Y_2$ (G)	Nucleotides cause an increase in surface expression of Mac-1 ATP (released from sympathetic nerves) is a potent chemoattractant	Akbar *et al.*, 1997[c] Rassendren *et al.*, 1997[b] Jin *et al.*, 1998[c] Gu *et al.*, 2000[b] Straub *et al.*, 2000[c] Mehta *et al.*, 2001[b] Aga *et al.*, 2002[b]
Cell lines							
THP-1		$P2Y_2$ (B)		$P2X_7$ (G)	$P2Y_2$ (G) $P2Y_6$ (G)	$P2X_7$ R mediate IL-1β and IL-18 release when primed with LPS UDP, via $P2Y_6$ R, mediates IL-8 production	Humphreys and Dubyak, 1996[b] Clifford *et al.*, 1997[c] Grahames *et al.*, 1999[b] Warny *et al.*, 2001[c] Connon *et al.*, 2003[b]
U-937				$P2X_7$ (G)	$P2Y_1$ (G) $P2Y_2$ (G)	$P2X_7$ R mediate cell death	Ventura and Thomopoulos, 1995[c] Weisman *et al.*, 1998a[c]
Mast cells		$P2Y_1$ (B) $P2Y_2$ (B)			$P2Y_1$ (G) $P2Y_2$ (G)	ATP releases histamine and causes degranulation	McCloskey *et al.*, 1999[c] Schulman *et al.*, 1999, 2002[c]
Cell lines							
MC9				$P2X_7$ (GH)		P2Y R mediate cell migration and chemoattraction	Sudo *et al.*, 1996[b]
Hematopoietic cell lines	See Table XXVII						

[a]See footnote *a* for Table III.
[b]References refer to P2X receptors.
[c]References refer to P2Y receptors.
[d]References refer to P2X and P2Y receptors.
[e]References refer to uncharacterized P2 receptors.

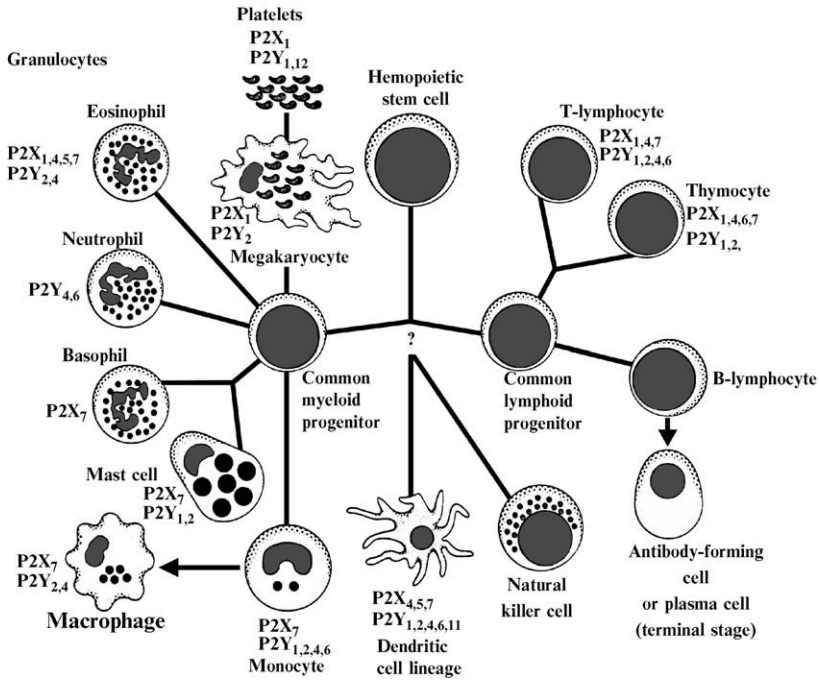


FIG. 5 P2 receptor subtype distribution in immune cells. All these cells are derived from pluripotent stem cells, which give rise to two main lineages: one for lymphoid cells and the other for myeloid cells. The common lymphoid progenitor has the capacity to differentiate into either T cells or B cells depending on the microenvironment (T cells develop in the thymus while B cells develop in the fetal liver and bone marrow). The precise origin of some antigen-presenting cells and the natural killer cells is not certain, although they do develop ultimately from the hemopoietic cells.

Andrus, 1953; Schenberg, 1956; Szent-Györgyi, 1953; Versprille, 1963, 1965) ventricles. Not surprisingly, the responses to ATP of isolated whole hearts and those produced by injection into intact animals were complex (cats: Bielschowsky *et al.*, 1946; Emmelin and Feldberg, 1948; Green and Stoner, 1950; dogs: Angelakos and Glassman, 1961; Emmelin and Feldberg, 1948; rabbit: Buckley *et al.*, 1961; Sydow and Ahlquist, 1954; guinea pig: Rand *et al.*, 1955; Stafford, 1966; rat: Versprille and Van Duyn, 1966; human: Leclercq and Coumel, 1978; Wayne *et al.*, 1949). They appeared to be dominated by chronotropic effects, which tended to obscure the no less interesting inotropic effects. The interpretation of experiments with intact animals is further complicated because ATP is rapidly degraded *in vivo* by extrinsic 5′-nucleotidases, which produce ADP, AMP, and adenosine (Arch

and Newsholme, 1978), so that adenosine acting via P1 receptors might be partly responsible for the inhibitory effects of ATP (Burnstock, 1978; Hopkins, 1973; Pelleg *et al*., 1985b; Ragazzi *et al*., 1991).

Debate about the mechanisms underlying the activity of ATP in the heart followed (Burnstock and Meghji, 1983; Clemens and Forrester, 1982; De Young and Scarpa, 1989; James, 1965; Kontos *et al*., 1968; Michel and Humphrey, 1993; Stafford, 1966; Scamps and Vassort, 1990; Takikawa *et al*., 1990; Zheng *et al*., 1992b). ATP enhanced cytosolic Ca^{2+} in isolated ventricular myocytes (Christie *et al*., 1992; Danziger *et al*., 1988; Hirano *et al*., 1991; Pucéat *et al*., 1991; Qu *et al*., 1993; Zheng *et al*., 1992a). ATP (largely via adenosine) was proposed for acute therapy of paroxysmal supraventricular tachycardia (Belhassen and Pelleg, 1984; Motté *et al*., 1972). ATP applied to the heart can trigger a vagal reflex via P2X receptors (Munoz *et al*., 1983; Pelleg *et al*., 1985a, 1993).

It was concluded from studies of the frog ventricle, that ATP had a dual effect, an initial rapid increase in contractility associated with an increase in $[Ca^{2+}]_i$ and partly by production of prostaglandins, followed by a fall in twitch amplitude, perhaps associated with cAMP via the inhibitory action of adenosine (Flitney and Singh, 1980). Interestingly it was also shown that UTP enhanced frog ventricular contractility (Flitney and Singh, 1979). Slow inhibitory potentials produced by adenosine nucleotides were also described in frog sinus venosus (Hartzell, 1979).

Allen and Burnstock (1990) were the first to show ATP-related excitation of intrinsic cardiac neurons, later confirmed and extended (Fieber and Adams, 1991; Huang *et al*., 1993a). The first hint that the excitatory action of ATP on atrial muscle was via P2X receptors since α,β-meATP blocked the response (Dorigo *et al*., 1988; Friel and Bean, 1990), via P2Y receptors in ventricular myocytes (Björnsson *et al*., 1989; Scamps *et al*., 1992; Yamada *et al*., 1992) and cultured intracardiac neurons (Allen and Burnstock, 1990). The possibility that two different P2 receptors were present in ventricular myocytes was raised (Giannattasio *et al*., 1992).

There was an early suggestion that the ATP affect on conductance between paired ventricular myocytes was probably through a specific ligand–receptor interaction between ATP and gap junctional channel protein (Sugiura *et al*., 1990). The presence of an Ap_4A receptor in mouse heart cells was suggested (Walker *et al*., 1993).

Table XXIII summarizes the receptor subtypes present in the heart based on mRNA, protein, and pharmacological and biochemical profiles. The functions claimed for the receptors together with key references are included (cf. Tables XXIV, XLII, XLIII, and XLV).

Release of ATP from the heart during hypoxia was first demonstrated in the early 1970s (Forrester and Williams, 1977; Paddle and Burnstock, 1974). However, it was uncertain whether the ATP was from nerves, blood vessels,

TABLE XXIII
Heart[a]

Cellular component	Receptor mRNA		Receptor protein	Pharmacological and biochemical profile		Function	References
Whole heart—fetal	$P2X_1$ (AB) $P2X_3$ (B) $P2X_4$ (ABC) $P2X_5$ (AC)	$P2Y_2$ (B) $P2Y_4$ (B) $P2Y_6$ (B)					Bogdanov *et al.*, 1998a[d] Soto *et al.*, 2003[b]
Whole heart—neonatal			$P2X_2$ (D) $P2X_5$ (D)			ATP inhibits NA-induced hypertrophy of myocytes	Hansen *et al.*, 1999a[b]
Whole heart—adult	$P2X_3$ (B) $P2X_4$ (A) $P2X_5$ (B)	$P2Y_2$ (A) $P2Y_6$ (A)	$P2X_1$ (D) $P2X_3$ (D) $P2X_4$ (D) $P2X_5$ (D) $P2X_6$ (D)	P2X (G)	P2Y (G)	ATP produces negative chronotropic effects on cardiac pacemakers and reduces conduction velocity of AV node ATP triggers vagal reflex	Parr *et al.*, 1994[c] Stark *et al.*, 1994[c] Pelleg *et al.*, 1996[c] Communi *et al.*, 1996[c] Garcia-Guzman *et al.*, 1997a,b[b] Dhulipala *et al.*, 1998[b] Mei and Liang, 2001[b] Stavrou *et al.*, 2001[c]
Atrium	$P2X_5$ (B)		$P2X_1$ (D) $P2X_2$ (D) $P2X_3$ (D) $P2X_4$ (D) $P2X_5$ (D) $P2X_6$ (D)	P2X (G)	$P2Y_2$ (G)	ATP and UTP produce positive inotropic effects	Froldi *et al.*, 1994,[d] 1997[b] Garcia-Guzman *et al.*, 1996[b] Hansen *et al.*, 1999a[b]
Isolated atrial myocytes					$P2Y_2$ (G)	ATP activates muscarinic K^+ channels	Fu *et al.*, 1995[c] Matsuura *et al.*, 1996[c] Hara and Nakaya, 1997[c] Matsuura and Ehara, 1997[c] Wu *et al.*, 1998[c] Yamamoto *et al.*, 1999[c]

Sinoatrial node			$P2X_1$ (G) $P2X_2$? (G)		ATP and α,β-meATP act on L-type channels ATP activates cation current	Qi and Kwan, 1996[b] Shoda *et al.*, 1997[b]
Ventricle		$P2X_1$ (D) $P2X_3$ (D) $P2X_4$ (D) $P2X_5$ (D) $P2X_6$ (D)				Hansen *et al.*, 1999a[b]
Isolated ventricular myocytes	$P2X_4$ (B)	$P2X_1$ (D) $P2X_3$ (D) $P2X_4$ (DEF) $P2X_5$ (D) $P2X_6$ (D) $P2X_7$ (DE)	P2X (G)	$P2Y_1$ (GH) $P2Y_2$ (G)	ATP enhances delayed rectifier K^+ current ATP activates an atypical K^+ current ATP triggers oscillating $[Ca^{2+}]_i$ and contractions ATP increases myocytes contractile rate (positive inotropic effect) and amplitude ATP increases L-type Ca^{2+} current via P2Y R ATP modulates Cl^- conductance ATP inhibits glucose transport ATP triggers arrhythmias in electrically stimulated myocytes ATP regulates MAPK pathways $P2X_4$ and $P2X_7$ R expressed in the t-tubular network UTP causes hypertrophy	Kaneda *et al.*, 1994[c] Scamps and Vassort, 1994[c] Horackova *et al.*, 1994[c] Levesque and Hume, 1995[c] Pucéat and Vassort, 1996[c] Zhang *et al.*, 1996a, 2001[c] Vulchanova *et al.*, 1996[b] Zheng *et al.*, 1996[e] Babenko and Vassort, 1997[c] Froldi *et al.*, 1997[b] Von zur Mühlen *et al.*, 1997[b] Fischer *et al.*, 1999a,[b] 1999b[c] Matsubayashi *et al.*, 1999[c] Verrecchia *et al.*, 1999[c] Aimond *et al.*, 2000[c] Musa *et al.*, 2000[b] Hu *et al.*, 2001a, 2002[b] Oketani *et al.*, 2002[c] Markou *et al.*, 2003[c] Pham *et al.*, 2003[c]

(*continued*)

TABLE XXIII (*continued*)

Cellular component	Receptor mRNA	Receptor protein	Pharmacological and biochemical profile	Function	References
Ventricular cardiac plasma membranes		P2Y (F)	P2Y (G)	ATP stimulates L-type calcium channels	Blouse *et al.*, 1998[c] Liu and Rosenberg, 2001[c]
Papillary muscle			$P2Y_2$ (G)	UTP prolongs action potentials	Qin *et al.*, 2001[c]
Sympathetic nerves	See Table XLII				
Intracardiac ganglia	See Table XLIII				
Sensory nerves	See Table XLV				
Coronary vessels	See Table XXIV				

[a]See footnote *a* for Table III.
[b]References refer to P2X receptors.
[c]References refer to P2Y receptors.
[d]References refer to P2X and P2Y receptors.
[e]References refer to uncharacterized P2 receptors.

or myocardial cells (Borst and Schrader, 1991; Darius *et al.*, 1987; Dobolyi *et al.*, 1998; Fredholm *et al.*, 1982; Katsuragi *et al.*, 1993, 1995; Williams and Forrester, 1983). The response of the toad sinus venosus to sympathetic nerve stimulation was mediated by both ATP and adrenaline, suggesting that they may be cotransmitters (Bramich *et al.*, 1990). Activation of Cl^- currents in guinea pig atrial cells by ATP released as a sympathetic nerve cotransmitter was also claimed (Matsuura and Ehara, 1992). Ectoenzymes for the breakdown of ATP released to the heart have been identified, including Ca^{2+}/Mg^{2+} ecto-ATPase and 5′-nucleotidase in isolated myocytes (Beaudoin *et al.*, 1997; Bowditch *et al.*, 1985; Darvish *et al.*, 1993; Espinosa *et al.*, 1996; Meghji *et al.*, 1992; Menezes de Oliveira *et al.*, 1997; Tuana and Dhalla, 1988; Zinchuk *et al.*, 1999).

In summary, mRNA and protein for multiple P2X and P2Y receptor subtypes have been identified in cardiomyocytes although their function is largely unknown and the receptors not fully characterized, with the exception of $P2Y_1$ and $P2Y_2$ receptors.

2. Blood Vessels

a. Aortal ATP and α,β-meATP were both shown to constrict the smooth muscle of the rat aorta, which had not been preconstricted with NA (White *et al.*, 1985b). In cultured rat aortic myocytes, ATP, but not α,β-meATP (Tawada *et al.*, 1987), was found to stimulate the accumulation of inositol phosphates and mobilization of $[Ca^{2+}]_i$ (Phaneuf *et al.*, 1987; Tsuda *et al.*, 1988) and activate both Ca-dependent K^+ and Cl^- currents (von der Weid *et al.*, 1993). In bovine aortic smooth muscle cells ATP, ATPγS, and UTP stimulated the release of prostacyclin via a receptor distinct from P2X and P2Y subtypes (Demolle *et al.*, 1988). In pig cultured aortic smooth muscle cells, ATP was found to induce Ca^{2+} release from intracellular stores, which then activated a Cl^- current (Droogmans *et al.*, 1991; Mahoney *et al.*, 1993), UTP was found to be more potent than the effect of ATP (Kalthof *et al.*, 1993). On rabbit cultured aortic myocytes, both ATP and UTP induced depolarization of membrane (Pavenstädt *et al.*, 1991). ATP was also shown to have a mitogenic effect on porcine aortic smooth muscle cells (Wang *et al.*, 1992) and the activity of ATP and UTP on rat myocytes characterized the response as acting through a nucleotide receptor (Erlinge *et al.*, 1993).

Strips of porcine aorta with an intact endothelium were found to relax in response to ATP (Gordon and Martin, 1982) and in culture aortic endothelial cells release prostaglandins in response to ATP and ADP (Pearson *et al.*, 1983; Van Coevorden and Boeynaems, 1984). Since 2-methylthio ATP (2-MeSATP) also induced relaxation (Martin *et al.*, 1985) and prostaglandin production (Needham *et al.*, 1987) it was suggested that ATP was acting on

P2Y receptors. P2Y receptors were also characterized in aortic endothelial cells of the rat (White *et al.*, 1985b) and rabbit (Chinellato *et al.*, 1992). UTP also induces vasodilatation of the bovine aorta via the endothelium by acting on a nucleotide receptor (Allsup and Boarder, 1990; Motte *et al.*, 1993). In bovine aortic endothelial cells, ATP and ADP increase proliferation via a P2Y receptor (Van Daele *et al.*, 1992).

b. Cerebral Blood Vessels The canine basilar artery was found to contract in the presence of exogenous ATP whereas the middle cerebral artery contracted to ATP only at high concentrations (Muramatsu and Kigoshi, 1987; Muramatsu *et al.*, 1980, 1983). Isolated smooth muscle cells of the dog middle cerebral artery were found to depolarize in the presence of ATP (Suzuki and Fujiwara, 1982), decrease the membrane resistance, and produce a contraction (Fujiwara *et al.*, 1982b). Pial arterial smooth muscle from rabbit, cat, and humans all contracted in the presence of exogenous ATP (Hardebo *et al.*, 1987a). In the rabbit isolated basilar artery, both ATP and UTP were found to induce vasoconstriction, ATP activating P2X receptors and UTP activating a distinct nucleotide receptor (Von Kügelgen and Starke, 1990). Examination of the goat cerebrovascular circulation revealed that α,β-meATP decreased and ATP increased cerebral blood flow. In contrast, on goat isolated middle cerebral artery, both ATP and α,β-meATP induced vasoconstriction, which was susceptible to desensitization and acting via P2X receptors (Torregrosa *et al.*, 1990). Cerebral arteries from humans and dog were found to develop long lasting constrictions to exogenous UTP; in some vessels rhythmic oscillations accompanied the increase in tension (Urquilla, 1978). In canine cerebral arteries UTP was found to initiate constriction by releasing membrane bound Ca^{2+} store, depolarizing the cell membrane and opening receptor-operated Ca^{2+} channels (Shirasawa *et al.*, 1983).

ATP was found to dilate cerebral arteries of the rabbit, cat, dog, and baboon (Forrester *et al.*, 1979; Nakagomi *et al.*, 1988; Toda *et al.*, 1982), but constrict the dog basilar artery by acting on P2 receptors on the endothelium (Shirahase *et al.*, 1988). ATP and UTP dilated human pial vessels (Hardebo *et al.*, 1987a,b) and ADP dilated rat cerebral arterioles (Frelin *et al.*, 1993; Mayhan, 1992), suggesting that multiple P2 receptor subtypes are present. 2-MeSATP and ATP stimulate the proliferation of human brain capillary endothelial cells (Rathbone *et al.*, 1992).

c. Coronary Artery ATP was found to induce hyperpolarization of smooth muscle cells of the guinea pig coronary artery (Takata and Kuriyama, 1980). A bolus injection of ATP into the isolated perfused rat heart induced a biphasic response, an increase followed by a decrease in perfusion pressure. The initial vasoconstrictor response was mimicked by α,β-meATP indicating

that the vasoconstriction was mediated via P2X receptors (Hopwood and Burnstock, 1987).

ATP and ADP induced vasodilatation of isolated canine, guinea pig, and rabbit coronary arteries (Keef *et al.*, 1992; Toda *et al.*, 1982) and the coronary vasculature of the guinea pig and rat heart via an action on P2Y receptors on the endothelium (Hopwood and Burnstock, 1987; Nees, 1989). Vasodilatation in response to ATP induced the formation of NO in the guinea pig and dog heart (Houston *et al.*, 1987; Keef *et al.*, 1992; Lee *et al.*, 1990; White and Angus, 1987). Since UTP and 2-MeSATP both induce vasodilatation of the guinea pig coronary vasculature (Vials and Burnstock, 1993) the presence of two separate P2 receptors is indicated.

d. Ear Artery Ionophoretic administration of exogenous ATP to smooth muscle cells of the rabbit ear artery induced a rapidly desensitizing depolarization (Suzuki, 1985) with an associated rise in internal Ca^{2+} concentrations (Benham, 1989; Benham *et al.*, 1987). ATP and UTP induced vasoconstriction of isolated rabbit ear arteries via P2X receptors (Kennedy and Burnstock, 1985a; La and Rand, 1993; Leff *et al.*, 1990; Miyahara and Suzuki, 1987; O'Connor *et al.*, 1990; Taylor *et al.*, 1989) and a separate P2 receptor, respectively (Von Kügelgen *et al.*, 1987).

e. Femoral Artery ATP induced vasodilatation of the canine, cat, rabbit, and rat femoral artery (De Mey and Vanhoutte, 1981; Dézsi *et al.*, 1990; Kennedy *et al.*, 1985; Melkumyants *et al.*, 1992; Pohl *et al.*, 1987) by acting at P2Y receptors.

f. Hepatic Artery The isolated hepatic artery of the rabbit responded to EFS with vasoconstrictor responses; part of this response was sensitive to desensitization with α,β-meATP and the responses to EFS could be mimicked by the application of ATP and α,β-meATP, indicating the presence of contractile P2X receptors (Brizzolara and Burnstock, 1990, 1991; Karashima and Takata, 1979; Reilly *et al.*, 1987).

ATP decreased rat hepatic blood flow (Lee and Filkins, 1988) acting on a P2Y receptor (Haussinger *et al.*, 1987), and ATP and 2-MeSATP induced vasodilatation of the hepatic vascular bed of the rabbit (Ralevic *et al.*, 1991) via NO production (Mathie *et al.*, 1991). These actions were considered important in shock protection.

g. Internal Maxillary Vein ATP and UTP were both observed to constrict the canine internal maxillary vein in the absence of the endothelium, although the type of response differed with agonist. ATP induced rapid transient constrictions via P2X receptors, whereas UTP induced sustained vasoconstriction via separate receptors (Saïag *et al.*, 1992).

h. Intestinal Arteries In the cat perfused intestinal arteries, α,β-meATP induced vasoconstriction via activation of P2X receptors (Taylor and Parsons, 1991; Taylor *et al.*, 1989) and α,β-meATP was shown to desensitize a proportion of the initial rapid response to EFS, particularly at low frequencies of stimulation (Taylor and Parsons, 1989) mediated by activation of P2X receptors (Evans and Surprenant, 1992).

i. Lymphatic Vessels In sheep mesenteric lymphatic vessels, α,β-meATP was found to cause an intense excitatory response followed by an inhibition of spontaneous contractions, although the receptor subtype responsible for this response was not characterized (Harty *et al.*, 1993).

j. Mesenteric Artery ATP was found to induce a vasoconstrictor response of the isolated mesenteric artery in the dog (Ueda and Ohtski, 1977) and rabbit (Krishnamurty and Kadowitz, 1983; Mathieson and Burnstock, 1985) as did α,β-meATP, both acting via P2X receptors (Burnstock and Warland, 1987b). ATP was also found to induce depolarization of the muscle, an activity shared with α,β-meATP in both the rabbit and guinea pig (Ishikawa, 1985); the effect of α,β-meATP was found to desensitize rapidly in the guinea pig mesenteric artery, inhibiting responses to ATP and itself (Nagao and Suzuki, 1988). In small rat mesenteric arteries, UTP was also shown to induce vasoconstriction (Juul *et al.*, 1992) via receptors distinct from P2X receptors (Juul *et al.*, 1993). ATP was found to have similar actions on the mesenteric arterial bed, in that ATP and α,β-meATP initiated an increase in perfusion pressure as a result of vasoconstriction by acting on P2X receptors (Ralevic and Burnstock, 1988) whereas UTP induced vasoconstriction via pyrimidinoceptors (Ralevic and Burnstock, 1991b).

The rat mesenteric arterial bed possesses coexisting P2Y and P2U receptors both mediating vasodilatation (Criscione *et al.*, 1989; Ralevic and Burnstock, 1988, 1991b) responding to 2-MeSATP, ATP, and UTP.

k. Penile Artery The canine and bovine penile arterial smooth muscle relaxed in the presence of ATP (Bowman and Gillespie, 1983; Klinge and Sjöstrand, 1977) and on the canine penile artery α,β-meATP induced a strong contraction implying the presence of both an inhibitory P2Y and a constrictor P2X receptor (Kimoto and Ito, 1987).

l. Pulmonary Artery In both human and rat isolated small pulmonary arteries, ATP and α,β-meATP were shown to induce vasoconstriction via P2X receptors (Liu *et al.*, 1989a,b). This response to ATP and α,β-meATP also occurred when the two agonists where applied to the pulmonary vascular bed of the cat and rat, again acting via P2X receptors (McCormack *et al.*, 1989; Neely *et al.*, 1989, 1991).

ATP and ADP stimulate prostacyclin synthesis in rabbit pulmonary artery endothelial cells (Boeynaems and Galand, 1983), whereas ATP and UTP stimulate prostacyclin synthesis in bovine pulmonary artery endothelial cells (Lustig *et al.*, 1992). Both ATP and ADP induce endothelium-dependent vasodilatation of human pulmonary artery segments (Dinh Xuan *et al.*, 1990; Greenberg *et al.*, 1987). In lambs, ATP induced endothelium-dependent vasodilatation (Fineman *et al.*, 1991), although the subtype of receptor was not identified.

m. Renal Artery Prostaglandins are released from the perfused rabbit kidney in response to exogenously applied ATP and ADP (Schwartzman *et al.*, 1981) by acting on separate receptors. ATP stimulates Ca^{2+} mobilization and release of endothelium-dependent hyperpolarizing factor (EDHF) in glomerular endothelial cells (Marsden *et al.*, 1990).

n. Retinal Pericytes Bovine retinal microvascular pericytes in culture contract to ATP but not GTP (Das *et al.*, 1988); it was thought that these cells might play a role in regulating blood flow in the microcirculation.

o. Saphenous Artery Electrical stimulation of perivascular nerves of the guinea pig saphenous artery elicited excitatory junction potentials (EJPs) that were inhibited by the P2 receptor antagonist $ANAPP_3$ (Cheung and Fujioka, 1986). Similarly the vasoconstrictor responses to EFS in isolated rabbit saphenous artery ring preparations were partially inhibited following desensitization of P2X receptors with α,β-meATP (Burnstock and Warland, 1987a; Nally and Muir, 1992) and nifedipine (Bulloch *et al.*, 1991).

p. Skeletal Muscle Vascular Bed Exogenously applied ATP to the hind limb vasculature of the cat and rabbit induces vasodilatation, the receptor being more sensitive to ADP than ATP in the cat vasculature (Gangarosa *et al.*, 1979; Shimada and Stitt 1984) and identified as a P2Y receptor. At higher concentrations of agonist a vasoconstrictor response is observed, acting via a P2X receptor (Taylor *et al.*, 1989). The rat hind limb vasculature dilated in the presence of UTP (Clark *et al.*, 1990). In the canine ischemic gracilis muscle, perfusion with ATP reduces the extent of necrosis, thought to be due to its vasodilator activity (Hayes *et al.*, 1990).

q. Skin Vessels On isolated human omentum and subcutaneous fat resistance vessels, exogenously applied ATP and α,β-meATP induced vasoconstriction via P2X receptors (Martin *et al.*, 1991).

r. Tail Artery Exogenous ATP was found to noncompetitively inhibit the antispasmogenic activity of hydralazine on isolated rat tail arteries

(Chevillard *et al.*, 1981) via an action on sympathetic nerve terminals. Exogenously applied ATP and α,β-meATP also induced vasoconstriction in isolated segments of rat tail artery via activation of smooth muscle P2X receptors (Bao and Stjärne, 1993; Bao *et al.*, 1989), whereas UTP induced vasoconstriction via pyrimidinoceptors (Saïag *et al.*, 1990).

s. Portal Vein The longitudinal muscle of the rabbit portal vein has an NANC inhibitory innervation (Hughes and Vane, 1967) and ATP dilated this vessel acting on P2Y receptors (Burnstock *et al.*, 1979; Kennedy and Burnstock, 1985b; Su, 1978a). On isolated rat portal veins, ATP was found to inhibit spontaneous mechanical activity, and at high concentrations induce a contraction (Sjöberg and Wahlstrom, 1975). The contractile response of ATP in the rat portal vein was mimicked by α,β-meATP, and the constrictor response was found to be rapidly desensitizing and classified as a P2X receptor (Reilly and Burnstock, 1987). Microelectrode recordings from rat portal vein smooth muscle cells revealed that ATP was causing a depolarization of the membrane (Karashima and Takata, 1979). The receptor subtype responsible for the constrictor response of the isolated rabbit portal vein to ATP and α,β-meATP was also characterized as a P2X subtype (Reilly *et al.*, 1987). Electrophysiological recordings from dispersed rabbit portal vein smooth muscle cells revealed that ATP induced transient inward currents that were susceptible to desensitization with α,β-meATP (Xiong *et al.*, 1991).

t. Umbilical Vein Cultured endothelial cells from human umbilical vein release prostacyclin in response to ATP and 2-MeSATP via activation of a P2Y receptor (Carter *et al.*, 1988; McIntyre *et al.*, 1985).

Table XXIV summarizes the receptor subtypes present in blood vessels based on mRNA, protein, and pharmacological and biochemical profiles. The functions claimed for the receptors together with key references are included (cf. Table XLII; see Fig. 6).

ATP is stored and co-released with NA from sympathetic perivascular nerves. This phenomena has been shown for various vascular systems, particularly in the rat tail artery (Bao and Stjärne, 1993; Kawamoto *et al.*, 1998; Westfall *et al.*, 1987), but also in the renal artery (Rump *et al.*, 1996), hepatic artery (Brizzolara and Burnstock, 1990), pulmonary artery (Mohri *et al.*, 1993), submucosal arterioles (Evans and Surprenant, 1992), and femoral and ear arteries (Ishii *et al.*, 1996; Su, 1975) to name a few.

Endothelial cells are a rich source of ATP and UTP, released when the cells are stimulated by various stimuli such as hypoxia (Bodin *et al.*, 1992; Bodin and Burnstock, 1995), shear stress (Bodin and Burnstock, 2001; Bodin *et al.*, 1991; Milner *et al.*, 1990; Saïag *et al.*, 1995), inflammation (Bodin and Burnstock, 1998), hypotonic stress (Grygorczyk and Guyot, 2001; Koyama *et al.*, 2001), perivascular nerve stimulation (Sedaa *et al.*, 1990; Westfall *et al.*,

TABLE XXIV

Blood Vessels[a]

Cellular component	Receptor mRNA	Receptor protein	Pharmacological and biochemical profile	Function	References
Adrenal gland vessels					
Smooth muscle		$P2X_2$ (D)		ATP regulates blood flow in adrenal medulla	Afework and Burnstock, 1999, 2000a,b[b]
Endothelial cells			$P2Y_2$ (G)		Castro *et al.*, 1994[c]
Aorta					
Smooth muscle	$P2X_1$ (BC) $P2Y_2$ (B) $P2X_2$ (BC) $P2Y_4$ (B) $P2X_4$ (BC) $P2Y_6$ (B)	$P2X_1$ (D)	$P2X_1$ (GH) $P2Y_1$ (GH) $P2Y_2$ (GH) $P2Y_4$ (G) $P2Y_6$ (I)	ATP induces contraction via P2X R ATP induces both contraction and relaxation via P2Y R UTP and ATP regulate plasminogen activator inhibitor-1 (PAI-1) UTP and UDP via $P2Y_2$ and $P2Y_6$ R stimulate SMC migration UTP and ATP act through $P2Y_4$ and $P2Y_6$ R to promote mitogenesis via p42 and p44 MAPK UTP and ATP partially mediate cell cycle progression	Erlinge *et al.*, 1995,[d] 1996[e] Pacaud *et al.*, 1995[d] Malam-Souley *et al.*, 1996[c] Miyagi *et al.*, 1996a[c] Harper *et al.*, 1998[c] López *et al.*, 1998, 2000[b] Muraki *et al.*, 1998[d] Hansen *et al.*, 1999b[b] Pediani *et al.*, 1999[c] Bouchie *et al.*, 2000[c] Sauzeau *et al.*, 2000[c] Schlatter *et al.*, 2000[c] Hou *et al.*, 2002[c] Payne *et al.*, 2002[c] Pillois *et al.*, 2002[c]
Endothelial cells	$P2X_1$ (AB) $P2X_2$ (B) $P2X_3$ (B) $P2X_4$ (AB) $P2X_5$ (B) $P2X_7$ (B)	$P2X_4$ (DE) $P2X_5$ (E) $P2X_7$ (D)	$P2X_4$ (G) $P2Y_1$ (G) $P2Y_2$ (G) or $P2Y_4$ (G)	P2Y R mediate NO release and vasodilation P2Y R stimulate prostacyclin release P2Y R stimulate MAPK	Wilkinson *et al.*, 1994[c] Communi *et al.*, 1995[c] Brown *et al.*, 1996[c] Graham *et al.*, 1996[c] Miyagi *et al.*, 1996a[c] Patel *et al.*, 1996[c] Hansmann *et al.*, 1997[c] Dol-Gleizes *et al.*, 1999[c] Yamamoto *et al.*, 2000b[b]

(*continued*)

TABLE XXIV (*continued*)

Cellular component	Receptor mRNA		Receptor protein	Pharmacological and biochemical profile		Function	References
							Kaiser and Buxton, 2002[c] Ramirez and Kunze, 2002[b]
Cultured endothelial cells					$P2Y_1$ (G) $P2Y_2$ (G)	ATP induces dephosphorylation of myosin light chain	Duchêne and Takeda, 1997[c] Noll *et al.*, 2000[c]
Basilar artery							
Smooth muscle	$P2X_1$ (B)	$P2Y_2$ (B)	$P2X_1$ (D) $P2X_4$ (D) $P2X_5$ (D)	$P2X_1$ (G)	$P2Y_2$ (G)	ATP induces contraction via P2X R ATP and UTP increase $[Ca^{2+}]_i$	Kohno *et al.*, 1995[b] Lewis and Evans, 2000a[b] Aoki *et al.*, 2000[c] Carpenter *et al.*, 2001[d]
Cultured smooth muscle cells					$P2Y_2$ (H)	ATP and UTP increase $[Ca^{2+}]_i$	Sima *et al.*, 1997[c]
Bladder vasculature		$P2Y_1$ (BC)	$P2X_1$ (D)				Obara *et al.*, 1998[c] Lee *et al.*, 2000b[b]
Carotid artery							
Endothelial cells					$P2Y_1$ (G) $P2Y_2$ (G)	$P2Y_1$ R mediate NO release and vasodilation $P2Y_2$ R mediate non-NO-mediated vasodilation and induce mitogenic activation of SMC	Malmsjö *et al.*, 1998[c] Seve *et al.*, 2002[c]
Cerebral vessels							
Smooth muscle	$P2X_1$ (B) $P2X_4$ (B) $P2X_5$ (B)	$P2Y_1$ (B) $P2Y_2$ (B) $P2Y_6$ (B)	$P2X_1$ (D)	$P2X_1$ (G)	$P2Y_2$ (GH) $P2Y_4$ (G) $P2Y_6$ (G)	$P2Y_2$ R mediate endothelial-dependent vasodilation $P2Y_4$ R mediate constriction	Miyagi *et al.*, 1996a[c] Bo *et al.*, 1998a[b] Aoki *et al.*, 2000[c] Lewis *et al.*, 2000[d] Lacza *et al.*, 2001[b] Horiuchi *et al.*, 2001[d], 2003[c] Saino *et al.*, 2002[d] Malmsjö *et al.*, 2003a[d], 2003b[c]
Endothelial cells							
Large vessels					$P2Y_1$ (G)	P2X R mediate cell proliferation	Ikeuchi and Nishizaki, 1995b[c]

					$P2Y_2$ (G) or $P2Y_4$ (G)	ATP and ADP mediate both NO and EDHF-mediated relaxation	Miyagi *et al.*, 1996b[c] You *et al.*, 1997, 1999[c] Zhang *et al.*, 1997[c]
Microvascular		$P2Y_1$ (B) $P2Y_2$ (B) $P2Y_4$ (B) $P2Y_6$ (B) $P2Y_{12}$ (B)	$P2X_2$ (D)		$P2Y_1$ (G)		Janigro *et al.*, 1996[c] Webb *et al.*, 1996[c] Anwar *et al.*, 1999[c] Sipos *et al.*, 2000[c] Loesch and Burnstock, 2000[b] Verma *et al.*, 2002[c]
Cultured				P2X (G)	$P2Y_1$ (G) $P2Y_2$ (G) or $P2Y_4$ (G) $P2Y_{12}$ (G)		Nobles *et al.*, 1995[c] Albert *et al.*, 1997[c] Vigne *et al.*, 1998, 2000[c] Simon *et al.*, 2001[c]
Chorionic artery	$P2X_1$ (B) $P2X_4$ (B) $P2X_5$ (B) $P2X_6$ (B) $P2X_7$ (B)			$P2X_1$ (G)	$P2Y_1$ (G) $P2Y_2$ (G)	P2X R induce smooth muscle vasoconstriction P2Y R induce endothelium-dependent vasodilatation	Dobronyi *et al.*, 1997[b] Ralevic *et al.*, 1997[d] Valdecantos *et al.*, 2003[b]
Cochlear blood flow				P2X (G)	P2Y (G)	ATP modulates blood flow	Ren *et al.*, 1997[b] Muñoz *et al.*, 1999a[b] Takago *et al.*, 2001[d]
Coronary artery							
Smooth muscle	$P2X_1$ (BC) $P2X_2$ (BC) $P2X_4$ (BC)	$P2Y_1$ (B) $P2Y_2$ (B) $P2Y_4$ (B) $P2Y_6$ (B)	$P2X_3$ (D) $P2X_4$ (D) $P2X_5$ (D)	$P2X_1$ (G)	$P2Y_1$ (G) $P2Y_2$ (G) or $P2Y_4$ (G)	ATP induces contraction via P2X R and relaxation via P2Y R ATP acts alone and synergistically with insulin to stimulate smooth muscle proliferation	Corr and Burnstock, 1994[d] Vials and Burnstock, 1994[c] Strøbæk *et al.*, 1996[c] Matsumoto *et al.*, 1997[c] Simonsen *et al.*, 1997[d] Wilden *et al.*, 1998[c] Nori *et al.*, 1998[b] Erlinge, 1998[c] Seiler *et al.*, 1999[c] Lewis and Evans, 2000a, 2001[b] Malmsjö *et al.*, 2000a[d] Agazie *et al.*, 2001[c] Welsh and Brayden, 2001[c] Weirich *et al.*, 2001[c]

(*continued*)

TABLE XXIV (*continued*)

Cellular component	Receptor mRNA	Receptor protein	Pharmacological and biochemical profile		Function	References
Endothelial cells	$P2X_4$ (B) $P2X_5$ (B)	$P2X_4$ (E) $P2X_5$ (E)		$P2Y_1$ (GH) $P2Y_2$ (GH)	P2Y R mediate NO release and vasodilation P2Y R mediate secretion of von Willebrand factor $P2Y_2$ R mediate mitogenic and chemotactic actions Ap_4A induces vasoconstriction via P2X R and vasodilation via $P2Y_1$ R	Manabe *et al.*, 1995[c] Yang *et al.*, 1996[c] Hansmann *et al.*, 1998[c] Vischer and Wollheim, 1998[c] Satterwhite *et al.*, 1999[c] Zünkler *et al.*, 1999[c] Moccia *et al.*, 2001[c] Alexander *et al.*, 2002[c] van der Giet *et al.*, 2002[c] Westhoff *et al.*, 2003[d]
Ear artery						
Smooth muscle			$P2X_1$ (G)	P2Y (G)	ATP induces contraction via P2X R and relaxation via P2Y R	Ziganshin *et al.*, 1994[b] Martin *et al.*, 1995[b] Xie *et al.*, 1997[c]
Eye vasculature						
Microvascular pericytes			$P2X_7$ (H)	$P2Y_2$ (H)	ATP increases $[Ca^{2+}]_i$ and induces pericytes contraction	Kawamura *et al.*, 2003a[d]
Opththalmic artery			$P2X_1$ (G)		ATP induces contraction via P2X R	Toda *et al.*, 1999[b]
Femoral artery						
Smooth muscle	$P2X_1$ (BC) $P2X_2$ (BC) $P2X_4$ (BC)		$P2X_1$ (G)		ATP induces contraction via P2X R	Macdonald *et al.*, 1998[b] Nori *et al.*, 1998[b]
Hepatic artery						
Smooth muscle	$P2X_1$ (B) $P2X_4$ (B) $P2X_5$ (B) $P2X_7$ (B)		$P2X_1$ (G)	$P2Y_6$? (G)	ATP induces contraction via P2X R UDP induces constriction	Phillips *et al.*, 1998[b] Vial and Evans, 2002[d]
Endothelial cells				$P2Y_1$ (G) $P2Y_2$ (G)	$P2Y_1$ R mediate NO release and vasodilation $P2Y_2$ R mediate non-NO-mediated vasodilation	Takemura *et al.*, 1998[c] Malmsjö *et al.*, 2000c[c]

Portal vein								
Smooth muscle	$P2X_1$ (B) $P2X_3$ (B) $P2X_4$ (B) $P2X_5$ (B)				$P2X_1$ (G)	$P2Y_1$ (G) $P2Y_2$ (G)	P2X and $P2Y_2$ R mediate contraction P2Y R mediate dilation UTP is an antiproliferation regulator	Pacaud *et al.*, 1994[b] Orre *et al.*, 1996[d] Ishizaki *et al.*, 1997[c] Minamiyama *et al.*, 1998[c] Mironneau *et al.*, 2001[b]
Endothelial cells						P2Y (G)	P2Y R mediate NO release and vasodilation	Takemura *et al.*, 1998[c]
Intestinal vessels					$P2X_1$ (G)		ATP induces contraction via P2X R	Galligan *et al.*, 1995[b]
Lingual artery								
Smooth muscle					$P2X_1$ (G)		ATP (co-released with NA) acts via P2X R to mediate vasoconstriction	Toda *et al.*, 1997[b] Okamura *et al.*, 1998[b]
Mammary artery								
Smooth muscle	$P2X_1$ (B)	$P2Y_2$ (B) $P2Y_6$ (B)	$P2X_1$ (E)	$P2Y_2$ (E) $P2Y_6$ (E)	$P2X_1$ (G)	$P2Y_2$ (G) or $P2Y_4$ (G)	ATP induces contraction via P2X R ATP and UTP increase $[Ca^{2+}]_i$ via P2Y R	White *et al.*, 2000[c] Wang *et al.*, 2002b[d] Wihlborg *et al.*, 2003[b]
Endothelial cells			$P2X_1$ (D) $P2X_2$ (D) $P2X_3$ (D) $P2X_7$ (D)	$P2Y_2$ (D)		$P2Y_1$ (G) $P2Y_2$ (G) or $P2Y_4$ (G) $P2Y_6$ (G)	P2Y R mediate NO release and vasodilation	Ray *et al.*, 2002[d] Mistry *et al.*, 2003[c] Wihlborg *et al.*, 2003[c]
Mesenteric artery								
Smooth muscle	$P2X_1$ (B) $P2X_4$ (B) $P2X_5$ (B) $P2X_7$ (B)	$P2Y_1$ (B) $P2Y_2$ (B) $P2Y_6$ (B)	$P2X_1$ (D) $P2X_2$ (D) $P2X_4$ (D)		$P2X_1$ (G)	$P2Y_1$ (G) $P2Y_2$ (G) or $P2Y_4$ (G) $P2Y_6$ (G) $P2Y_{11}$ (G)	ATP induces contraction via P2X R and relaxation via P2Y R	Windscheif *et al.*, 1994[d] Lagaud *et al.*, 1996[d] Hansen *et al.*, 1999b[b] Phillips and Hill, 1999[b] Ohkubo *et al.*, 2000[b] Steinmetz *et al.*, 2000[c] Lewis and Evans, 2000a,b[b] Gitterman and Evans, 2000, 2001[b] Malmsjö *et al.*, 2000b[b] Morita *et al.*, 2002[c] Vial and Evans, 2002[d]

(*continued*)

TABLE XXIV (*continued*)

Cellular component	Receptor mRNA	Receptor protein	Pharmacological and biochemical profile	Function	References
Endothelial cells			$P2Y_1$ (G) $P2Y_2$ (G)	$P2Y_1$ R mediate NO release and vasodilation $P2Y_2$ R mediate non-NO-mediated vasodilation	Kakuyama *et al.*, 1998[c]
Mesenteric bed					
Smooth muscle	$P2Y_6$ (B)		$P2X_1$ (G)	$P2Y_1$ (G) $P2Y_2$ (G)	ATP induces contraction via P2X R and relaxation via P2Y R	Ohara *et al.*, 1998[d] Ralevic *et al.*, 2001[d] Bivalacqua *et al.*, 2002[b] Ralevic, 2002[d] Buvinic *et al.*, 2002[c]
Endothelial cells	$P2Y_1$ (B) $P2Y_2$ (B)			$P2Y_1$ (G) $P2Y_2$ (G) or $P2Y_4$ (G) $P2Y_{11}$ (G)	$P2Y_1$ R mediate NO release and vasodilation $P2Y_2$ R mediate EDHF-mediated vasodilation	Ralevic and Burnstock, 1996a,b[c] Stanford *et al.*, 2001[c] Buvinic *et al.*, 2002[c] Malmsjö *et al.*, 2002[c]
Mesenteric vein						
Smooth muscle			$P2X_1$ (G)	$P2Y_1$ (G) $P2Y_2$ (G) or $P2Y_4$ (G)	P2Y R mediate constriction	Mutafova-Yambolieva *et al.*, 2000[d]
Mesenteric lymphatic vessels			$P2X_1$ (GH)	$P2Y_2$ (G)	ATP induces contraction ATP modulates lymphatic pacemaking	Hollywood and McHale, 1994[b] Gao *et al.*, 1998, 1999a[c] Zhao and van Helden, 2002[d]
Ovarian vessels						
Smooth muscle		$P2X_1$ (D) $P2X_2$ (D)				Bardini *et al.*, 2000[b]
Ovarian vein Smooth muscle			$P2X_1$ (G)		ATP and NA are cotransmitters mediating sympathetic constriction	Stones *et al.*, 1994[b]
Pancreatic vessels						
Smooth muscle		$P2X_1$ (D) $P2Y_1$ (D) $P2X_2$ (D) $P2Y_2$ (D)				Coutinho-Silva *et al.*, 2001a, 2003[d]

Endothelial cells					P2Y (G)	2Y R mediate NO release and vasodilation and PGE release	Saïag *et al.*, 1996[c]
Penile artery							
Smooth muscle		$P2Y_1$ (BC)	$P2X_1$ (D) $P2X_2$ (D)				Obara *et al.*, 1998[c] Lee *et al.*, 2000a[b]
Pulmonary artery							
Smooth muscle	$P2X_1$ (B) $P2X_2$ (B) $P2X_4$ (B)	$P2Y_6$ (B)	$P2X_1$ (D) $P2X_2$ (D) $P2X_4$ (D)	$P2X_1$ (GH)	$P2Y_2$ (GH) $P2Y_6$ (G)	ATP induces contraction via P2X R and relaxation via P2Y R UTP and UDP induce contraction via P2Y R	Guibert *et al.*, 1996[d] Rubino and Burnstock, 1996[d] Hartley and Kozlowski, 1997[d] Qasabian *et al.*, 1997[c] Hartley *et al.*, 1998[c] Chootip *et al.*, 2002[c] Kennedy *et al.*, 2002[c]
Endothelial cells	$P2X_4$ (AB) $P2X_5$ (B)		$P2X_4$ (E) $P2X_5$ (E)		$P2Y_1$ (GH) $P2Y_2$ (GH)	P2Y R mediate stimulation of prostacyclin synthesis	Cutaia *et al.*, 1997[c] Balestrieri *et al.*, 1998[c] Yamamoto *et al.*, 2000b[b]
Cultured endothelial cells		$P2Y_1$ (B) $P2Y_2$ (B)		$P2X_4$ (H)	$P2Y_1$ (GH) $P2Y_2$ (GH)	ATP and ADP initiate propagation of Ca^{2+} waves ATP and UTP promote leukocyte adherence Endogenously released ATP mediates shear stress-induced Ca^{2+} influx	Parker *et al.*, 1996[c] Chen and Lin, 1999[c] Moerenhout *et al.*, 2001[c] Yamamoto *et al.*, 2003[b]
Pulmonary bed				$P2X_1$ (G)		ATP via P2X R induces constriction	Bivalacqua *et al.*, 2002[b]
Renal artery							
Smooth muscle			$P2X_1$ (D) $P2X_2$ (D) $P2X_4$ (D)	$P2X_1$ (GH)	P2Y (H)	ATP induces contraction via P2X R ATP and UTP increase $[Ca^{2+}]_i$	Inscho *et al.*, 1994, 1999[b] Von Kügelgen *et al.*, 1995b[b] Rump *et al.*, 1996[b] White *et al.*, 2001[b]
Endothelial cells				$P2Y_1$ (D)	$P2Y_1$ (G)	$P2Y_1$ R mediate NO release and vasodilation	Rump *et al.*, 1998[c] Turner *et al.*, 2003[c]
Perfused kidney			$P2X_1$ (G)	$P2Y_2$ (G)		ATP via smooth muscle P2X R induces constriction Endothelial P2Y R mediate dilation ATP modulates renin secretion	Eltze and Ullrich, 1996[d] Van der Giet *et al.*, 2001[b] Zhao *et al.*, 2001[b]

(*continued*)

TABLE XXIV (*continued*)

Cellular component	Receptor mRNA	Receptor protein	Pharmacological and biochemical profile	Function	References
Intrarenal vessels		$P2X_1$ (D) $P2Y_1$ (D) $P2X_2$ (D)			Turner *et al.*, 2003[d]
Saphenous artery Smooth muscle			$P2X_1$ (G)	ATP induces contraction via P2X R	Lambrecht, 1996[b] Ziyal *et al.*, 1997[b]
Saphenous vein Smooth muscle			P2X (GH)		Loirand and Pacaud, 1995[b] Hiraoka *et al.*, 2000[b]
Endothelial cells	$P2Y_1$ (B) $P2Y_2$ (B)	$P2X_1$ (D) $P2Y_2$ (D) $P2X_2$ (D) $P2X_3$ (D) $P2X_4$ (D) $P2X_7$ (D)	$P2Y_1$ (H) $P2Y_2$ (H)		Conant *et al.*, 2000[c] Ray *et al.*, 2002[d]
Skeletal muscle Vascular bed			$P2X_1$ (G) $P2Y_1$ (G) $P2Y_2$ (G)	ATP induces contraction via P2X R ATP induces vasodilation via an NO-dependent mechanism UTP induces vasodilation via an NO-independent mechanism	McCullough *et al.*, 1997[d] Boston *et al.*, 1999[c] Champion and Kadowitz, 2000[c] Shah *et al.*, 2001[c] Bivalacqua *et al.*, 2002[b] Buckwalter *et al.*, 2002, 2003[b]
Palmar lateral vein			$P2X_1$ (G) P2Y (G)	ATP induces vasoconstriction or vasodilation	Alexander *et al.*, 2001[d]
Skin vessels	$P2X_1$ (AB) $P2X_3$ (AB) $P2X_4$ (AB) $P2X_5$ (AB) $P2X_7$ (AB)				Yamamoto *et al.*, 2000b[b]

Radial artery			$P2X_1$ (D) $P2X_2$ (D) $P2X_3$ (D) $P2X_7$ (D)	$P2Y_2$ (D)				Ray *et al.*, 2002[d]
Splenic artery								
Smooth muscle					$P2X_1$ (G)		ATP induces contraction via a P2X R	Jobling, 1994[b] Ren *et al.*, 1994, 1996[b] Ren and Burnstock, 1997[b] Yang and Chiba, 1999, 2000, 2002[b] Ren and Zhang, 2002[b] Chiba and Yang, 2003[b]
Tail artery								
Smooth muscle					$P2X_1$ (G)	$P2Y_2$ (G) or $P2Y_4$ (G)	ATP induces contraction via P2X R ATP induces both contraction and relaxation via P2Y R	Evans and Kennedy, 1994[b] McLaren *et al.*, 1998[d] Fukumitsu *et al.*, 1999[d]
Endothelial cells						P2Y (H)	ATP via P2Y R decreases cell size	Tanaka *et al.*, 2003[c]
Testis blood vessels								
Smooth muscle			$P2X_1$ (D) $P2X_2$ (D)					Glass *et al.*, 2001[b]
Thymus vessels								
Smooth muscle			$P2X_1$ (D) $P2X_2$ (D) $P2X_4$ (D) $P2X_5$ (D)					Glass *et al.*, 2000[b]
Endothelial cells	$P2X_2$ (A) $P2X_3$ (A)	$P2Y_2$ (C)	$P2X_2$ (D) $P2X_3$ (D)					Glass *et al.*, 2000[b] Loesch and Burnstock, 2002[c]

(*continued*)

TABLE XXIV (*continued*)

Cellular component	Receptor mRNA		Receptor protein		Pharmacological and biochemical profile		Function	References
Thyroid vessels								
Smooth muscle			$P2X_1$ (D) $P2X_2$ (D) $P2X_5$ (D) $P2X_6$ (D) $P2X_7$ (D)					Glass and Burnstock, 2001[b]
Endothelial cells			$P2X_3$ (DE) $P2X_4$ (DE) $P2X_7$ (DE)					Glass and Burnstock, 2001[b]
Umbilical artery								
Smooth muscle	$P2X_1$ (B) $P2X_4$ (B) $P2X_5$ (B) $P2X_6$ (B) $P2X_7$ (B)		$P2X_1$ (DF)		$P2X_1$ (G)		ATP induces contraction via P2X R	Bo *et al.*, 1998b[b] Valdecantos *et al.*, 2003[b]
Umbilical vein								
Smooth muscle	$P2X_1$ (B) $P2X_4$ (B) $P2X_5$ (B) $P2X_6$ (B) $P2X_7$ (B)		$P2X_1$ (DF)		P2X (G)		ATP induces contraction via P2X R	Bo *et al.*, 1998b[b] Valdecantos *et al.*, 2003[b]
Endothelial cells	$P2X_4$ (AB) $P2X_5$ (B)	$P2Y_1$ (AB) $P2Y_2$ (AB)	$P2X_4$ (D) $P2X_5$ (E) $P2X_6$ (D)	$P2Y_1$ (E) $P2Y_2$ (E) $P2Y_4$ (E)	$P2X_4$ (H) $P2X_7$ (I)	P2Y (I)	ATP antagonizes thrombin-induced barrier failure $P2X_4$ R mediate Ca^{2+} influx	Jin *et al.*, 1998[c] Goepfert *et al.*, 2000[b] Yamamoto *et al.*, 2000a,b[b]

		$P2Y_4$ (B) $P2Y_6$ (AB) $P2Y_{11}$ (AB)	$P2Y_6$ (E) $P2Y_{11}$ (E)			$P2Y_2$ R inhibit TNF-α-stimulated protein kinase activity	Glass *et al.*, 2002[b] Gündüz and Schäfer, 2002[c] Parodi *et al.*, 2002[c] Schwiebert *et al.*, 2002b[b] Wang *et al.*, 2002b[c]
HUVEC cell lines					$P2Y_1$ (GH) $P2Y_2$ (GH)	ATP and UTP increase $[Ca^{2+}]_i$	Conant *et al.*, 1998[c] Paul *et al.*, 2000[c]
Ureter vasculature		$P2X_1$ (D) $P2X_2$ (D) $P2X_4$ (D) $P2X_7$ (D)					Lee *et al.*, 2000b[b]
Urethra vasculature		$P2X_1$ (D) $P2X_2$ (D)					Lee *et al.*, 2000a[b]
Uterine blood vessels							
Smooth muscle							
Nonpregnant		$P2X_1$ (D) $P2X_2$ (D)		P2X (G)	P2Y (G)	ATP increases $[Ca^{2+}]_i$ ATP and NA are sympathetic cotransmitters	Fontes Ribeiro *et al.*, 1999[c] Neta *et al.*, 1999[b] Bardini *et al.*, 2000[b] Okamura *et al.*, 2000[b]
Endothelium							
Nonpregnant					P2Y (GH)	ATP increases $[Ca^{2+}]_i$ ATP stimulates PGI_2 synthesis	Bird *et al.*, 2000[c] Di *et al.*, 2001[c]
Pregnant					P2Y (GH)	ATP stimulates NO and PGI_2 synthesis	Bird *et al.*, 2000[c] Di *et al.*, 2001[c]
Sympathetic cotransmission	See Table XLII						

[a]See footnote *a* for Table III.
[b]References refer to P2X receptors.
[c]References refer to P2Y receptors.
[d]References refer to P2X and P2Y receptors.
[e]Uncharacterized P2 receptors.

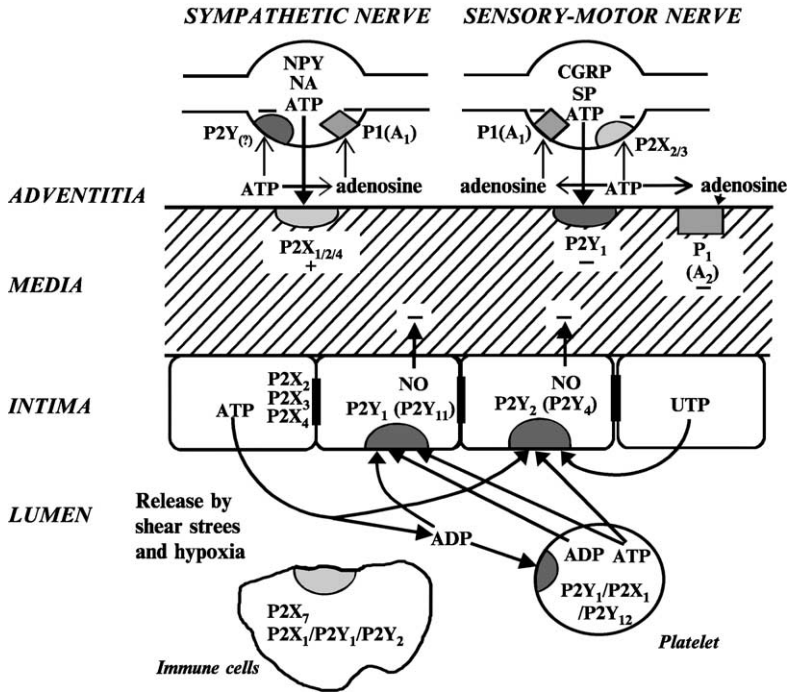


FIG. 6 Short-term (acute) purinergic signaling controlling vascular tone. Schematic illustrating the main receptor subtypes for purine and pyrimidines present in most blood vessels. Perivascular nerves in the adventitia release ATP as a cotransmitter: ATP, i.e., released with NA and neuropeptide Y (NPY) from sympathetic nerves to act on smooth muscle $P2X_1$ and in some vessels $P2X_2$ and $P2X_4$ receptors, resulting in vasoconstriction. It is released with calcitonin gene-related peptide (CGRP) and substance P (SP) from sensory nerves during "axon reflex" activity to act on smooth muscle P2Y receptors resulting in vasodilatation; P1 (A_1) receptors on nerve terminals of sympathetic and sensory nerves mediate adenosine (arising from enzymatic breakdown of ATP) modulation of transmitter release. $P2X_3$ receptors are present on a subpopulation of sensory nerve terminals. P1 (A_2) receptors on vascular smooth muscle mediate vasodilatation. Endothelial cells release ATP and UTP during shear stress and hypoxia to act on $P2Y_1$, $P2Y_2$, and sometimes $P2Y_4$ receptors leading to the production of NO and subsequent vasodilatation. ATP, following its release from aggregating platelets, also acts on these endothelial receptors. Blood-borne platelets possess $P2Y_1$ and $P2Y_{12}$ ADP-selective receptors as well as $P2X_1$ receptors, while immune cells of various kinds possess $P2X_7$, as well as $P2X_1$, $P2Y_1$, and $P2X_2$ receptors. $P2X_2$, $P2X_3$, and $P2X_4$ receptors have also recently been identified on endothelial cell membranes. (Figure reproduced and modified with permission from Burnstock, 2002.)

1987), and agonists including NA (Hashimoto *et al.*, 1997; Shinozuka *et al.*, 1994, 1997), bradykinin, ACh, 5-HT (Yang *et al.*, 1994), and ATP (Bodin and Burnstock, 1996; Buxton *et al.*, 2001). Several release mechanisms have been suggested; nicorandil-induced release of ATP was found to be

associated with an increase in $[Ca^{2+}]_i$ (Hashimoto *et al.*, 2001), whereas hypotonic stress-induced ATP release is thought to involve the Rho kinase and tyrosine kinase pathways (Grygorczyk and Guyot, 2001; Koyama *et al.*, 2001), and shear stress induces release by vesicular exocytosis (Bodin and Burnstock, 2001).

In summary, mRNA and protein for multiple P2X and P2Y receptor subtypes have been identified on smooth muscle and endothelium of blood vessels. Functionally, vascular smooth muscle cells generally express $P2X_1$ receptors and $P2Y_1$, $P2Y_2$, or $P2Y_4$ and $P2Y_6$ receptors. Endothelial cells express functional $P2Y_1$, $P2Y_2$ or $P2Y_4$, and $P2Y_6$ receptors.

3. Erythrocytes

There was early interest in the relationship between the shape of erythrocytes and the ATP found in them (Nakao *et al.*, 1961; Nishiguchi *et al.*, 1980; Quist, 1980; Weed *et al.*, 1969). It was recognized that erythrocytes contained high levels of ATP (Planker *et al.*, 1983), which could be released in a variety of circumstances. The presence of ecto-ATPases and 5′-nucleotidases in red blood cells was also detailed in the early literature (Bontemps *et al.*, 1988; Maretzki *et al.*, 1980; Parker, 1970; Patel and Fairbanks, 1986).

Extracellular actions of ATP on erythrocytes in increasing permeability to cations were also recognized (Bennekou and Stampe, 1988; Elford, 1975; Kuperman *et al.*, 1964; Parker and Snow, 1972; Parker *et al.*, 1977; Romualdez *et al.*, 1976; Shimizu *et al.*, 1985).

The group in North Carolina was the first to propose that ATP was acting via P2Y G protein-coupled receptors in erythrocytes (Berrie *et al.*, 1989; Boyer *et al.*, 1989; Downes *et al.*, 1988).

Table XXV summarizes the receptor subtypes present in erythrocytes based on mRNA, protein, and pharmacological and biochemical profiles. The functions claimed for the receptors together with key references are included.

It has been known for many years that exposure of erythrocytes to strong hypotonic solutions results in the release of adenine nucleotides (Deyrup, 1951). In addition, other stimuli can induce ATP release, including brief pulses of hypoxia (Bergfeld and Forrester, 1989, 1992; Bozzo *et al.*, 1999; Ellsworth *et al.*, 1998; Jagger *et al.*, 2000), shear stress (Sprague *et al.*, 1998a), deformation (Sprague *et al.*, 1998b, 1999, 2001, 2003), AA (Knöfler *et al.*, 1996), and ADP (Knöfler *et al.*, 1997).

Release of ATP from erythrocytes has been postulated as contributing to the regulation of vascular tone by acting as an O_2 sensor and effector of changes in O_2 delivery (Dietrich *et al.*, 2000; Ellsworth, 2000; Ellsworth *et al.*, 1995; Jagger *et al.*, 2001), released ATP binding with vascular purinoceptors and in the pulmonary circulation stimulation of NO synthesis (Sprague *et al.*, 1996, 2003).

TABLE XXV
Erythrocytes[a]

Cellular component	Receptor mRNA	Receptor protein	Pharmacological and biochemical profile		Function	References
Mudpuppy (*Necturus*)			$P2X_2$ (G)	P2Y (G)	ATP potentiates regulatory volume decrease	Light *et al.*, 1999, 2001[d] Boyer *et al.*, 1996[c]
Turkey				$P2Y_2$ (G)		Sak, 2000[c]

[a]See footnote *a* for Table III.
[c]References refer to P2Y receptors.
[d]References refer to P2X and P2Y receptors.

In summary, currently no information as to the expression of mRNA or protein for either P2X or P2Y receptor subtypes is available for erythrocytes, although, functionally, $P2X_2$ and $P2Y_2$ receptors have been identified.

4. Platelets and Megakaryocytes

Hellem (1960) showed that a low-molecular-weight compound derived from red blood cells induced adhesion of cells to glass. The same compound was later found to aggregate platelets (Olligard, 1961) and identified as ADP (Gaarder *et al.*, 1961). Born (1962) first showed that ADP induced platelet aggregation *in vitro* and ATP and β,γ-meATP inhibited ADP-induced aggregation (Evans, 1978; MacFarlane and Mills, 1975; Salzman *et al.*, 1966; Wang *et al.*, 1977). The receptor was identified as being specific for ADP and was called $P2Y_T$ (later named $P2Y_{12}$) when it was reported that ADP was a potent inhibitor of plasma membrane adenylate cyclase (Cooper and Rodbell, 1979; MacFarlane *et al.*, 1983); this was supported later by pharmacological evidence (Hall and Hourani, 1993). There were early hints that there may be multiple purinoceptors on platelets (Jefferson *et al.*, 1988) and the possibility that P2X receptors as well as the $P2_T$ receptor was also raised (Soslau *et al.*, 1993).

The responsiveness of megakaryocytes to ADP to cause process formation and cellular spreading was first reported in the early 1980s (Kawa, 1990; Leven and Nachmias, 1982; Leven *et al.*, 1983).

Table XXVI summarizes the receptor subtypes present in platelets and megakaryocytes based on mRNA, protein, and pharmacological and biochemical profiles. The functions claimed for the receptors together with key references are included.

The platelet aggregation induced by thrombin and collagen was suggested to be due to the release of ADP from intracellular stores (Haslam, 1964, 1967) and following the induced aggregation of platelets by ADP, it was noted that the concentration of ADP appearing in the plasma containing the platelets was up to seven times the concentration added (Mills *et al.*, 1968).

In addition to ADP, ATP has also been shown to be released from platelets and megakaryocytes in response to thrombin (Detwiler and Feinman, 1973; Miller, 1983) and can be continuously measured by the luciferin/luciferase luminescence method (Goldenberg *et al.*, 2001; Higashi *et al.*, 1985).

In summary, mRNA, protein, and a functional $P2X_1$ receptor have been identified on platelets. Similarly, mRNA, protein, and a functional $P2Y_1$ receptor have been identified on platelets, in addition to mRNA and a functional $P2Y_{12}$ receptor. Megakaryocytes express mRNA, protein, and a functional $P2Y_1$ receptor and mRNA and functional $P2Y_{12}$ receptors. Megakaryocytes express functional $P2X_1$ and $P2Y_2$ receptors; a functional $P2Y_1$ receptor is also postulated. In contrast, megakaryocyte cell lines

TABLE XXVI

Platelets and Megakaryocytes[a]

Cellular component	Receptor mRNA		Receptor protein		Pharmacological and biochemical profile		Function	References
Platelets	$P2X_1$ (AB)	$P2Y_1$ (B) $P2Y_{12}$(AB)	$P2X_1$ (EF)	$P2Y_1$ (F)	$P2X_1$ (GH)	$P2Y_1$ (G) $P2Y_{12}$ (G)	ATP increases $[Ca^{2+}]_i$ via $P2X_1$ R and may act as a positive regulator of responses to collagen, be involved in shape change, and contribute to the formation of platelet thrombi in the presence of P2Y R P2Y R mediate release of AA $P2Y_1$ R mediate platelet cell shape change and aggregation $P2Y_{12}$ R mediate platelet aggregation	Gachet *et al.*, 1995[c] Soslau *et al.*, 1995[c] MacKenzie *et al.*, 1996[b] Léon *et al.*, 1997[c] Savi *et al.*, 1997[b], 1998[c] Vial *et al.*, 1997, 2002[b] Daniel *et al.*, 1998[d] Clifford *et al.*, 1998[b] Geiger *et al.*, 1998[d] Fagura *et al.*, 1998[c] Jin *et al.*, 1998, 2002[c] Scase *et al.*, 1998[b] Sun *et al.*, 1998[b] Jantzen *et al.*, 1999[c] Park and Hourani, 1999[c] Takano *et al.*, 1999[d] Cusack and Hourani, 2000[d] Jarvis *et al.*, 2000[c] Mahaut-Smith *et al.*, 2000[d] Greco *et al.*, 2001[b] Hollopeter *et al.*, 2001[c] Oury *et al.*, 2001[b] Rolf *et al.*, 2001[b] Goto *et al.*, 2002[c] Mateos-Trigos *et al.*, 2002[c] Fontana *et al.*, 2003[c] Hechler *et al.*, 2003[c]

						Jagroop *et al.*, 2003[c] Reséndiz *et al.*, 2003[c] Wang *et al.*, 2003b[c]
Megakaryocytes			$P2X_1$ (GH)	$P2Y_1$? (G) $P2Y_2$ (G)	ATP elicits $[Ca^{2+}]_i$ influx and induces Ca^{2+} oscillations ADP produces changes in cytoskeleton and cell spreading	Somasundaram and Mahaut-Smith, 1994[c] Uneyama *et al.*, 1994a,b[c] Kawa, 1996[c] Hussain and Mahaut-Smith, 1998[c] Vial *et al.*, 2002[b]
Cell lines						
Dami cells	$P2X_1$ (B)	$P2Y_1$ (B) $P2Y_2$ (B) $P2Y_4$ (B) $P2Y_6$ (B)		$P2Y_1$ (G) $P2Y_2$ (G)	ATP and ADP elevate $[Ca^{2+}]_i$	Murgo *et al.*, 1994[c] Léon *et al.*, 1997[c] Vial *et al.*, 1997[b] Jin *et al.*, 1998[c]
K562 cells	$P2X_1$ (B)	$P2Y_1$ (B)		$P2Y_2$ (G) $P2Y_{12}$ (H)	ADP elevates $[Ca^{2+}]_i$	Léon *et al.*, 1997[c] Vial *et al.*, 1997[b] Jin *et al.*, 1998[c]
MEG-01 cells	$P2X_1$ (B)	$P2Y_1$ (B)				Hechler *et al.*, 1995[c] Léon *et al.*, 1997[c] Vial *et al.*, 1997[b]
CHRF-288 cells	$P2X_1$ (B)	$P2Y_1$ (B)				Hechler *et al.*, 1995[c] Léon *et al.*, 1997[c] Vial *et al.*, 1997[b]
HEL cells	$P2X_1$ (B)	$P2Y_1$ (B)				Hechler *et al.*, 1995[c] Léon *et al.*, 1997[c] Vial *et al.*, 1997[b]
HL-60 cells	$P2X_1$ (B) $P2X_4$ (B) $P2X_7$ (B)	$P2Y_1$ (B) $P2Y_2$ (B) $P2Y_6$ (B)		$P2Y_2$ (G) $P2Y_{11}$ (G)	ATP and UTP promote adhesion to endothelium ATP triggers differentiation via $P2Y_{11}$ R	Montero *et al.*, 1995[c] Parker *et al.*, 1996[c] Jiang *et al.*, 1997[c] Song *et al.*, 1997[c]

(*continued*)

TABLE XXVI (*continued*)

Cellular component	Receptor mRNA	Receptor protein	Pharmacological and biochemical profile	Function	References
					Vial *et al.*, 1997[b]
					Jin *et al.*, 1998[c]
					Adrian *et al.*, 2000[d]
					Communi *et al.*, 2000[c]
CMK 11-5 cells	$P2X_1$ (B)		$P2Y_2$ (H)		Greco, 1997[c]
		$P2X_1$ (E)			Vial *et al.*, 1997[b]
Y10/L8057 cells	$P2Y_1$ (B)				Hechler *et al.*, 2001[c]
U937 cells	$P2Y_2$ (B)		$P2X_7$ (G)		Jin *et al.*, 1998[c]
	$P2Y_6$ (B)				Schneider *et al.*, 2001[b]

[a]See footnote *a* for Table III.
[b]References refer to P2X receptors.
[c]References refer to P2Y receptors.
[d]References refer to P2X and P2Y receptors.

express mRNA for multiple P2X and P2Y receptor subtypes, although only functional P2Y receptors have been shown of the $P2Y_1$, $P2Y_2$, $P2Y_{11}$, and $P2Y_{12}$ subtypes.

H. Exocrine Glands

1. Salivary Glands

The first report of the effects of extracellular ATP on salivary glands was demonstrated when ATP induced vasodilatation in the cat submandibular gland when administered intra-arterially (Jones *et al.*, 1980). ATP elicited an augmentation of ionic permeability and a rise in $[Ca^{2+}]_i$ in suspensions from rat submandibular glands and parotid acinar cells via P2 receptors (Dehaye, 1993; Gallacher, 1982; McMillian *et al.*, 1988, 1993; Soltoff *et al.*, 1990). Further studies showed that benzoyl ATP (Bz-ATP) was more potent than ATP at stimulating rat parotid acinar cells and the receptor was identified as of the P_{2Z} subtype (Soltoff *et al.*, 1992). The presence of two distinct P2 receptors was suggested when it was shown that ATP produced a biphasic increase in $[Ca^{2+}]_i$ in rat parotid acinar cells, a P2Z and a second P2X-like ionotropic receptor (McMillian *et al.*, 1993).

Salivary acinar and ductal cell lines have been developed and these also express P2 receptors. The first reported was in a human submandibular duct cell line (HSG-PA) exhibiting P_{2U} receptors, since ATP and UTP were found to be equipotent (Yu and Turner, 1991).

Table XXVII summarizes the receptor subtypes present in salivary glands based on mRNA, protein, and pharmacological and biochemical profiles. The functions claimed for the receptors together with key references are included.

Spontaneous efflux and high K^+ depolarization-evoked purine release from rat submaxillary glands have been demonstrated; however, it could not be determined whether the release was from glandular elements or from sympathetic nerve endings (Filinger *et al.*, 1989).

In summary, functional $P2Y_2$ receptors and protein for this receptor have been identified in sweat gland epithelial cells, typically situated on the basolateral membrane. In addition, functional $P2X_4$ and $P2X_7$ receptors ($P2X_7$ receptors located on the luminal membrane) have been demonstrated, together with the mRNA and protein for these receptors.

2. Lachrymal Glands

ATP induced a rise in $[Ca^{2+}]_i$ in lachrymal gland epithelial cells via P2 receptors (Sasaki and Gallacher, 1990, 1992; Vincent, 1992).

TABLE XXVII
Salivary Glands[a]

Cellular component	Receptor mRNA		Receptor protein	Pharmacological and biochemical profile		Function	References
Parotid gland							
Acinar cells	$P2X_4$ (B) $P2X_7$ (B)		$P2X_4$ (DE)	$P2X_4$ (H) $P2X_7$ (GI)	$P2Y_2$ (G)	ATP is involved in the regulation of ionic balance ATP increases $[Ca^{2+}]_i$	Jørgensen *et al.*, 1995[b] Fukushi *et al.*, 1997[b] Tojyo *et al.*, 1997[b] Mizuno-Kamiya *et al.*, 1998[c] Tenneti *et al.*, 1998[b] Fukushi, 1999[b] Arkle and Douzenis, 2000[b] Gibbons *et al.*, 2001[b] Arreola and Melvin, 2003[b] Bo *et al.*, 2003[b]
Duct cells			$P2X_4$ (DE)				Bo *et al.*, 2003[b]
Cell lines							
SV40 immortalized acinar cells		$P2Y_2$ (B)			$P2Y_2$ (G)		Quissell *et al.*, 1998[c] Turner *et al.*, 1998b[c]
Par—C10 cells		$P2Y_2$ (B)			$P2Y_2$ (G)		Turner *et al.*, 1998a[c]
HSY cells					P2Y (G)	ATP increases $[Ca^{2+}]_i$	Carmel *et al.*, 1999[c] Tojyo *et al.*, 2001[c]
Submandibular gland							
Acinar cells	$P2X_4$ (A)	$P2Y_2$ (B)	$P2X_4$ (DE)	$P2X_4$ (H) $P2X_7$ (GH)	$P2Y_2$ (GH)	ATP increases $[Ca^{2+}]_i$ ATP regulates saliva secretion ATP regulates zinc uptake	Hurley *et al.*, 1994[b] Dehaye, 1995[b] Lachish *et al.*, 1996[b] Lee *et al.*, 1997[d] Chaïb *et al.*, 2000[b]

							Fernandez *et al.*, 2001[b] Perez-Andres *et al.*, 2002[b] Bo *et al.*, 2003[b] Pochet *et al.*, 2003[b]
Duct cells		$P2Y_1$ (B)	$P2X_4$ (DE)	$P2X_7$ (H)	$P2Y_1$ (H) $P2Y_2$ (GH)	ATP increases $[Ca^{2+}]_i$ ATP stimulates release of AA $P2X_7$ R mediate increased proton permeability	Amsallem *et al.*, 1996[d] Lee *et al.*, 1997, 1998[d] Park *et al.*, 1997[c] Zeng *et al.*, 1997[d] Alzola *et al.*, 1998[b] Chaïb *et al.*, 1998[b] Dehaye *et al.*, 1999[b] Kabré *et al.*, 1999[b]
Cell lines							
HSG cells			$P2X_1$ (DE) $P2X_2$ (DE) $P2X_3$ (DE) $P2X_4$ (DE) $P2X_5$ (DE) $P2X_6$ (DE) $P2X_7$ (F)	$P2X_7$ (G)	$P2Y_2$ (G)	UTP potentiates regulatory volume decrease in response to increased osmolarity	Kim *et al.*, 1996a[c] Kurihara *et al.*, 1997[d] Liu *et al.*, 1999c[d] Worthington *et al.*, 1999a[b]
ST_{885} cells					$P2Y_1$ (H) $P2Y_2$ (H)	ATP increases $[Ca^{2+}]_i$	Gibb *et al.*, 1994[c]
Labial salivary gland					$P2Y_2$ (H)	ATP and UTP increase $[Ca^{2+}]_i$	Pedersen *et al.*, 2000[c]
Salivary gland serosal cells	$P2X_4$ (A)						Buell *et al.*, 1996[b]

[a]See footnote *a* for Table III.
[b]References refer to P2X receptors.
[c]References refer to P2Y receptors.
[d]References refer to P2X and P2Y receptors.

Table XXVIII summarizes the receptor subtypes present in lachrymal glands based on mRNA, protein, and pharmacological and biochemical profiles. The functions claimed for the receptors together with key references are included.

Human tears contain diadenosine polyphosphates and ATP (Pintor *et al.*, 2002a).

In summary, functional $P2Y_2$ receptors have been identified on lachrymal gland acinar cells. To date this is the only example of P2 receptors in this tissue.

3. Sweat Glands

ATP induced sweating in primate sweat glands *in vitro* (Sato *et al.*, 1991) and induced a slow rise in $[Ca^{2+}]_i$ in cultured human sweat gland epithelial cells (Pickles and Cuthbert, 1992).

Table XXIX summarizes the receptor subtypes present in sweat glands based on mRNA, protein, and pharmacological and biochemical profiles. The functions claimed for the receptors together with key references are included (cf. Table XLV).

In summary, functional $P2Y_2$ receptors and protein for this receptor have been identified in eccrine gland cells. In addition, functional $P2Y_1$ and $P2Y_4$ receptors have been demonstrated, together with the protein for these receptors.

4. Exocrine Pancreas

ATP inhibited Ca^{2+}-activated nonselective cation channels in guinea pig isolated pancreatic acinar cells (Suzuki and Petersen, 1988), whereas in the mouse, ATP had a dual effect (Thorn and Petersen, 1992). The continuous presence of ATP was required for operation of the cation channels (probably through the action of adenosine) and ATP also closed the channel, probably via a P2X receptor. Intracellular perfusion of mouse acinar cells with high concentrations of ATP increased the probability that the ACh-evoked short lasting Ca^{2+} spikes would initiate more substantial Ca^{2+} waves (Petersen *et al.*, 1991).

Table XXX summarizes the receptor subtypes present in the exocrine pancreas based on mRNA, protein, and pharmacological and biochemical profiles. The functions claimed for the receptors together with key references are included.

Release of ATP from single rat pancreatic acini cells has been visualized using the luciferin/luciferase method in response to various stimuli such as cholinergic stimulation (Sørensen and Novak, 2001). Acini contain low

TABLE XXVIII
Lachrymal Glands[a]

Cellular component	Receptor mRNA	Receptor protein	Pharmacological and biochemical profile	Function	References
Lacrimal gland					
Acinar cells			$P2Y_2$ (G)	ATP increases $[Ca^{2+}]_i$ ATP, UTP, and Ap_4A produce changes in Cl^- conductance	Gromada *et al.*, 1995[c] Murakami *et al.*, 2000[c] Pintor *et al.*, 2002b[c]

[a]See footnote *a* for Table III.
[c]References refer to P2Y receptors.

TABLE XXIX
Sweat Glands[a]

Cellular component	Receptor mRNA	Receptor protein	Pharmacological and biochemical profile	Function	References
Eccrine gland cells		$P2Y_1$ (D)	$P2Y_1$ (G)	ATP increases $[Ca^{2+}]_i$	Ko *et al.*, 1994, 1997[c]
		$P2Y_2$ (D) $P2Y_4$ (D)	$P2Y_2$ (GH) $P2Y_4$ (G)	$P2Y_2$ R in apical membranes of equine cultured epithelia regulate electrolyte transport UDP increases short circuit currents (I_{sc})	Wilson *et al.*, 1998[c] Clunes *et al.*, 1999[c] Hongpaisan and Roomans, 1999[c] Bovell *et al.*, 2000[c] Lindsay *et al.*, 2002[c] Wong and Ko, 2002[c]
Cell lines					
NCL-SG3			P2Y (G)	ATP induces transepithelial-potential changes	Ring and Mörk, 1997[c]
Sensory nerves	See Table XLV				

[a]See footnote *a* for Table III.
[c]References refer to P2Y receptors.

TABLE XXX

Exocrine Pancreas[a]

Cellular component	Receptor mRNA		Receptor protein	Pharmacological and biochemical profile		Function	References
Intralobular ducts	$P2X_1$ (B) $P2X_4$ (B) $P2X_7$ (B)	$P2Y_1$ (B) $P2Y_2$ (B) $P2Y_4$ (B) $P2Y_5$ (B)	$P2Y_1$ (D) $P2Y_2$ (D)	$P2X_1$ (H) $P2X_4$ (H) $P2X_7$ (GH)	$P2Y_1$ (H) $P2Y_2$ (H) $P2Y_4$ (H)	ATP and UTP increase $[Ca^{2+}]_i$	Christoffersen *et al.*, 1998[d] Dubyak, 1999[d] Hede *et al.*, 1999[d] Ishiguro *et al.*, 1999[c] Luo *et al.*, 1999[d] Coutinho-Silva *et al.*, 2001a, 2003[d] Henriksen and Novak, 2003[b]
Basolateral membrane	$P2X_1$ (B) $P2X_4$ (B) $P2X_7$ (B)	$P2Y_1$ (B)		$P2X_1$ (H) $P2X_4$ (GH) $P2X_7$ (GH)	$P2Y_1$ (G) $P2Y_2$ (GH)	ATP and UTP increase $[Ca^{2+}]_i$	Luo *et al.*, 1999[d]
Luminal membrane	$P2X_1$ (B) $P2X_4$ (B) $P2X_7$ (B)	$P2Y_2$ (B)		$P2X_7$ (G)	$P2Y_2$ (H)	P2X R may contribute to regulation of secretion	Hede *et al.*, 1999[d] Luo *et al.*, 1999[d]
Pancreatic duct epithelial cells	$P2X_4$ (B)	$P2Y_2$ (B) $P2Y_4$ (B)			$P2Y_2$ (G)	ATP and UTP increase $[Ca^{2+}]_i$ ATP and UTP stimulate mucin secretion	Nguyen *et al.*, 1998[c] Hede *et al.*, 1999[d] Luo *et al.*, 1999[d] Novak *et al.*, 2002, 2003[b]
Cystic fibrosis pancreatic duct cells					$P2Y_2$ (G) $P2Y_4$ (G)	Purinergic regulation of anion secretion	Chan *et al.*, 1996[c]
Acini cells	$P2X_1$ (B) $P2X_4$ (B)	$P2Y_2$ (B) $P2Y_4$ (B)			$P2Y_2$ (H)	ATP and UTP increase $[Ca^{2+}]_i$	Novak *et al.*, 2002, 2003[d]
CFPAC-1 cells		$P2Y_2$ (A) $P2Y_4$ (B)					Communi *et al.*, 1999[c]

[a]See footnote *a* for Table III.
[b]References refer to P2X receptors.
[c]References refer to P2Y receptors.
[d]References refer to P2X and P2Y receptors.

numbers of functional P2 receptors, thought to reflect the fact that they release ATP and as such would avoid autocrine stimulation and initiation of autodigestive processes, such as occurs in pancreatitis (Novak *et al.*, 2002, 2003).

In summary, pancreatic ducts express $P2X_1$, $P2X_4$, and $P2X_7$ mRNA and functional receptors, although to date immunohistochemical data for the exocrine pancreas are lacking. In addition, mRNA and protein for $P2Y_1$ and $P2Y_2$ receptor subtypes together with functional receptors appear to predominate, although other receptor subtypes have been identified. Pancreatic epithelial and acini cells express mRNA for $P2X_4$, $P2Y_2$, and $P2Y_4$ receptors and functionally $P2Y_2$ receptors have been identified.

I. Endocrine Glands

1. Pituitary Gland and Pineal Gland

Extracellular ATP activated PLC and mobilized $[Ca^{2+}]_i$ in primary cultures of sheep, rat, and baboon pituitary cells, although none of the major pituitary hormones appeared to be released by ATP or UTP (Davidson *et al.*, 1990; van der Merwe *et al.*, 1989).

Table XXXI summarizes the receptor subtypes present in the pituitary and pineal glands based on mRNA, protein, and pharmacological and biochemical profiles. The functions claimed for the receptors together with key references are included (Fig. 7).

ATP is released simultaneously with oxytocin and vasopressin from posterior and prolactin from anterior rat isolated pituitary preparations, visualized using luciferin/luciferase and biochemical techniques (Nuñez *et al.*, 1997; Sperlágh *et al.*, 1999).

Calcium-ATPase was distributed mainly on the membrane of rat anterior pituitary granular cells (Soji *et al.*, 1991) and it was later demonstrated on plasma membranes surrounding nerve endings and pituicytes of the posterior pituitary (Thirion *et al.*, 1996).

In summary, the anterior pituitary expresses mRNA for multiple P2X receptors and this is reflected in the presence of multiple functional P2X receptors; in contrast, $P2Y_2$ receptors are the only P2Y subtype identified by mRNA and as a functional receptor. The posterior pituitary expressed protein for $P2X_2$ and $P2X_6$ receptors and of these a functional $P2X_2$ receptor has been demonstrated. An as yet unclassified functional P2Y receptor has also been described. The pineal gland expressed mRNA for $P2Y_4$ receptors although functionally a $P2Y_1$ receptor has been described in addition to a P2X receptor.

TABLE XXXI

Pituitary Gland and Pineal Gland[a]

Cellular component	Receptor mRNA		Receptor protein	Pharmacological and biochemical profile		Function	References
Anterior pituitary							
Mixed cells from pituitary	$P2X_{2a}$ (B) $P2X_{2b}$ (B) $P2X_3$ (B) $P2X_4$ (B) $P2X_7$ (B)			P2 (GI)		ATP stimulates prolactin release	Nuñez *et al.*, 1997[c] Koshimizu *et al.*, 2000[d]
Lactotrophs	$P2X_3$ (B) $P2X_4$ (B) $P2X_7$ (B)	$P2Y_2$ (B)		$P2X_3$ (H) $P2X_4$ (H) $P2X_7$ (H)	$P2Y_2$ (H)	ATP increases $[Ca^{2+}]_i$	Carew *et al.*, 1994[c] Stojilkovic *et al.*, 2000[b]
Somatotrophs	$P2X_{2a}$ (B) $P2X_{2b}$ (B)			$P2X_2$ (H)		ATP increases $[Ca^{2+}]_i$	Stojilkovic *et al.*, 2000[b]
Gonadotrophs	$P2X_{2a}$ (B) $P2X_{2b}$ (B)			$P2X_2$ (H)	$P2Y_2$ (H)	ATP increases $[Ca^{2+}]_i$ P2Y R mediate release of LH ATP regulates prolactin release	Chen *et al.*, 1994b, 1995c[c] Tomić *et al.*, 1996[b] Stojilkovic *et al.*, 2000[b]
Corticotrophs				$P2X_2$ (H)	$P2Y_2$ (H)	ATP increases $[Ca^{2+}]_i$	Villalobos *et al.*, 1997[d]
Thyrotrophs				$P2X_2$ (H)	$P2Y_2$ (H)	ATP increases $[Ca^{2+}]_i$	Villalobos *et al.*, 1997[d]
Folliculostellate cells					$P2Y_2$ (H)	ATP increases $[Ca^{2+}]_i$	Uchiyama *et al.*, 2001[c]
Cell lines							
αT3-1 cells					$P2Y_2$ (H)	ATP increases $[Ca^{2+}]_i$	Chen *et al.*, 1996b[c]
Tpit/F1 cells					$P2Y_2$ (H)	ATP increases $[Ca^{2+}]_i$	Chen *et al.*, 2000b[c]
GH3 cells	$P2X_7$ (B)		$P2X_7$ (D)	$P2X_7$ (GH)		ATP increases $[Ca^{2+}]_i$	Chung *et al.*, 2000[b]
GH_4C_1 cells				$P2X_7$ (GH)			Kimm-Brinson *et al.*, 2001[b] Melo *et al.*, 2001[b]
Posterior pituitary							
Isolated posterior lobe				P2 (G)		ATP decreases vasopressin release	Sperlágh *et al.*, 1999[e]
Neurohypophysial terminals				$P2X_2$ (H)		ATP increases $[Ca^{2+}]_i$ ATP evokes vasopressin release	Troadec *et al.*, 1998[b]

(*continued*)

TABLE XXXI (*continued*)

Cellular component	Receptor mRNA	Receptor protein	Pharmacological and biochemical profile	Function	References
Hypothalamo-neurohypophysial explant			P2X (G)	ATP stimulates vasopressin and oxytocin release	Kapoor and Sladek, 2000[b] Lemos and Wang, 2000[b]
Neurohypophysial astrocytes (pituicytes)		$P2X_2$ (D) $P2X_6$ (D)	P2Y (H)	ATP increases $[Ca^{2+}]_i$	Loesch *et al.*, 1999[b] Troadec *et al.*, 1999, 2000[c] Loesch and Burnstock, 2001[b]
Pineal gland	$P2Y_4$ (B)		P2X (G)	ATP and NA are sympathetic cotransmitters inducing release of melatonin	Ferreira *et al.*, 1994[b] Webb *et al.*, 1998[c] Mortani Barbosa *et al.*, 2000[b]
Pinealocytes			$P2Y_1$ (G)	ATP increases acidification rate	Ferreira and Markus, 2001[c] Ferreira *et al.*, 2003[c]

[a]See footnote *a* for Table III.
[b]References refer to P2X receptors.
[c]References in blue refer to P2Y receptors.
[d]References refer to P2X and P2Y receptors.
[e]References refer to uncharacterized P2 receptors.

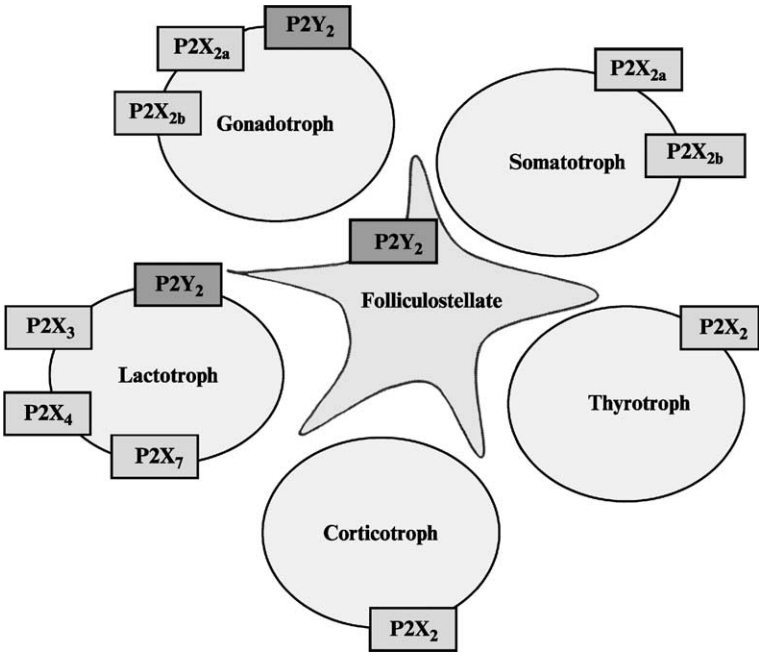


FIG. 7 Distribution of P2 receptors in endocrine pituitary and folliculostellate cells. Functional G protein-coupled $P2Y_2$ receptors have been identified in gonadotrophs and lactotrophs and mediate the release of luteinizing hormone (LH) by ATP. Functional $P2Y_2$ receptors are also present in folliculostellate cells. In gonadotrophs and somatotrophs, RT-PCR studies have demonstrated mRNA expression of the $P2X_{2a}$ receptor and its spliced form $P2X_{2b}$ only. In contrast, lactotrophs express mRNA transcripts for $P2X_3$, $P2X_4$, and $P2X_7$, and studies have confirmed the functional nature of the latter. P2X receptors have also been identified in corticotrophs and thyrotrophs, probably of the $P2X_2$ subtype. (Figure based on the figure by Rees *et al.*, *Clin. Sci.* **104,** 467–481, 2003.)

2. Adrenal Gland

As early as 1955, chromaffin granules obtained from bovine adrenal medulla were found to be rich in ATP (Hillarp *et al.*, 1955). It was soon demonstrated that the granules with a high concentration of ATP also had a high concentration of catecholamines (Blaschko *et al.*, 1956), the complex of catecholamines and ATP existing in a ratio of 4:1 (Hillarp, 1958; Van Dyke *et al.*, 1977). The mechanism by which ATP is taken up into chromaffin granules was thought to be carrier-mediated (Kostron *et al.*, 1977). Isolated adrenal medullary secretary granules could be stimulated by ATP to release catecholamines and soluble proteins (Poisner and Triféro, 1967), the release of the

hormones being evoked by calcium influx through voltage-dependent channels in the plasma membrane (Diverse-Pierluissi *et al.*, 1991). The release was accompanied by an osmotic expansion and lysis of the vesicle membrane (Warashina, 1985). Nonhydrolyzable analogues of ATP such as β,γ-meATP also stimulated release from bovine isolated secretory granules, suggestive of a P2X receptor subtype (Casey *et al.*, 1976; Hoffman *et al.*, 1976a; Pollard *et al.*, 1976). In contrast, ATP inhibited the ACh-stimulated secretion from isolated bovine adrenal medullary cells (Chern *et al.*, 1987) by down-regulating the calcium channel via a pertussis toxin-sensitive G protein-coupled receptor (Doupnik and Pun, 1993; Gandía *et al.*, 1993).

In addition to ATP and catecholamines, adrenal chromaffin cells also store and release diadenosine tetraphosphate (Ap_4A) (Castillo *et al.*, 1992). Ap_4A has an inhibitory action on induced catecholamine release from chromaffin cells via an action on P2Y receptors (Castro *et al.*, 1992; Pintor *et al.*, 1991). P2Y receptors on chromaffin cells may also modulate adenosine transport (Sen *et al.*, 1993).

Before entering the bloodstream, catecholamines and ATP secreted by the adrenal medulla pass through an endothelial cell barrier. Of the secretory products of the adrenal medulla, only ATP induced prostacyclin formation from the endothelial cells (Forsberg *et al.*, 1987). The order of agonist potency was inconsistent with known P2 receptor subtypes (Allsup and Boarder, 1990).

The outer cortex of the adrenal gland secretes glucocorticoids. Extracellular ATP stimulated steroidogenesis in bovine adrenocortical fasciculate cells via a P2Y receptor (Kawamura *et al.*, 1991; Matsui, 1991; Niitsu, 1992).

Table XXXII summarizes the receptor subtypes present in the adrenal gland based on mRNA, protein, and pharmacological and biochemical profiles. The functions claimed for the receptors together with key references are included (cf. Table XXIV).

ATP is known to be stored with catecholamines in adrenal medullary chromaffin cells. The amount of ATP and catecholamines within adrenal medullary chromaffin cells was reduced following nerve stimulation (Carlsson *et al.*, 1957) and in response to stimuli such as ACh from splanchnic nerve terminals and ATP (Hoffman *et al.*, 1976b; Stevens *et al.*, 1975; Uvnäs and Åborg, 1988) indicating concomitant release of both ATP and catecholamines. Secretion of ATP and catecholamines in response to stimuli such as muscarinic and nicotinic agonists required external free Ca^{2+} (Rojas *et al.*, 1985; Xu *et al.*, 1991) but this has not been shown for release of ATP and NA in response to EFS (Jurányi *et al.*, 1997).

In summary, proteins for multiple P2X receptor subtypes have been identified in adrenal tissues, although the principal P2Y receptor expressed as mRNA, protein, and as a functional receptor is of the $P2Y_2$ subtype.

TABLE XXXII
Adrenal Gland[a]

Cellular component	Receptor mRNA	Receptor protein	Pharmacological and biochemical profile		Function	References
Medullary chromaffin cells		$P2X_2$ (D) $P2X_3$ (D) $P2X_5$ (D) $P2X_6$ (D) $P2X_7$ (D)	$P2X_2$ (G)	P2Y (GH) $P2Y_2$ (H)	ATP modulates CA secretion ATP modulates aldosterone secretion	Castro *et al.*, 1995[c] Lin *et al.*, 1995[c] Reichsman *et al.*, 1995[c] Lim *et al.*, 1997[c] Afework and Burnstock, 1999, 2000a,b[b] Liu *et al.*, 1999a[b] Harkins and Fox, 2000[c] Powell *et al.*, 2000[c]
Cortex						
Zona reticularis—inner		$P2X_1$ (D) $P2X_2$ (D) $P2X_4$ (D)				Afework and Burnstock, 1999, 2000a,b[b]
Zona reticularis—outer		$P2X_2$ (D) $P2X_4$ (D)				Afework and Burnstock, 1999, 2000a,b[b]
Zona fasciculata	$P2Y_2$ (B)	$P2X_5$ (D) $P2X_6$ (D) $P2X_7$ (D)		P2Y (G) $P2Y_2$ (GH)	ATP and UTP enhance steroidogenesis	Nishi, 1999, 2001[c] Xu and Enyeart, 1999[c] Kawamura *et al.*, 2001, 2003b[c] Nishi and Kawamura, 2002[c] Nishi *et al.*, 2002[c]
Zona glomerulosa			P2 (G)		ATP induces aldosterone production	Szalay *et al.*, 1998[e]

(*continued*)

TABLE XXXII (*continued*)

Cellular component	Receptor mRNA	Receptor protein	Pharmacological and biochemical profile	Function	References
Nerves					
Intrinsic neurons		$P2X_2$ (D) $P2X_3$ (D) $P2X_5$ (D)			Afework and Burnstock, 1999, 2000a,b[b]
Extrinsic preganglionic sympathetic neurones		$P2X_1$ (D) $P2X_5$ (D)			
Perfused adrenal glands			P2 (G)	ATP increases CA secretion	Asano *et al.*, 1995[e]
Blood vessels	See Table XXV				

[a]See footnote *a* for Table III.
[b]References refer to P2X receptors.
[c]References refer to P2Y receptors.
[e]References refer to uncharacterized P2 receptors.

3. Thyroid

The activity of the pig thyroid H_2O_2 generator increased in the presence of ATP (Nakamura and Ohtaki, 1990; Nakamura *et al.*, 1987); this response was specific to ATP since neither ADP nor GTP had a similar effect.

Primary cultures of dog thyroid cells, when exposed to ATP, responded with an increase in $[Ca^{2+}]_i$ concentration (Rani *et al.*, 1989) and an increase in the generation of inositol phosphates (Raspé *et al.*, 1991a). This was also true of human thyroid cells, the receptor being identified as a P2Y receptor (Raspé *et al.*, 1989; 1991b). ATP similarly mobilized $[Ca^{2+}]_i$ in bovine (Nemeth and Kosz, 1989) and human parathyroid cells (Conigrave *et al.*, 1992) via P2 receptors.

ATP has effects on cell lines derived from thyroid tissue. One is the FRTL-5 cell line, a continuous line of epithelial cells from normal rat thyroid. In these cells, ATP stimulated iodide efflux associated with IP_3 production, PLC activation, and $[Ca^{2+}]_i$ mobilization (Okajima *et al.*, 1988; Törnquist, 1991a,b) via a P2Y receptor (Törnquist, 1992). ATP-induced changes in $[Ca^{2+}]_i$ in the rat FRT thyroid cell line are thought to function as a signal to enhance Ca^{2+} influx from extracellular stores via a P2 receptor-operated Ca^{2+} channel (Aloj *et al.*, 1993). Stimulation of PLC by ATP and other purine agonists was linked to G protein activation and therefore of the P2Y subtype of receptor (Okajima *et al.*, 1989). ATP directly stimulated adenylate cycles in pertussis toxin-treated cells although the receptor subtype was not identified (Sato *et al.*, 1992); in addition, ATP activated a Ca^{2+}-dependent Cl^- current and was thought to be acting on a novel nucleotide receptor type (Martin, 1992).

Table XXXIII summarizes the receptor subtypes present in the thyroid gland based on mRNA, protein, and pharmacological and biochemical profiles. The functions claimed for the receptors together with key references are included (cf. Table XXIV).

In summary, $P2Y_2$ receptor mRNA, protein, and functional receptors are prevalent on thyroid epithelial cells, although $P2Y_4$ and $P2Y_6$ receptors have also been identified. mRNA and protein for multiple P2X receptor subtypes are present.

4. Endocrine Pancreas

The effect of purine compounds, particularly ATP, on insulin secretion is well documented. As early as 1963, it was reported that ATP injected intravenously increased blood insulin activity in the rat (Candela and Garcia-Fernandez, 1963). This effect was later found to also occur when ATP was applied to the isolated perfused rat pancreas (Loubatières *et al.*, 1972; Loubatières-Mariani *et al.*, 1976, 1979; Sussman *et al.*, 1969) and hamster pancreas (Feldman and Jackson, 1974). ATP also stimulated secretion of

TABLE XXXIII

Thyroid[a]

Cellular component	Receptor mRNA		Receptor	Pharmacological and biochemical profile		Function	References
Follicle cells (cuboid epithelial cells)			$P2X_3$ (D) $P2X_4$ (D) $P2X_5$ (D)		$P2Y_2$ (G)	$P2Y_2$ R located on apical membrane mediate inhibition of Na^+ absorption	Bourke *et al.*, 1999[c] Glass and Burnstock, 2001[b]
Thyrocytes					$P2Y_2$ (H)	ATP and UTP increase $[Ca^{2+}]_i$	Schöfl *et al.*, 1995[c]
Cell lines							
FRTL-5 cells	$P2X_3$ (B) $P2X_4$ (B) $P2X_5$ (B)	$P2Y_2$ (B) $P2Y_4$ (B) $P2Y_6$ (B)		$P2X_5$ (H)	$P2Y_2$ (GH) $P2Y_4$ (G) $P2Y_6$ (G)	ATP increases $[Ca^{2+}]_i$ ATP stimulates cell proliferation ATP stimulates AA release ATP and UTP stimulate DNA synthesis	Bizzarri and Corda, 1994[d] Smallridge and Gist, 1994[c] Törnquist *et al.*, 1996[c] Vainio and Törnquist, 2000[c] Ekokoski *et al.*, 2000, 2001[c]
PC-C13 cells		$P2Y_2$ (B)			$P2Y_2$ (H)	ATP and UTP increase $[Ca^{2+}]_i$	Marsigliante *et al.*, 2002[c]
PC-E1 Araf cells		$P2Y_2$ (B)			$P2Y_2$ (H)	ATP and UTP increase $[Ca^{2+}]_i$	Elia *et al.*, 2003[c]
Thyroid vasculature	See Table XXV						

[a]See footnote *a* for Table III.
[b]References refer to P2X receptors.
[c]References refer to P2Y receptors.
[d]References refer to P2X and P2Y receptors.

both glucagon (Loubatières-Mariani *et al.*, 1976; Weir *et al.*, 1975) and somatostatin (Bertrand *et al.*, 1990) from the isolated pancreas, the secretion of insulin and glucagon being glucose dependent (Loubatières-Mariani *et al.*, 1976). It was found that ATP induced insulin release by stimulating P2 receptors on β cells (Bertrand *et al.*, 1987; Chapal and Loubatières-Mariani, 1981), identified as P2Y receptors (Bertrand *et al.*, 1989; Ribes *et al.*, 1988).

Within the pancreatic vascular system, ATP and other purine compounds are recognized as possessing vasoconstrictor activity. A P2 receptor was identified on the smooth muscle of the pancreatic vascular bed (Chapal and Loubatières-Mariani, 1983); later, the presence of a vasodilating P2Y receptor was also characterized (Hillaire-Buys *et al.*, 1991).

Table XXXIV summarizes the receptor subtypes present in the endocrine pancreas based on mRNA, protein, and pharmacological and biochemical profiles. The functions claimed for the receptors together with key references are included (cf. Table XXIV).

In summary, functional $P2Y_2$ receptors have been demonstrated on pancreatic epithelial cells, although $P2Y_1$ and $P2Y_4$ receptors have also been identified. Protein for P2X receptor of the $P2X_1$, $P2X_4$, and $P2X_7$ subtypes has been demonstrated.

5. Endocrine Ovary

Exogenous ATP partially inhibited the steroidogenic effect of luteinizing hormone (LH) on rabbit ovarian follicles. This effect was reversible (Losier *et al.*, 1980). ATP induced sedimentation of chick oviduct progesterone receptors (Moudgil *et al.*, 1985). Both ATP and NA are stored in small noradrenergic vesicles of the cat ovary, and the amount of each transmitter decreased after ovulation, following sympathetic discharge.

Table XXXV summarizes the receptor subtypes present in the endocrine ovary based on mRNA, protein, and pharmacological and biochemical profiles. The functions claimed for the receptors together with key references are included. For the endocrine function of the testis (Leydig cells), see Table XII.

In summary, granulosa-luteal cells express mRNA for $P2Y_2$ receptors and a functional $P2Y_2$ receptor has also been demonstrated. Granulosa cells have functional $P2Y_1$ and $P2Y_2$ receptors.

J. Musculoskeleletal System

1. Bone and Cartilage

Extracellular nucleotides elevated $[Ca^{2+}]_i$ in rat osteoblast-like cells and human osteoblasts (Kumagai *et al.*, 1989, 1991; Reimer and Dixon, 1992; Schöfl *et al.*, 1992). Studies on rat osteoblast-like cells revealed that at least

TABLE XXXIV
Endocrine Pancreas[a]

Cellular component	Receptor mRNA	Receptor protein		Pharmacological and biochemical profile		Function	References
Islets							
α cells (glucagon)		$P2X_7$ (D)	$P2Y_4$ (D)				Coutinho-Silva *et al.*, 2001a, 2003[d]
β cells (insulin)		$P2X_1$ (D)	$P2Y_2$ (D) $P2Y_4$ (D)	P2X (G)	P2Y (G)	ATP stimulates insulin release	Squires *et al.*, 1994[d] Petit *et al.*, 1998[d]
Nerves		$P2X_5$ (D)					Coutinho-Silva *et al.*, 2001a[b]
Cell lines							
CFPAC-1					$P2Y_2$ (G)	ATP and UTP increase $[Ca^{2+}]_i$	Galietta *et al.*, 1994[c]
Pancreatic blood vessels	See Table XXV						

[a]See footnote *a* for Table III.
[b]References refer to P2X receptors.
[c]References refer to P2Y receptors.
[d]References refer to P2X and P2Y receptors.

TABLE XXXV
Endocrine Ovary[a]

Cellular component	Receptor mRNA	Receptor protein	Pharmacological and biochemical profile	Function	References
Granulosa cells			$P2Y_1$ (H) $P2Y_2$ (H)	ATP increases $[Ca^{2+}]_i$ ATP and UTP antagonize estradiol and progesterone secretion	Kamada *et al.*, 1994[c] Morley *et al.*, 1994[c]
Granulosa-luteal cells	$P2Y_2$ (AB)		$P2Y_2$ (H)	ATP increases $[Ca^{2+}]_i$ ATP and UTP antagonize estradiol and progesterone secretion	Lee *et al.*, 1996b[c] Squires *et al.*, 1997[c] Tai *et al.*, 2000, 2001[c]

[a]See footnote *a* for Table III.
[c]References refer to P2Y receptors.

two P2 receptor subtypes were present (Reimer and Dixon, 1992; Yu and Ferrier, 1993a) with pharmacological profiles characteristic of $P2Y_1$ and $P2Y_2$ receptors. PGE_2 was claimed to be a potent mediator of ATP actions on osteoblast-like cells (Suzuki *et al.*, 1993). Evidence that rabbit osteoclasts respond to nucleotides by an induction of a $[Ca^{2+}]_i$ pulse was also presented (Yu and Ferrier, 1993b).

ATP hydrolyzing activity was recognized in calf cartilage (Kanabe *et al.*, 1983) and extracellular ATP stimulated resorption of bovine nasal cartilage (Leong *et al.*, 1990). Evidence was presented for the presence of P2 purinoceptors at the surface of human articular chondrocytes (Caswell *et al.*, 1991). Adult articular cartilage was shown to mineralize in the presence of ATP, suggesting a role for ATP in chondrocalcinosis (Ryan *et al.*, 1992) and both interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) enhanced the response of human articular chondrocytes to ATP (Caswell *et al.*, 1992; Leong *et al.*, 1993).

Table XXXVI summarizes the receptor subtypes present in bone based on mRNA, protein, and pharmacological and biochemical profiles. The functions claimed for the receptors together with key references are included (Fig. 8).

ATP was released from osteoblasts constitutively by real-time luciferin/luciferase chemiluminescence in the nanomolar range (Bowler *et al.*, 1998a; Buckley *et al.*, 2003; Dixon *et al.*, 1998) and shear and hypotonic stress and mechanical stimulation significantly increase ATP release (Bowler *et al.*, 1998a, 2001; Pines *et al.*, 2003; Romanello *et al.*, 2001). Similarly, continuous ATP release from chondrocytes in culture has been shown, which increases considerably with mechanical loading (Graff *et al.*, 2000, 2003).

In summary, mRNA for multiple P2X and P2Y receptor subtypes is expressed in osteoblasts, and protein for multiple P2X receptor subtypes has also been shown. Functional $P2X_7$, $P2Y_1$, and $P2Y_2$ receptors have been demonstrated. Osteoclasts exhibit a similar distribution of P2X and P2Y receptor mRNA and protein, although in addition, a functional $P2X_4$ receptor has been shown.

2. Skeletal Muscle

The effect of ATP on adult skeletal muscle was first described in an amphibian species. ATP released muscle contraction and sensitized the effect of ACh on the frog gastrocnemius muscle (Buchthal and Kolkow, 1944, 1948); this was later demonstrated on the isolated mammalian nerve-muscle preparation, where ATP potentiated the response to ACh at the nicotinic receptor (Akasu *et al.*, 1981; Ewald, 1976). This effect has also been observed in cultured *Xenopus* skeletal muscle cells (Igusa, 1988) and rat isolated skeletal muscle cells (Lu and Smith, 1991). The receptor subtype mediating the effect

TABLE XXXVI
Bone and Cartilage[a]

Cellular component	Receptor mRNA		Receptor protein	Pharmacological and biochemical profile		Function	References
Osteoblasts							
Neonatal bone		$P2Y_2$ (C)	$P2X_5$ (D)				Jones *et al.*, 1997[c]
Cultured neonatal bone	$P2X_2$ (C) $P2X_4$ (C) $P2X_7$ (B)	$P2Y_1$ (C) $P2Y_2$ (C)		$P2X_7$ (G)	$P2Y_1$ (G) $P2Y_2$ (G)	ATP and UTP inhibit bone nodule formation via $P2Y_2$ R ADP via $P2Y_1$ R stimulates osteoclast formation	Hoebertz *et al.*, 2000[d] Hoebertz *et al.*, 2000, 2001, 2002, 2003[d] Ke *et al.*, 2003[b]
Cultured adult bone	$P2X_2$ (C) $P2X_4$ (C) $P2X_7$ (B)	$P2Y_1$ (B) $P2Y_2$ (BC)	$P2X_2$ (D) $P2X_4$ (D) $P2X_5$ (D) $P2X_2$ (DE) $P2X_4$ (D) $P2X_5$ (D) $P2X_7$ (D)	$P2X_7$ (I)	$P2Y_1$ (H) $P2Y_2$ (H)	ATP and UTP increase $[Ca^{2+}]_i$ High concentrations of ATP cause cell death ATP increases $[Ca^{2+}]_i$	Bowler *et al.*, 1999[c] Dixon *et al.*, 1997a[c] Gartland *et al.*, 2001[b] Nam *et al.*, 2002[e]
Osteoblastic cell lines							
MG-63 cells	$P2X_4$ (B) $P2X_5$ (B) $P2X_6$ (B) $P2X_7$ (B)	$P2Y_1$ (B) $P2Y_2$ (B) $P2Y_4$ (B) $P2Y_6$ (B) $P2Y_7$ (B)		P2X (H)	P2Y (H)	ATP increases proliferation via $P2X_5$ R ATP increases DNA synthesis and enhances resorption effects of growth factors via P2X R	Nakamura *et al.*, 2000[b] Maier *et al.*, 1997[c]
OHS-4 cells		$P2Y_1$ (B) $P2Y_2$ (B) $P2Y_4$ (B) $P2Y_6$ (B) $P2Y_7$ (B)					Maier *et al.*, 1997[c]

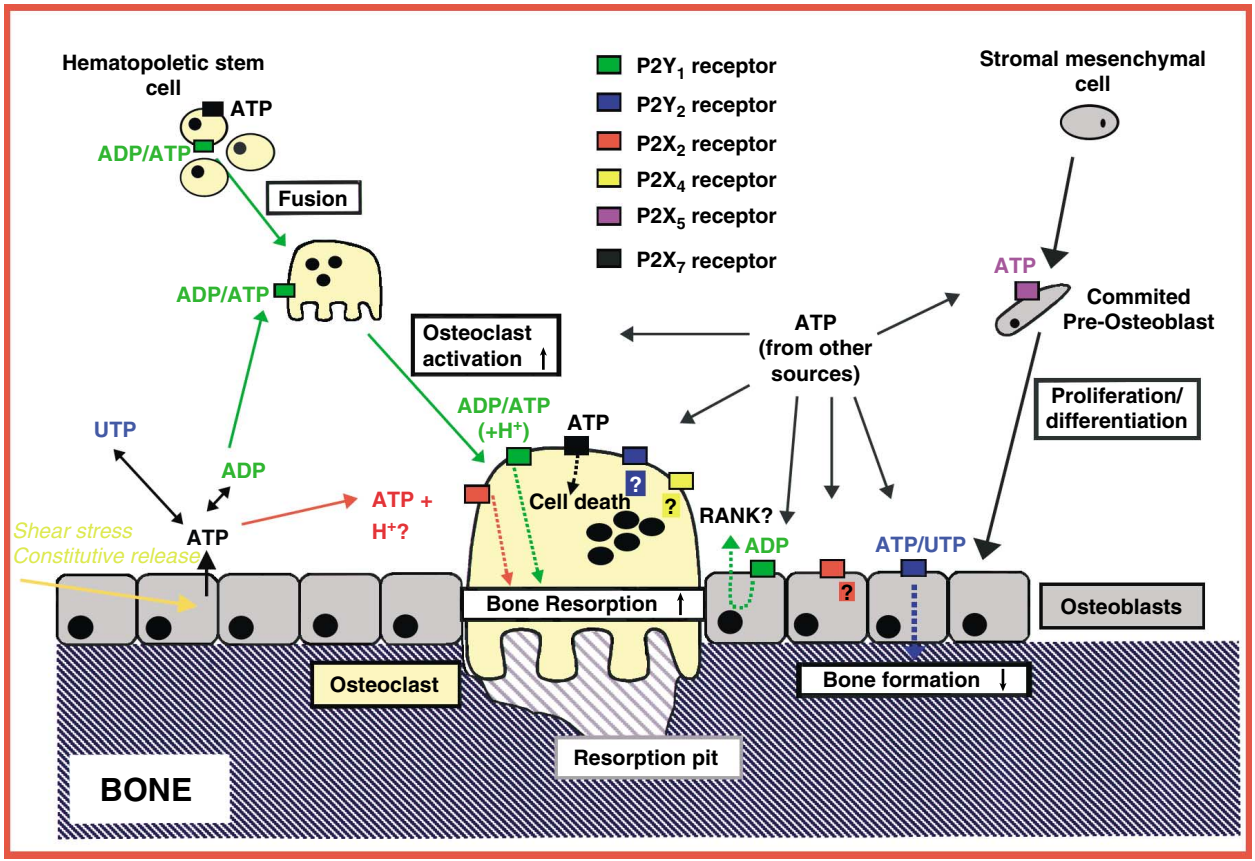
(*continued*)

TABLE XXXVI (*continued*)

Cellular component	Receptor mRNA		Receptor protein		Pharmacological and biochemical profile		Function	References
MC3T3-E1 cells						$P2Y_2$ (H)	ATP increases $[Ca^{2+}]_i$ ATP (probably via adenosine) acts as a mitogen ATP activates PLD and release of AA and synthesis of PGE_2	Suzuki *et al.*, 1995a[c] Shimegi, 1996[c] Watanabe-Tomita *et al.*, 1997[c] You *et al.*, 2002[c]
HOBIT cells		$P2Y_1$ (B) $P2Y_2$ (B)					ATP increases $[Ca^{2+}]_i$ ATP increases Egr-1 protein levels	Pines *et al.*, 2003[c]
Osteoclasts								
Neonatal bone	$P2X_2$ (C)		$P2X_2$ (D)					Hoebertz *et al.*, 2000[b]
Cultured neonatal bone	$P2X_2$ (C) $P2X_4$ (BC)	$P2Y_2$ (C) $P2Y_2$ (C)	$P2X_2$ (D) $P2X_4$ (D) $P2X_7$ (D)	$P2Y_1$ (D)	$P2X_4$ (GH) $P2X_7$ (GHI)	$P2Y_1$ (G) $P2Y_2$ (GH)	ATP stimulates resorption pit formation ATP increases osteoclast activity via $P2X_2$ R ATP via $P2X_7$ R inhibits bone resorption ATP regulates acid transport ATP produces a transient decrease in intracellular pH ATP increases intercellular communication	Modderman *et al.*, 1994[b] Yu and Ferrier, 1995[e] Weidema *et al.*, 1997, 2001[d] Morrison *et al.*, 1998[b] Naemsch *et al.*, 1999, 2001[b] Wiebe *et al.*, 1999[d] Hoebertz *et al.*, 2000, 2001, 2003[d] Ke *et al.*, 2003[b]

Cultured adult bone	$P2X_7$ (B)	$P2Y_1$ (B) $P2Y_2$ (B)	$P2X_1$ (B) $P2X_5$ (B) $P2X_6$ (B)	$P2Y_1$ (B) $P2Y_4$ (B) $P2Y_6$ (B) $P2Y_{11}$ (B)	$P2X_7$ (HI)	$P2Y_1$ (H)	ATP via P2Y R increases $[Ca^{2+}]_i$ Intercellular Ca^{2+} signaling between osteoclasts and osteoblasts requires activation of $P2X_7$ R	Bowler *et al.*, 1995[c] Jørgensen *et al.*, 1997,[c] 2002[b] Buckley *et al.*, 2002[d]
Cartilage chondrocytes								
Embryonic	$P2X_2$ (C)	$P2Y_1$ (C)	$P2X_5$ (D)			$P2Y_1$ (H)	ADP increases $[Ca^{2+}]_i$	Hung *et al.*, 1997[c]
Neonatal		$P2Y_2$ (C)	$P2X_2$ (D) $P2X_5$ (D)			$P2Y_2$ (H) or $P2Y_4$ (H)	ATP and UTP increase $[Ca^{2+}]_i$ ATP enhances basic fibroblast growth factor-induced proliferation	Bulman *et al.*, 1995[c] Kaplan *et al.*, 1996[c] Hoebertz *et al.*, 2000, 2001[d]
Adult		$P2Y_2$ (B)				$P2Y_2$ (GH)	ATP and UTP increase IL-1-mediated PGE_2 release ATP and UTP increase $[Ca^{2+}]_i$	Koolpe and Benton, 1997[c] Koolpe *et al.*, 1999[e] Elfervig *et al.*, 2001[c]
Cultured chondrocytes		$P2Y_2$ (B)				P2Y (I) $P2Y_2$ (G)	ATP stimulates cartilage resorption and PGE_2 production	Leong *et al.*, 1994[c] Berenbaum *et al.*, 2003[c]

[a]See footnote *a* for Table III.
[b]References refer to P2X receptors.
[c]References refer to P2Y receptors.
[d]References refer to P2X and P2Y receptors.
[e]References refer to uncharacterized P2 receptors.


Hematopoletic stem cell
ATP
ADP/ATP
Fusion
ADP/ATP
P2Y1 receptor
P2Y2 receptor
P2X2 receptor
P2X4 receptor
P2X5 receptor
P2X7 receptor
Stromal mesenchymal cell
ATP
Commited Pre-Osteoblast
Osteoclast activation
ATP (from other sources)
Proliferation/ differentiation
UTP
ADP
ADP/ATP (+H+)
ATP
Cell death
?
?
ATP + H+?
Shear stress
Constitutive release
ATP
RANK?
ADP
ATP/UTP
?
Bone Resorption
Osteoblasts
Osteoclast
Bone formation
Resorption pit
BONE

of ATP on mature mammalian skeletal muscle cells myotubes has been investigated using cultured mouse myotubes (C2C12 cells) and has been identified as a nucleotide receptor (Henning *et al.*, 1992, 1993).

At developing *Xenopus* neuromuscular synapses, ATP potentiated spontaneous ACh release, possibly acting as a trophic factor (Fu and Poo, 1991), since α,β-meATP had a similar action; the effect is probably via a P2X receptor subtype (Fu *et al.*, 1993). On cultured embryonic chick myoblasts and myotubes, ATP has transmitter-like actions (Häggblad *et al.*, 1985; Kolb and Wakelam, 1983); the receptor subtype was not identified, although it was reported that α,β-meATP and β,γ-meATP were ineffective (Hume and Honig, 1986). Further studies revealed that ATP stimulated IP_3 accumulation and activated a PLC-coupled G protein (Häggblad and Heilbronn, 1987, 1988) indicating that the receptor belonged to the P2Y family of receptors. The presence of multiple P2 receptors on developing chick skeletal muscle cells was proposed since the presence of cation channels activated by ATP has been reported (Hume and Thomas, 1988; Thomas and Hume, 1990a); since the response to ATP was found to desensitize, it can be surmised that the receptor is either a $P2X_1$ or $P2X_3$ subtype (Thomas and Hume, 1990b; Thomas *et al.*, 1991).

Another action of ATP on skeletal muscle is its role in the regulation of sugar transport. ATP regulates the availability of sugar to the metabolic needs of the cell, although the possibility that ATP may be involved in the mechanism whereby insulin modulates muscle sugar transport was not discounted (Yu and Gould, 1978).

FIG. 8 Schematic diagram illustrating the potential roles played by extracellular nucleotides and P2 receptors in modulating bone cell function. ATP, released from osteoclasts (e.g., through shear stress or constitutively) or from other sources, can be degraded to ADP or converted into UTP via ectonucleotidases. All three nucleotides can act separately on specific P2 receptor subtypes, as indicated by the color coding. ATP is a universal agonist, whereas UTP is active only at the $P2Y_2$ receptor and ADP is active only at the $P2Y_1$ receptor. ADP via $P2Y_1$ receptors appears to stimulate both the formation (i.e., fusion) of osteoclasts from hematopoietic precursors and the resorptive activity of mature osteoclasts. For the latter, a synergistic action of ATP and protons has been proposed via the $P2X_2$ receptor. ADP could also stimulate resorption indirectly through actions on osteoclasts, which in turn release proresorptive factors (e.g., receptor activator of nuclear factor κB ligand [RANKL]). ATP at high concentrations might facilitate fusion of osteoclast progenitors through $P2X_7$ receptor pore formation or induce cell death of mature osteoclasts via $P2X_7$ receptors. In osteoblasts, ATP, via $P2X_5$ receptors, might enhance proliferation and/or differentiation. By contrast, UTP, via $P2Y_2$ receptors, is a strong inhibitor of bone formation by osteoblasts. For some receptors (e.g., $P2X_4$ and $P2Y_2$ receptors on osteoclasts or $P2X_2$ receptors on osteoblasts) evidence for expression has been found but their role is still unclear (question marks). Dashed lines indicate signaling events in the cell. (Reproduced with permission from Hoebertz *et al.*, 2003.)

Table XXXVII summarizes the receptor subtypes present in skeletal muscle based on mRNA, protein, and pharmacological and biochemical profiles. The functions claimed for the receptors together with key references are included (cf. Table XXIV).

ATP is released from mammalian motor nerve terminals, such as the rat diaphragm (Santos *et al.*, 2003; Silinsky, 1975; Silinsky and Hubbard, 1973) and extensor digitorum (Smith, 1991). ATP release has been demonstrated in amphibian innervated skeletal muscle (Cunha and Sebastião, 1993; Redman and Silinsky, 1994), where ATP is released synchronously with ACh in response to individual nerve impulses (Silinsky and Redman, 1996; Silinsky *et al.*, 1999). ATP release from *Torpedo* electromotor synapses has been demonstrated (Morel and Meunier, 1981; Zimmermann, 1978). Under normal physiological conditions, the concentration of ATP in the synaptic cleft could be approximately 0.1–1 m*M*, sufficient to induce near maximal effects on P2 receptors in *in vivo* preparations (Henning, 1997; Tsim and Barnard, 2002).

In summary, mRNA and protein for multiple P2X receptor subtypes have been demonstrated for skeletal muscle; the functional receptor has not been characterized for developing and young animals, but for adults, $P2X_1$, $P2X_3$, and $P2X_5$ receptors have been described. mRNA for $P2Y_1$ receptors has been shown in developing skeletal muscle whereas in the adult mRNA for $P2Y_2$ receptors is expressed. This receptor has not been fully characterized functionally as yet. Neuromuscular junctions express mRNA, protein, and functional $P2Y_1$ receptors, in addition to protein and functional $P2X_7$ receptors.

K. Skin

When applied to, or injected intradermally, ATP, ADP, and adenosine all induce intense pain in humans by stimulating sensory nerve endings in the skin (Bleehen *et al.*, 1976; Coutts *et al.*, 1981). Animal studies showed a similar action of ATP, activating nociceptors (Bean, 1990; Bleehen, 1978; Krishtal *et al.*, 1983). ATP injected intracutaneously into the abdomen of rats induced an inflammatory response (Arvier *et al.*, 1977; Chahl, 1977).

Table XXXVIII summarizes the receptor subtypes present in skin based on mRNA, protein, and pharmacological and biochemical profiles. The functions claimed for the receptors together with key references are included (cf. Tables XXIV and LI; see Fig. 9).

ATP is released from skin cells following damage (Cook and McCleskey, 2002), which then stimulates nociceptors to initiate pain.

In summary, mammalian keratinocytes express mRNA and protein for $P2Y_1$ and $P2Y_2$ receptors, and both receptors have been identified

TABLE XXXVII

Skeletal Muscle[a]

Cellular component	Receptor mRNA	Receptor protein	Pharmacological and biochemical profile	Function	References
Early development					
Mammalian		$P2X_2$ (D) $P2X_5$ (D) $P2X_6$ (D) $P2X_7$ (D)	P2X (H)	ATP increases $[Ca^{2+}]_i$	Parson *et al.*, 2000[b] Ryten *et al.*, 2001[b] Collet *et al.*, 2002[b]
Avian	$P2X_1$ (A) $P2Y_1$ (AC) $P2X_4$ (AC) $P2X_5$ (AC) $P2X_6$ (AB)	$P2X_5$ (D) $P2X_6$ (D)			Meyer *et al.*, 1999a[b], 1999b[c] Bo *et al.*, 2000[b] Soto *et al.*, 2003[b]
Amphibian			P2X (G) P2Y (G)	ATP potentiates ACh responses ATP modulates motor pattern generation	Fu, 1994[b] Fu and Huang, 1994[b] Lu and Fu, 1995[b] Dale and Gilday, 1996[c]
Adult					
Mammalian	$P2X_1$ (A) $P2Y_2$ (B) $P2X_5$ (B) P2XM (A)	$P2X_2$ $P2X_5$ (D) $P2X_7$ (D)	$P2X_1$ (GH) $P2X_3$ (G) $P2X_5$ (H)	ATP increases ACh channel opening frequency ATP inhibits proliferation and stimulates differentiation via $P2X_5$ R ATP increases rate of myotube formation ATP increases $[Ca^{2+}]_i$ ATP stimulates the exercise pressor reflex via $P2X_3$ R	Brake *et al.*, 1994[b] Ayyanathan *et al.*, 1996[b] Henning, 1997[b] Urano *et al.*, 1997[b] Betto *et al.*, 1999[b] Csernoch *et al.*, 2000a[b] Parson *et al.*, 2000[b] Zambon *et al.*, 2000[c] Cseri *et al.*, 2002[b] Ryten *et al.*, 2002[b] Hanna and Kaufman, 2003[b]
Amphibian			P2X (G)	ATP inhibits ACh release	Giniatullin and Sokolova, 1998[b] Camacho and Sanchez, 2002[b]

(*continued*)

TABLE XXXVII (*continued*)

Cellular component	Receptor mRNA	Receptor protein		Pharmacological and biochemical profile		Function	References
Myotube cell lines							
C2C12 cells					$P2Y_2$ (GH)	ATP and UTP increase $[Ca^{2+}]_i$ ATP stimulates glucose uptake	Henning *et al.*, 1996[c] Kim *et al.*, 2002b[c]
Skeletal NMJ							
Mammalian	$P2Y_1$ (A)	$P2X_7$ (D)	$P2Y_1$ (D)		$P2Y_1$ (GH)	ATP upregulates ACh R expression ATP inhibits ACh release	Choi *et al.*, 2001, 2003b[c] Deuchars *et al.*, 2001[b] Galkin *et al.*, 2001[c] Tsim and Barnard, 2002[c]
Avian	$P2Y_1$ (A)		$P2Y_1$ (D)		$P2Y_1$ (GH)	ATP upregulates ACh R expression	Sugiura and Ko, 2000[c] Choi *et al.*, 2001, 2003b[c]
Amphibian			$P2Y_1$ (D)			ATP inhibits evoked ACh release	Choi *et al.*, 2001[c]
Motor nerve terminals							
Mammalian		$P2X_7$ (D)		$P2X_7$ (G)		ATP stimulates exocytosis of synaptic vesicles ATP facilitates ACh release	Parson and Iqbal, 2000[b] Parson *et al.*, 2000, 2002[b] Salgado *et al.*, 2000[b] Deuchars *et al.*, 2001[b]
Skeletal muscle vasculature	See Table XXIV						

[a]See footnote *a* for Table III.
[b]References refer to P2X receptors.
[c]References refer to P2Y receptors.

TABLE XXXVIII
Skin[a]

Cellular component	Receptor mRNA	Receptor protein	Pharmacological and biochemical profile	Function	References
Keratinocytes in stratified epithelium	$P2Y_1$ (B) $P2Y_2$ (BC) $P2Y_4$ (B) $P2Y_6$ (B)	$P2X_5$ (D) $P2Y_1$ (D) $P2X_7$ (D) $P2Y_2$ (D)	$P2Y_1$ (G) $P2Y_2$ (G) $P2Y_4$ (G)	$P2X_5$ R mediate differentiation $P2X_7$ R mediate cell death $P2Y_1/P2Y_2$ R mediate basal cell proliferation	Dixon *et al.*, 1999[c] Gröschel-Stewart *et al.*, 1999a[b] Burrell *et al.*, 2003[c] Greig *et al.*, 2003a[d]
Amphibian skin epithelium	P2X (B)		P2X (GH) $P2Y_1$ (G) $P2Y_2$ (H) or $P2Y_4$ (H)	ATP and UTP increase $[Ca^{2+}]_i$ ATP induced a fast transient decrease in short circuit current	Brodin and Nielsen, 2000a,[b] 2000b[c] Holbird *et al.*, 2001[b] Jensik *et al.*, 2001[d]
Hair follicle Merkel cells		$P2Y_2$ (D)			Tachibana *et al.*, 2003[c]
Cell lines HaCaT			P2 (H)	ATP increases $[Ca^{2+}]_i$	Csernoch *et al.*, 2000b[e]
Sweat glands	See Table XXIX				
Sensory nerves	See Table XLV				
Cancer cells	See Table LI				
Vasculature	See Table XXIV				

[a]See footnote *a* for Table III.
[b]References refer to P2X receptors.
[c]References refer to P2Y receptors.
[d]References refer to P2X and P2Y receptors.
[e]References refer to uncharacterized P2 receptors.

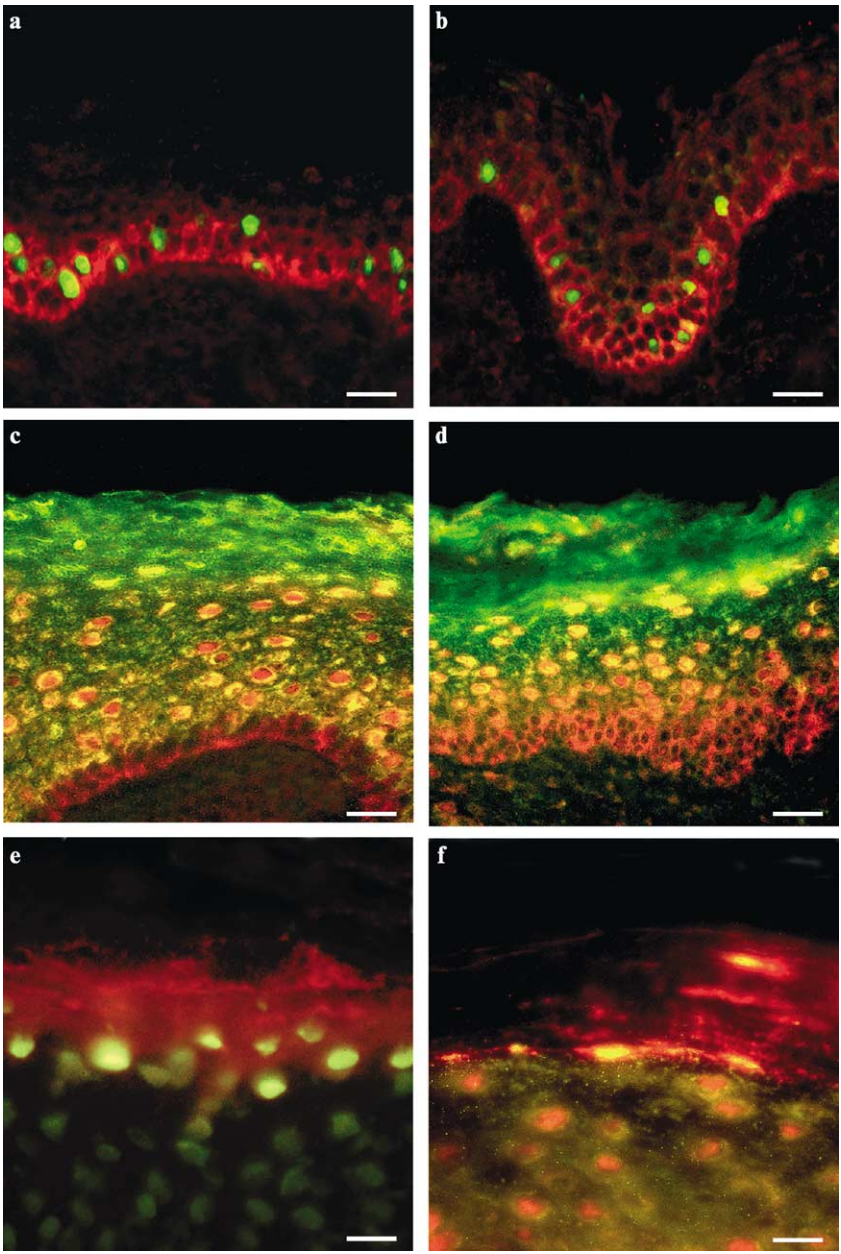


FIG. 9 Double labeling of $P2Y_1$ and $P2Y_2$ receptors with markers of proliferation shows colocalization within a subpopulation of basal and parabasal keratinocytes. Double labeling of $P2X_5$ receptors with markers of differentiated keratinocytes shows colocalization within the stratum spinosum, and double labeling of $P2X_7$ receptors with markers of apoptosis in human

functionally. In addition, protein for $P2X_5$ and $P2X_7$ receptors has been shown and a functional $P2Y_4$ receptor identified. Amphibian skin epithelium expresses mRNA and a functional uncharacterized P2X receptor; in addition, functional $P2Y_1$, $P2Y_2$, or $P2Y_4$ receptors have been characterized.

L. Connective Tissue

1. Fibroblasts

There were early reports of the effects of ATP on membrane permeability of a transformed mouse fibroblast cell (Swiss mouse 3T6 cells) (De and Weisman, 1984; Kitagawa and Akamatsu, 1982; Roselino *et al.*, 1980; Rozengurt *et al.*, 1977; Weisman *et al.*, 1984). The effect of ATP on the production of cAMP in the cultured fibroblasts line (LM cells) was reported (Westcott *et al.*, 1979) and on electrical membrane responses of cultured mouse L cells (Okada *et al.*, 1984). A later study showed that ATP caused contraction of human dermal (Ehrlich *et al.*, 1986) and rabbit ocular fibroblasts (Joseph *et al.*,

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leg skin shows colocalization within the stratum corneum. (a) Ki-67 immunolabeling (a marker for proliferation) stained the nuclei (green) of a subpopulation of keratinocytes in the basal and parabasal layers of the epidermis. $P2Y_1$ receptor immunostaining (red) was found in the basal layer on cells also staining for Ki-67. Scale bar: 30 μm. (b) PCNA immunolabeling (a marker for proliferation) stained the nuclei (green) of a subpopulation of keratinocytes. These nuclei were often distributed in clusters and found in the basal and parabasal layers of the epidermis. $P2Y_2$ receptor immunostaining (red) was also expressed in basal and parabasal epidermal cells. Scale bar: 30 μm. (c) $P2X_5$ receptor immunostaining (red) showed overlap (yellow) with cytokeratin K10 (green), an early marker of keratinocyte differentiation. $P2X_5$ receptors were present in the basal layer of the epidermis up to the mid-granular layer. Cytokeratin K10 was distributed in most suprabasal keratinocytes. The stratum basale stained only for $P2X_5$ receptors, indicating that no differentiation was taking place in these cells. The colocalization of $P2X_5$ receptors and cytokeratin K10 appeared mainly in the cytoplasm of differentiating cells within the stratum spinosum and partly in the stratum granulosum. Note that the stratum corneum also stained for cytokeratin K10, which labeled differentiated keratinocytes, even in dying cells. Scale bar: 30 μm. (d) $P2X_5$ receptor immunostaining (red) showed overlap (yellow) with involucrin (green). $P2X_5$ receptors were present in the basal layer of the epidermis up to the mid-granular layer. Note that the pattern of staining with involucrin was similar to that seen with cytokeratin K10, except that cells from the stratum basale up to the mid-stratum spinosum were not labeled with involucrin, which is a late marker of keratinocyte differentiation. Scale bar: 30 μm. (e) TUNEL (green) labeled the nuclei of cells at the uppermost level of the stratum granulosum and $P2X_7$ antibody (red) mainly stained cell fragments within the stratum corneum. Scale bar: 15 μm. (f) Anti-caspase-3 (green) colocalized with areas of $P2X_7$ receptor immunostaining (red) both at the junction of the stratum granulosum and within the stratum corneum. Areas of colocalization are yellow. Note that the differentiating keratinocytes in the upper stratum granulosum were also positive for anti-caspase-3. Scale bar: 15 μm. (Reproduced, with permission, from Greig *et al.*, 2003a.)

1988). There was a study that hinted at the involvement of $P2Y_2$ or $P2Y_4$ receptors, since it was shown that ATP and UTP were equipotent in mobilizing Ca^{2+} in human fibroblasts grown from forearm skin biopsies (Fine *et al.*, 1989) and two distinct P2 receptors for ATP were proposed for Swiss 3T6 mouse fibroblasts (Gonzalez *et al.*, 1989). Untransformed 3T3 cells and mouse embryo fibroblasts were reported not to respond to ATP (Kitagawa *et al.*, 1988), while long-term exposure of transformed 3T6 cells to ATP resulted in redifferentiation and reduction in tumorigenicity (Belzer and Friedberg, 1989). ATP was shown to be a mitogen for 3T3 and 3T6 cells and to act synergistically with other growth factors (Huang *et al.*, 1989). This was reported to be mediated by a P2Y receptor (Gonzalez *et al.*, 1990). There was a hint that $P2X_7$ receptors may be present on fibroblasts, where Bz-ATP and high concentrations of ATP were shown to induce an increase in permeability of large molecules in transformed 3T6 cells (Erb *et al.*, 1990; Saribas *et al.*, 1993). The presence of P2Y receptors in normal NIH 3T3 cells and in NIH 3T3 cells overexpressing c-*ras* was proposed (Giovannardi *et al.*, 1992). P2Y-mediated stimulation of mitogenesis was shown to involve induction of prostaglandin synthesis (Huang *et al.*, 1991). ATP was shown to stimulate aged human lung fibroblasts via suppression of arachidonate metabolism (Huang *et al.*, 1993b).

Table XXXIX summarizes the receptor subtypes present in fibroblasts based on mRNA, protein, and pharmacological and biochemical profiles. The functions claimed for the receptors together with key references are included.

Mouse fibroblast cells (L929) responded to the physical stress of saline movement over the cells by an increase in $[Ca^{2+}]_i$ that could be reduced by apyrase. It was suggested that this was due to the autocrine release of ATP into the extracellular medium in a manner similar to the release of ATP from vascular endothelial cells undergoing shear stress (Grierson and Meldolesi, 1995). There is also evidence that hypoxia can induce ATP release from bovine lung adventitial fibroblasts, which is then involved in the regulation of DNA synthesis (Gerasimovskaya *et al.*, 2002; Stenmark *et al.*, 2002).

In summary, mRNA, protein, and functional $P2X_7$ receptors have been demonstrated in human fibroblasts; in addition, mRNA and functional $P2Y_1$ and $P2Y_2$ receptors have been shown.

2. Adipose Tissue

In 1974, Chang and Cuatrecasas reported that ATP induced a 5-fold increase in the apparent affinity of fat cells for glucose. In contrast, further studies suggested that ATP decreased insulin-stimulated glucose transport (Halperin *et al.*, 1978; Loten *et al.*, 1976). This effect was found to occur when ATP was administered *in vivo* (Filkins, 1978). It was hypothesized that ATP inhibited

TABLE XXXIX
Fibroblasts[a]

Cellular component	Receptor mRNA	Receptor protein	Pharmacological and biochemical profile		Function	References
Human fibroblast	$P2X_7$ (B)	$P2X_7$ (DE)	$P2X_7$ (HI)		ATP increases $[Ca^{2+}]_i$ via P2X R ATP R participate in the pathogenesis of vascular complications of diabetes	Tepel *et al.*, 1996[b] Solini *et al.*, 2000[b]
Immortalized human fibroblasts				P2Y (G)	ATP inhibits proliferation	Katayama *et al.*, 1998[c] Li *et al.*, 2000d[c]
Bovine pulmonary artery adventitial fibroblasts			P2X (G)	P2Y (G)	ATP induces proliferation	Gerasimovskaya *et al.*, 2002[d] Stenmark *et al.*, 2002[c]
Neonatal rat cardiac fibroblasts	$P2Y_1$ (A) $P2Y_2$ (A)			$P2Y_1$ (G) $P2Y_2$ (G)	P2Y R mediate activation of c-*fos* and inhibit DNA synthesis	Zheng *et al.*, 1998[c]
Mouse cell lines						
Transformed 3T3 cells			$P2X_7$ (I)		ATP increases cell permeability	Arav and Friedberg, 1996[b]
L929 and LM TK cells				$P2Y_2$ (H)	ATP (released by shear stress) produces Ca^{2+} oscillations ATP activates volume-regulated Cl^- currents	Grierson and Meldolesi, 1995[c] Davis *et al.*, 1999[c] Bryan-Sisneros *et al.*, 2000[c]
Hamster cell lines						
BHK-21 cells				P2Y (H)	ATP regulates $[Ca^{2+}]_i$ stores	Hofer *et al.*, 1996[c]

[a]See footnote *a* for Table III.
[b]References refer to P2X receptors.
[c]References refer to P2Y receptors.
[d]References refer to P2X and P2Y receptors.

insulin-stimulated glucose oxidation in fat cells (Hashimoto *et al.*, 1987; Tamura *et al.*, 1983), although the receptor type responsible for this effect was not characterized.

Table XL summarizes the receptor subtypes present in adipose tissue based on mRNA, protein, and pharmacological and biochemical profiles. The functions claimed for the receptors together with key references are included.

Human fat cells accumulate adenosine, which in itself has an effect on cellular metabolism. The source of the adenosine is thought to be almost exclusively from adenine nucleotides, released by leaking cells (Kather, 1988).

In summary, brown adipocytes express mRNA for multiple P2X and P2Y receptors and functional $P2Y_1$ and $P2Y_2$ or $P2Y_4$ receptors have been demonstrated in addition to an uncharacterized P2X receptor. An uncharacterized functional P2Y receptor is as yet all that has been demonstrated in white adipocytes.

M. Nervous System and Glial Cells

1. Central Nervous System

In the first study of the effects of ATP on neurons receiving direct synaptic input from primary afferents, neurons of the cuneate nucleus of the corticospinal tract were excited (Galindo *et al.*, 1967; Stone and Perkins, 1981; Stone and Taylor, 1978). Later studies showed ATP actions on cerebral cortical neurons (Phillis *et al.*, 1974, 1979), area postrema (Borison *et al.*, 1975), hippocampus (Di Cori and Henry, 1984; Inoue *et al.*, 1991, 1992; Lee *et al.*, 1981; Wieraszko and Seyfried, 1989a), trigeminal nucleus caudalis of the dorsal horn of the spinal cord (Salt and Hill, 1983), the spinal dorsal horn (Fyffe and Perl, 1984; Salter and Henry, 1985), lateral and medial vestibular nuclei (Mori *et al.*, 1985), mesenchephalic trigeminal neurons (Regenold *et al.*, 1988), medium eminence (Barnea *et al.*, 1991), and locus coeruleus (Harms *et al.*, 1992; Shen and North, 1993; Tschopl *et al.*, 1992). ATP depolarized terminals of primary afferent fibers within toad spinal cord (Phillis and Kirkpatrick, 1978). Jahr and Jessell (1983) showed that ATP has postsynaptic effects on 27% of cultured rat dorsal horn neurons; subsequently, whole-cell voltage-clamp experiments showed that ATP evoked conductance for both Na^{2+} and K^+ ions, activating nonspecific cationic currents anticipating that P2X receptors were involved (Jessell and Jahr, 1985).

The inhibitory component of the actions of ATP on spinal neurons was later shown to be due to adenosine, following ectoenzymatic breakdown of

TABLE XL
Adipose Tissue[a]

Cellular component	Receptor mRNA	Receptor protein	Pharmacological and biochemical profile	Function	References
White adipocytes			P2Y (G)	ATP increases cell membrane capacitance ATP stimulates lipogenesis	Lee and Pappone, 1997a[c]
Brown adipocytes	$P2X_1$ (B) $P2Y_1$ (B) $P2X_3$ (B) $P2Y_2$ (B) $P2X_4$ (B) $P2Y_4$ (B) $P2X_5$ (B) $P2Y_6$ (B) $P2X_7$ (B)		P2X (G) $P2Y_1$ (GH) $P2Y_2$ (GH) or $P2Y_4$ (GH)	ATP regulates exocytosis, secretion, growth, and development	Pappone and Lee, 1996[c] Lee and Pappone, 1997b, 1999[c] Omatsu-Kanbe and Matsuura, 1999[c] Wilson and Pappone, 1999[c] Omatsu-Kanbe *et al.*, 2002[d]
Preadipocytes			P2 (G) P2X (G)	ATP induces estrogen synthesis ATP promotes proliferation	Schmidt and Löffler, 1998[b] Wilson *et al.*, 1999b[e]
Adipose plasma membranes			P2Y (G)		Yegutkin and Burnstock, 1999[c]

[a]See footnote *a* for Table III.
[b]References refer to P2X receptors.
[c]References refer to P2Y receptors.
[d]References refer to P2X and P2Y receptors.
[e]References refer to uncharacterized P2 receptors.

ATP (Li and Perl, 1991; Phillis *et al.*, 1979). In anesthetized rats, inophoretic application of ATP excited the spinal cord-projection neurons in the rostral ventrolateral reticular nucleus of the medulla oblongata; the response was mimicked by α,β-meATP and blocked by suramin (Sun *et al.*, 1992).

Identification of ATP as a neurotransmitter in the CNS was first proposed by Wieraszko and Seyfried (1990) for the hippocampus and later evidence was presented for purinergic synaptic transmission in the medial habenula (Edwards *et al.*, 1992), although *in vivo* release of adenosine from cat basal ganglia was originally thought to support the existence of purinergic nerves in the brain (Barberis *et al.*, 1984).

ATP-gated currents were described in dissociated rat nucleus tractus solitarus (NTS) (Ueno *et al.*, 1992). Selective *in vivo* activation of P2 receptors in the NTS was shown to elicit distinct cardiorespiratory response patterns (Barraco *et al.*, 1993). Antidiuretic effects of ATP injected into the hypothalamic paraventricular nucleus were described (Mori *et al.*, 1992) as well as a regulatory role for ATP in the secretion of vasopressin (Day *et al.*, 1993). Isolated hypothalamic granules were shown to release luteinizing hormone-releasing hormone (LHRH) in response to ATP (Burrows and Barnea, 1982). ATP facilitated copper uptake and stimulation of the release of LHRH from the medium eminence of the hypothalamus (Barnea *et al.*, 1991). In the suprachiasmatic nucleus ATP induced long-term communication between glial cells, probably via gap junctions (van den Pol *et al.*, 1992).

Table XLI summarizes the receptor subtypes present in the CNS based on mRNA, protein, and pharmacological and biochemical profiles. The functions claimed for the receptors together with key references are included (cf. Tables XXIV and XLVI).

ATP release was demonstrated from electrically stimulated synaptosomes prepared from guinea pig cerebral cortex (Kuroda and McIlwain, 1974; Pull and McIlwain, 1972; Salgado *et al.*, 1996), at sensorimotor cortex (Sulakhe and Phillis, 1975) and rat hypothalamus (Fredholm *et al.*, 1983). Release of ATP from cat dorsal and ventral spinal cord synaptosomes (Sawynok *et al.*, 1993; White *et al.*, 1985a), dendrites on cat spinal motoneurons (Schubert and Kreutzberg, 1975), and cultured mice neostriatal neurons (Zhang *et al.*, 1988) was also demonstrated. 5′-Nucleotidase has been localized in the substantia gelatinosa (Nagy and Daddona, 1985; Suran, 1974). Various studies have determined whether ATP was released from hippocampal slices by field stimulation and then broken down extracellularly to adenosine or whether adenosine was released per se (Cunha *et al.*, 1996, 1998; Dunwiddie *et al.*, 1997; Jonzon and Fredholm, 1985; Terrian *et al.*, 1989; Wieraszko *et al.*, 1989b). ATP release occurred as a result of electrical or K^+-induced depolarization from cerebral tissues (Phillis and O'Regan, 2003), and trigeminal mesencephalic motor nucleus neurons (Khakh and Henderson, 1998), in

TABLE XLI

Central Nervous System[a]

Cellular component	Receptor mRNA	Receptor protein	Pharmacological and biochemical profile		Function	References
Spinal cord						
Spinal cord slices (mostly dorsal horn)	$P2X_2$ (B) $P2X_4$ (B) $P2X_6$ (B) $P2X_7$ (B)	$P2X_1$ (F) $P2X_2$ (D) $P2X_3$ (D) $P2X_4$ (D)	$P2X_{2/3}$ (G) $P2X_{1/5}$? (G) $P2X_{4/6}$? (G)	$P2Y_2$ (G)	ATP inhibits slow depolarization of substantia gelatinosa neurons via P2Y R ATP induces glycine release via presynaptic P2X R ATP augments the release of glutamate $P2X_7$ R on presynaptic terminals mediate modulation	Li and Perl, 1995[c] Tuyau *et al.*, 1997[b] Vulchanova *et al.*, 1997[b] Lê *et al.*, 1998[b] Li *et al.*, 1998[b] Xiang *et al.*, 1998[b] Atkinson *et al.*, 2000[b] Dunn *et al.*, 2001[b] Jang *et al.*, 2001[b] Nakatsuka and Gu, 2001[b] Wang *et al.*, 2001[b] Yoshida *et al.*, 2002[c] Nakatsuka *et al.*, 2003[b]
Spinal motor neurons	$P2X_2$ (C) $P2X_4$ (C) $P2X_6$ (C)	$P2X_2$ (D) $P2X_3$ (D)				Collo *et al.*, 1996[b] Boldogköi *et al.*, 2002[b] Stoeckel *et al.*, 2003[b]
Cultured spinal neurons			$P2X_2$ (G)	P2Y (G)	ATP increase $[Ca^{2+}]_i$ ATP via presynaptic $P2X_2$ R potentiates glycinergic transmission	Salter and Hicks, 1994[c] Ikeuchi and Nishizaki, 1996b[c] Laube, 2002[b]
Mechanically dissociated substantia gelatinosa neurons			P2X (G)		ATP facilitates spontaneous glycinergic IPSC frequency via presynaptic P2XR ATP induces growth cone turning	Rhee *et al.*, 2000[b]
Xenopus embryo spinal neurons				$P2Y_1$ (G)	ADP is involved in control of spinal motor pattern generation	Fu *et al.*, 1997[c] Brown and Dale, 2002a,b[c]
Whole brain		$P2Y_{12}$ (F)				Vasiljev *et al.*, 2003[c]

(*continued*)

TABLE XLI (*continued*)

Cellular component	Receptor mRNA	Receptor protein	Pharmacological and biochemical profile	Function	References
Brain stem					
Rostroventrolateral medulla (RVLM)		$P2X_1$ (D) $P2X_2$ (D) $P2X_3$ (D) $P2X_6$ (D)	$P2X_1$ (G) or $P2X_3$ (G) P2Y (G)	P2X R mediate central CO_2 chemoreception P2X R mediate excitation of both sympathoexcitatory and sympathoinhibitory neurons	Horiuchi *et al.*, 1999[b] Ralevic *et al.*, 1999[d] Kapoor and Sladek, 2000[b] Thomas and Spyer, 2000[b] Yao *et al.*, 2000, 2003b[b]
Nucleus tractus solitarus (NTS)				Presynaptic P2X R facilitate release of glutamate	
In vivo preparations			$P2X_1$ (G) or $P2X_3$ (G) $P2X_4$ (G)	P2X R mediate reduction in arterial blood pressure P2X R mediate inhibition of lumbar and renal sympathetic nerve activity P2X R mediate regulation of arterial baroreflexes	Ergene *et al.*, 1994[b] Barraco *et al.*, 1996[b] Phillis *et al.*, 1997[b] Scislo *et al.*, 1997, 1998[b] Kitchen *et al.*, 2001[b] Paton *et al.*, 2002[b] Vulchanova *et al.*, 1997[b]
Slices	$P2X_2$ (C) $P2X_4$ (C) $P2X_6$ (C) $P2X_7$ (B)	$P2X_1$ (D) $P2X_2$ (D) $P2X_3$ (D) $P2X_4$ (D) $P2X_5$ (D) $P2X_6$ (D) $P2X_7$ (D) $P2Y_1$ (D)	$P2X_{4/6}$? (G) $P2X_{1/5}$? (G)	$P2X_2$ and $P2X_7$ R localized on presynaptic vagal afferents	Llewellyn-Smith and Burnstock, 1998[b] Kanjhan *et al.*, 1999[b] Atkinson *et al.*, 2000[b] Moore *et al.*, 2000b[c] Deuchars *et al.*, 2001[b] Kato and Shigetomi, 2001[b] Yao *et al.*, 2001, 2003b[b] Ashur and Deuchars, 2002[b] Gourine *et al.*, 2002a[b] Shigetomi and Kato, 2002[b]
Area postrema		$P2X_2$ (D) $P2X_4$ (D) $P2X_6$ (D)		$P2X_7$ R on presynaptic nerve terminals modulate transmitter release	Atkinson *et al.*, 2000[b] Yao *et al.*, 2000[b]
Locus coeruleus (LC)	$P2X_2$ (C)	$P2X_2$ (D) $P2X_3$ (D) $P2X_6$ (D)	$P2X_1$ (G) or $P2X_3$ (G) P2Y (G)	ATP mediates fast EPSPs perhaps after release as a cotransmitter with NA	Illes *et al.*, 1994[c] Fröhlich *et al.*, 1996[c] Vulchanova *et al.*, 1996[b]

						Nieber *et al.*, 1997[b] Sansum *et al.*, 1998[b] Kanjhan *et al.*, 1999[b] Yao *et al.*, 2000[b] Masaki *et al.*, 2001[b] Poelchen *et al.*, 2001[b] Rocha *et al.*, 2001[b]
Trigeminal mesencephalic nucleus (MNV)	$P2X_4$ (C) $P2X_5$ (C) $P2X_6$ (C)	$P2X_2$ (D) $P2X_3$ (D)	$P2X_1$ (G) $P2X_2$ (G) or $P2X_5$ (G)		ATP facilitates glycine release P2X R is involved with processing of proprioceptive information ATP enhances glutamate release	Collo *et al.*, 1996[b] Khakh *et al.*, 1997[b] Khakh and Henderson, 1998[b] Yao *et al.*, 2000[b] Patel *et al.*, 2001[b] Boldogköi *et al.*, 2002[b] Cheung and Burnstock, 2002[b]
Dorsal motor nucleus of vagus neurons (DMV)	$P2X_2$ (B) $P2X_4$ (C) $P2X_6$ (C)	$P2X_2$ (D) $P2X_4$ (D)	$P2X_2$ (G) $P2X_{2/6}$ (G)			Nabekura *et al.*, 1995[b] Collo *et al.*, 1996[b] Yao *et al.*, 2000[b] Ueno *et al.*, 2001[b] Ashur and Deuchars, 2002[b]
Vestibular nucleus		$P2X_1$ (D) $P2X_2$ (D) $P2X_3$ (D) $P2X_5$ (D) $P2X_6$ (D)	P2X (G)	P2Y (G)		Chessell *et al.*, 1997b[d] Xiang *et al.*, 1999[b] Yao *et al.*, 2000[b]
Cuneate nucleus		$P2X_1$ (D) $P2X_2$ (D) $P2X_3$ (D) $P2X_5$ (D) $P2X_6$ (D)	$P2X_1$ (D)			Moore *et al.*, 2000b[c] Yao *et al.*, 2000[b]
Hypoglossal nucleus	$P2X_1$ (B) $P2X_{2-1}$ (B) $P2X_{2-2}$ (B) $P2X_3$ (B)	$P2X_2$ (D) $P2X_6$ (D)	$P2X_2$ (G)		ATP modulates inspiratory activity	Collo *et al.*, 1996[b] Funk *et al.*, 1997[b] Yao *et al.*, 2000[b] Lorier *et al.*, 2002[b]

(*continued*)

TABLE XLI (*continued*)

Cellular component	Receptor mRNA	Receptor protein	Pharmacological and biochemical profile	Function	References
	$P2X_4$ (B) $P2X_5$ (B) $P2X_6$ (B)				
Periaqueductal gray matter		$P2X_1$ (DE) $P2X_2$ (DE) $P2X_3$ (DE) $P2X_4$ (DE) $P2X_5$ (DE) $P2X_6$ (DE)	$P2X_1$ (G) or $P2X_3$ (G)	ATP regulates bladder function	Worthington *et al.*, 1999b[b] Rocha *et al.*, 2001[b]
Medulla oblongata					
Neonatal			$P2X_1$ (G)	ATP activates outwardly rectifying K^+ currents	Ikeuchi *et al.*, 1995a[c]
Adult	$P2X_7$ (BC)	$P2X_7$ (D)			Deuchars *et al.*, 2001[b]
Facial nucleus	$P2X_2$ (C) $P2X_4$ (ABC) $P2X_6$ (C)	$P2X_2$ (D)			Soto *et al.*, 1996a,b[b] Tuyau *et al.*, 1997[b] Kanjhan *et al.*, 1999[b]
Hypothalamus					
Slices	$P2X_2$ (BC)	P2X (F) $P2Y_1$ (D) $P2X_2$ (D)		ATP increases $[Ca^{2+}]_i$	Bo and Burnstock, 1994[d] Kidd *et al.*, 1995[b] Kanjhan *et al.*, 1999[b] Kittner *et al.*, 2003[c]
Cultured neurons			P2X (G)	ATP increases $[Ca^{2+}]_i$	Chen *et al.*, 1994a[b]
Dissociated neurons				ATP increases $[Ca^{2+}]_i$	Shibuya *et al.*, 1999[b]
Supraoptic nucleus	$P2X_2$ (C) $P2X_3$ (BC) $P2X_4$ (BC) $P2X_7$ (B)	$P2X_2$ (D)	$P2X_7$ (G)	ATP increases $[Ca^{2+}]_i$	Kanjhan *et al.*, 1999[b] Sorimachi *et al.*, 2001[b] Yao *et al.*, 2003b[b]
Paraventricular nucleus	$P2X_2$ (C) $P2X_3$ (BC) $P2X_4$ (BC)	$P2X_2$ (D) $P2X_3$ (D)	$P2X_2$ (G)		Whitlock *et al.*, 2001[b] Boldogköi *et al.*, 2002[b] Gourine *et al.*, 2002a[b]

Tuberomammillary nucleus	$P2X_2$ (BC)	$P2X_2$ (D)	$P2X_2$ (G) $P2X_{2/5}$? (G)	P2Y (G)	ATP induces inward currents	Furukawa *et al.*, 1994[c] Kanjhan *et al.*, 1999[b] Vorobjev *et al.*, 2003[b]
Anterior hypothalamus			$P2X_1$ (G) or $P2X_3$ (G)		ATP is involved in central control of temperature regulation	Gourine *et al.*, 2002b[b]
Supraoptic magnocellular neurosecretary cells (MNCs)		$P2X_2$ (D)	P2X (G)	$P2Y_2$ (G)	ATP and UTP may modulate neurohypophysial hormone release	Hiruma and Bourque, 1995[d] Buller *et al.*, 1996[b] Gourine *et al.*, 2002a[b]
Lateral hypothalamic neurons			P2X (G)		Concurrent activation of P2X and $GABA_A$ R mediates spontaneous and evoked postsynaptic currents	Jo and Role, 2002[b]
Thalamus		$P2X_4$ (D)		P2Y (G)		Mironov, 1994[c] Lê *et al.*, 1998[b]
Medial habenula			P2X (G)	$P2Y_2$ (G) $P2Y_4$ (G)	ATP is involved in synaptic transmission P2Y R mediate long-term potentiation of glutamatergic synaptic transmission	Sperlágh *et al.*, 1995[b] Robertson *et al.*, 1999[b] Price *et al.*, 2003[c]
Cerebellum						
Purkinje cells	$P2X_1$ (B) $P2X_2$ (BC) $P2X_3$ (B) $P2X_4$ (BC) $P2X_6$ (BC)	$P2X_1$ (DF) $P2X_2$ (D) $P2X_3$ (D) $P2X_4$ (D) $P2X_6$ (D)	$P2X_2$ (H) $P2X_4$? (H)	P2Y (H)	ATP is a fast neurotransmitter involved in motor learning and coordination of movement ATP increases $[Ca^{2+}]_i$	Balcar *et al.*, 1995[b] Collo *et al.*, 1996[b] Kanjhan *et al.*, 1996, 1999[b] Kirischuk *et al.*, 1996[c] Soto *et al.*, 1996a,b[b] Tanaka *et al.*, 1996[b] Lê *et al.*, 1998[b] Mateo *et al.*, 1998[b] García-Lecea *et al.*, 2001[b] Rubio and Soto, 2001[b] Soto and Rubio, 2001[b] Bo *et al.*, 2003[b]

(*continued*)

TABLE XLI (*continued*)

Cellular component	Receptor mRNA		Receptor protein		Pharmacological and biochemical profile		Function	References
Granule cells	$P2X_2$ (C) $P2X_4$ (BC)	$P2Y_1$ (B) $P2Y_4$ (B) $P2Y_6$ (B) $P2Y_{12}$ (B)	$P2X_1$ (D) $P2X_2$ (D) $P2X_3$ (D) $P2X_4$ (D) $P2X_7$ (D)		P2X (G)	$P2Y_1$ (H)	ATP increases the release of aspartate P2 R is involved in glutamate-mediated neurotoxicity	Merlo and Volonté, 1996[b] Loesch and Burnstock, 1998[b] Vitolo *et al.*, 1998[b] Volonté *et al.*, 1999[b] Hervás *et al.*, 2003[d]
Cultured neonatal cerebellar neurons	$P2X_1$ (B) $P2X_3$ (B) $P2X_4$ (B) $P2X_5$ (B) $P2X_7$ (B)	$P2Y_1$ (B) $P2Y_2$ (B) $P2Y_4$ (B) $P2Y_6$ (B)			$P2X_2$ (H)	P2Y (G)	ADP prevents apoptosis-induced low K^+	Ikeuchi and Nishizaki, 1996a[c] Castro *et al.*, 1999[b] García-Lecea *et al.*, 1999[b] Amadio *et al.*, 2002[d]
Cerebellar slices	$P2X_1$ (B) $P2X_2$ (BC) $P2X_3$ (B) $P2X_4$ (BC) $P2X_6$ (BC)		$P2X_1$ (E) $P2X_2$ (DE) $P2X_4$ (D)	$P2Y_1$ (D)	$P2X_{4/6}$ (GH)		ATP increases $[Ca^{2+}]_i$	Kanjhan *et al.*, 1996, 1999[b] Soto *et al.*, 1996a,b[b] Halliday and Gibb, 1997[b] García-Lecea *et al.*, 1999[b] Moore *et al.*, 2000b[c] Florenzano *et al.*, 2002[b] Bo *et al.*, 2003[b]
Striatum								
Dorsal striatum	$P2X_1$ (BC)				$P2X_2$ (G) $P2X_7$ (G)	P2Y (G)	ATP induces release of dopamine ATP also inhibits release of dopamine via presynaptic P2 R P2X R mediate cell death	Kidd *et al.*, 1995[b] Zhang *et al.*, 1995, 1996c[c] Trendelenburg and Bültmann, 2000[b]
Nucleus accumbens (ventral striatum)					P2X (G)	P2Y (G)	ATP increases $[Ca^{2+}]_i$ ATP induces release of dopamine	Ryu *et al.*, 2002[b] Krügel *et al.*, 1999, 2001a, 2003a[c] Kittner *et al.*, 2000[c] Sorimachi *et al.*, 2000[b]
Cultured striatal neurons						P2Y (G)	ATP evokes K^+ currents	Ikeuchi and Nishizaki, 1995c[c]
Ventral tegmental area				$P2Y_1$ (D)	P2X (G)	$P2Y_1$ (G)	$P2Y_1$ R activation enhances dopaminergic mechanisms *in vivo*	Krügel *et al.*, 2001b[c] Sorimachi *et al.*, 2002[b]

Midbrain								
Synaptosomes			$P2X_3$ (D)		$P2X_3$ (I)	Ap_5A R (H)	ATP increases $[Ca^{2+}]_i$ in presynaptic terminals	Giraldez *et al.*, 2001[b] Gómez-Villafuertes *et al.*, 2001, 2003[d]
Ependymal cells	$P2X_7$ (C)		$P2X_1$ (E) $P2X_2$ (E) $P2X_3$ (E) $P2X_4$ (E) $P2X_5$? (E) $P2X_6$? (E) $P2X_7$ (D)		$P2X_1$ (D) $P2X_2$ (D) $P2X_3$ (D) $P2X_4$ (D) $P2X_5$ (D) $P2X_6$ (D)		P2X R activity is modulated by $GABA_B$ R	Collo *et al.*, 1997[b] Worthington *et al.*, 1999b[b]
Hippocampus								
Slices (region not specified)	$P2X_1$ (B) $P2X_2$ (B) $P2X_3$ (B) $P2X_4$ (BC) $P2X_5$ (B) $P2X_6$ (BC) $P2X_7$ (B) $P2X_2$ (C)—several isoforms	$P2Y_1$ (AB) $P2Y_2$ (B) $P2Y_4$ (B) $P2Y_6$ (B)	P2X (F) $P2X_1$ (D) $P2X_2$ (D) $P2X_3$ (D) $P2X_4$ (D) $P2X_5$ (D) $P2X_6$ (D) $P2X_7$ (D)	$P2Y_1$ (D)	P2X (G)	P2Y (G)	ATP contributes to the induction of long-term potentiation $P2X_7$ R on presynaptic terminals regulate release of glutamate and GABA Presynaptic P2 R inhibit NA release	Wieraszko and Ehrlich, 1994[c] Balcar *et al.*, 1995[b] Kidd *et al.*, 1995[b] Collo *et al.*, 1996[b] Soto *et al.*, 1996a,b[b] Tanaka *et al.*, 1996[b] Koch *et al.*, 1997[c] Simon *et al.*, 1997[b] Deng *et al.*, 1998[c] Lê *et al.*, 1998[b] Pankratov *et al.*, 1999[b] Mendoza-Fernandez *et al.*, 2000[c] Moore *et al.*, 2000b[c] O'Kane and Stone, 2000[b] Wong *et al.*, 2000[b] Jabs *et al.*, 2002[b] Sperlágh *et al.*, 2002, 2003[b] Khakh, 2002[b] Almeida *et al.*, 2003[b]
Granule cells					$P2X_{4/6}$ (G)		P2 R modulate glutamate release	Edwards, 1995[b]
CA1 pyramidal neurons	$P2X_2$ (C) $P2X_4$ (C) $P2X_6$ (C)		$P2X_2$ (D) $P2X_4$ (D)		$P2X_2$ (G)	P2Y (G)	ATP, glutamate, and aspartate induce long-term potentiation	Fujii *et al.*, 1995a,b, 1999[c] Motin and Bennett, 1995[b] Pankratov *et al.*, 1998[b] Kanjhan *et al.*, 1999[b]

(*continued*)

TABLE XLI (*continued*)

Cellular component	Receptor mRNA	Receptor protein	Pharmacological and biochemical profile		Function	References
						Li *et al.*, 2000a[d] Soto and Rubio, 2001[b] Yamazaki *et al.*, 2002, 2003[b]
Cultured hippocampal neurons				P2 (G)	ATP inhibits NMDA R	Ortinau *et al.*, 2003[e]
Cultured CA1 pyramidal neurons			P2X (H)			Rogers and Dani, 1995[b] Ross *et al.*, 1998[b]
CA3 pyramidal neurons	$P2X_4$ (C) $P2X_6$ (C)	$P2X_4$ (D)	$P2X_1$ (G) or $P2X_3$ (G)		α,β-meATP increases spontaneous activity	Mironov, 1994[c] Nakazawa *et al.*, 1994[c]
Cultured CA3 pyramidal neurons			P2X (GH)	$P2Y_1$ (H) $P2Y_2$ (G)	ATP increases $[Ca^{2+}]_i$ ATP regulates $[Cl^-]_i$ ATP inhibits glutamate release via presynaptic P2 R ATP inhibits K^+ channels ATP co-released with glutamate induces synaptic response Diadenosine polyphosphates potentiate N-type Ca^{2+} channels	Inoue *et al.*, 1995[c] Inoue and Koizumi, 2001[c] Balachandran and Bennett, 1996[b] Dave and Mogul, 1996[b] Ikeuchi *et al.*, 1996a,b[c] Panchenko *et al.*, 1996[c] Koizumi and Inoue, 1997[c] Mori *et al.*, 2001[b]
CA3 pyramidal synaptosomes				Ap_5A R (G)	Diadenosine polyphosphates potentiate N-type Ca^{2+} channels	Panchenko *et al.*, 1996[c]
CA3 mossy fiber synapses		$P2X_7$ (EF)	$P2X_2$ (G) $P2X_7$ (G)		Presynaptic $P2X_7$ R activation depresses mossy fiber CA3 synaptic transmission	Armstrong *et al.*, 2002[b] Khakh *et al.*, 2003[b]
In vivo microdialysis of hippocampus			P2X (G)		P2X R modulate serotonergic transmission	Okada *et al.*, 1999[b]
Corpus callosum	$P2Y_1$ (A)					Deng *et al.*, 1998[c]
Cortex						
Whole brain	$P2X_2$ (C) $P2Y_{13}$ (AB)	P2X (F) $P2X_2$ (D)		P2Y (G)		Bo and Burnstock, 1994[b] Kanjhan *et al.*, 1999[b] Communi *et al.*, 2001a[c]
Whole brain membrane fraction		$P2Y_1$ (F)				Simon *et al.*, 1995[c]
Frontal cortex	$P2Y_1$ (A)					Deng *et al.*, 1998[c]

Cortical slices	$P2X_4$ (C) $P2X_6$ (C)		P2X (F)	$P2Y_1$ (D)		P2Y (G)	ATP inhibits stimulus-evoked glutamate release Presynaptic P2Y R inhibit NA release	Von Kügelgen *et al.*, 1994[c] Balcar *et al.*, 1995[b] Collo *et al.*, 1996[b] Worthington *et al.*, 1999b[b] Bennett and Boarder, 2000[c] Moore *et al.*, 2000b[c]
Sensorimotor cortex slices					P2X (H)	P2Y (H)	ATP increases $[Ca^{2+}]_i$	Lalo *et al.*, 1998[d]
Superior and inferior colloculus neurons						$P2Y_1$ (G)	ADP evokes outwardly rectifying K^+ currents	Ikeuchi and Nishizaki, 1995a[c] Ikeuchi *et al.*, 1995b[c]
Somato-sensory cortex pyramidal neurons					P2X (G)		P2X R mediate synaptic transmission	Pankratov *et al.*, 2002[b]
Prefrontal cortex pyramidal neurons						$P2Y_1$ (G) $P2Y_2$ (G)	ATP, UTP, and UDP act on presynaptic $P2Y_2$ R to potentiate responses to NMDA R activation $P2Y_1$ R mediate inhibition of NMDA R channels	Illes, 2002[c] Wirkner *et al.*, 2002, 2003[c] Luthardt *et al.*, 2003[c]
Olfactory bulb neurons	$P2X_6$ (C)		$P2X_2$ (D) $P2X_4$ (DE)				Presynaptic P2X R mediate enhancement of glutamate release	Soto *et al.*, 1996a[b] Lê *et al.*, 1998[b] Bobanovic *et al.*, 2002[b]
Cerebrocortical neurons cultured		$P2Y_1$ (B) $P2Y_4$ (B) $P2Y_6$ (B)			P2X (G)	$P2Y_1$ (G) $P2Y_2$ (G)	ATP and UTP increase $[Ca^{2+}]_i$ P2Y R modulate kainite and AMPA-induced currents	Nishizaki and Mori, 1998[c] Prothero *et al.*, 2000[c] Zona *et al.*, 2000[c] Bennett *et al.*, 2003[c]
Cerebrocortical synaptosomes				$P2Y_1$ (F)	P2X (FG) uridine	Ap_5A R (FG)	ATP and Ap_5A induce Ca^{2+} transients	Simon *et al.*, 1995[c] Schäfer and Reiser, 1997[d], 1999[c] Kardos *et al.*, 1999[e] Pintor *et al.*, 1999[b]
Neurohypophysis	See Table XXXI							
Glial cells	See Table XLVI							
Vasculature	See Table XXIV							

[a]See footnote *a* for Table III.
[b]References refer to P2X receptors.
[c]References refer to P2Y receptors.
[d]References refer to P2X and P2Y receptors.
[e]References refer to uncharacterized P2 receptors.

addition to swelling-induced release of ATP from rat cerebral cortex, was shown (Phillis and O'Regan, 2002). Reduced levels of ATP in the rabbit spinal cord after ischemia have been measured (Danielisová *et al.*, 1987), and hypoxia outflow of ATP from superfused hippocampal slices during ischemic-like conditions has been demonstrated (Jurányi *et al.*, 1999). A recent study showed release of ATP from *Xenopus* spinal neurons, evoked by activation of glutamate receptors (Brown and Dale, 2002b).

ATP release from noradrenergic afferents in the supraoptic nucleus is known (Buller *et al.*, 1996). ATP is co-released with NA from rat habenula and hypothalamic slices (Robertson and Edwards, 1998; Sperlágh *et al.*, 1997, 1998a,b), co-released with γ-aminobutyric acid (GABA) from lateral hypothalamic neurons (Jo and Role, 2002) and released and co-secreted with vasopressin and oxytocin from magnocellular neurons of the hypothalamus (Lemos and Wang, 2000; Troadec *et al.*, 1998). ATP release from affinity-purified cholinergic terminals from rat caudate nucleus has been described (Richardson and Brown, 1987).

Functional expression of P2Y receptors was demonstrated in *Xenopus* oocytes injected with brain mRNA (Honoré *et al.*, 1991).

In summary, the presence of mRNA and protein for multiple subtypes of P2X receptor has been demonstrated in the CNS and functionally it has been shown that P2X receptors are involved in fast synaptic transmission, principally of the $P2X_1$, $P2X_2$, and $P2X_3$ subtypes, although there is evidence for the involvement of heteromultimers. P2Y receptors are neuromodulators in the CNS and while mRNA for $P2Y_1$, $P2Y_2$, $P2Y_4$, $P2Y_6$, and $P2Y_{13}$ has been identified, only $P2Y_1$ receptor protein has been identified immunohistochemically throughout the CNS. Functionally, $P2Y_1$ and $P2Y_2$ receptor subtypes predominate, although the subtype has not been characterized in some regions of the CNS.

2. Sympathetic Neurons

The first report of ATP having an effect on sympathetic ganglia was published in 1948, when Feldberg and Hebb observed that intra-arterial perfusion of ATP in the cat superior cervical ganglion (SCG) induced contractions of the nictitating membrane (Feldberg and Hebb, 1948). This was followed by a later study also showing that ATP depolarized and excited the cat SCG postganglionic neurons (Theobald and de Groat, 1977) and subsequent recordings of single channels identified the response as that of a P2X receptor (Cloues *et al.*, 1993).

Intracellular recordings of frog sympathetic ganglia were obtained in the presence of ATP, where ATP produced a depolarization through a reduction in K^+ conductance (Akasu and Koketsu, 1985; Akasu *et al.*, 1983),

although the subtype of P2 receptor was not characterized. Further studies showed that the transduction mechanisms in response to UTP in bullfrog sympathetic neurons involved G proteins (Lopez and Adams, 1989) indicative of P2Y receptors. Purine and pyrimidine mononucleotides depolarized neurons of explanted amphibian sympathetic ganglia, again indicative of a P2Y receptor (Siggins *et al.*, 1977).

[^{3}H]NA outflow following transmural stimulation of the rat and rabbit portal veins was inhibited by ATP (Enero and Saidman, 1977; Su, 1978b) as was [^{3}H]NA overflow in the rabbit mesenteric artery (Ishikawa, 1985). In contrast, NA release in response to perivascular nerve stimulation increased in the presence of ATP but not α,β-meATP in the rabbit ear artery (Miyahara and Suzuki, 1987), rat mesenteric artery (Sjöblom-Widfeldt *et al.*, 1990), and dog basilar artery (Muramatsu *et al.*, 1981).

ATP and NA were found to be contransmitters from sympathetic perivascular nerves in the mesenteric artery of the rabbit (Ramme *et al.*, 1987; Von Kügelgen and Starke, 1985), dog (Machaly *et al.*, 1988; Muramatsu, 1986; Omote *et al.*, 1989), and rat (Yamamoto *et al.*, 1992), the cat intestinal vasculature (Taylor and Parsons, 1989), rabbit ileocolic, jejunal, hepatic, ear, and coronary arteries (Brizzolara and Burnstock, 1990; Bültmann *et al.*, 1991; Corr and Burnstock, 1991; Evans and Cunnane, 1992; Kennedy *et al.*, 1986). This has also been shown for canine saphenous vein (Flavahan and Vanhoutte, 1986), rat renal and intrapulmonary artery, and rat inferior vena cava (Inoue and Kannan, 1988; Schwartz and Malik, 1989; Wahlestedt *et al.*, 1992). The role of ATP and NA as sympathetic cotransmitters in the rat tail artery has been intensively studied (Bao *et al.*, 1989; Msghina *et al.*, 1992; Sneddon and Burnstock, 1984).

Table XLII summarizes the receptor subtypes present in sympathetic neurons based on mRNA, protein, and pharmacological and biochemical profiles. The functions claimed for the receptors together with key references are included.

ATP is released together with other transmitters including NA and neuropeptide Y (NPY) (see Burnstock, 1990a; Lundberg, 1996; Stjärne, 1989) from postganglionic sympathetic nerves from both vascular and nonvascular structures such as the vas deferens.

In summary, peripheral sympathetic neurons express mRNA and protein for multiple P2X receptor subtypes. Functionally responses of sympathetic neurons can be accounted for by the presence of $P2X_2$ and $P2X_3$ subunits in varying proportions of homomeric and heteromeric receptors. $P2X_1$ and $P2X_5$ receptors have also been identified functionally. Multiple P2Y receptor mRNAs have been identified and protein for $P2Y_1$, $P2Y_2$, and $P2Y_4$ receptor subunits has been identified, although functionally $P2Y_2$, $P2Y_4$, and $P2Y_6$ receptors predominate.

TABLE XLII
Sympathetic Neurons[a]

Cellular component	Receptor mRNA		Receptor protein		Pharmacological and biochemical profile		Function	References
Cell bodies								
SCG	$P2X_1$ (C) $P2X_2$ (BC) $P2X_3$ (B) $P2X_4$ (BC) $P2X_5$ (B) $P2X_6$ (BC)	$P2Y_1$ (A) $P2Y_2$ (A) $P2Y_4$ (A) $P2Y_6$ (A) $P2Y_{12}$ (A)	$P2X_1$ (D) $P2X_2$ (D) $P2X_3$ (D) $P2X_4$ (D) $P2X_5$ (D) $P2X_6$ (D) $P2X_7$ (D)	$P2Y_1$ (D) $P2Y_2$ (D) $P2Y_4$ (D)	$P2X_1$ (G) $P2X_2$ (G) $P2X_{1/5}$ (G) $P2X_{2/3}$ (G)	$P2Y_2$ (G) or $P2Y_4$ (G) $P2Y_6$ (G)	ATP and UTP evoke NA release Presynaptic P2X and P2Y R mediate positive and negative neuromodulation of transmitter release, respectively ATP increases $[Ca^{2+}]_i$ Zn^{2+} modulates P2X R	Connolly and Harrison, 1994, 1995[d] Reekie and Burnstock, 1994[d] Boehm *et al.*, 1995[d] Cloues, 1995[b] Khakh *et al.*, 1995[b] Lewis *et al.*, 1995[b] Buell *et al.*, 1996[b] Collo *et al.*, 1996[b] Simon *et al.*, 1997[b] Boehm, 1998, 1999[c] Xiang *et al.*, 1998[b] Li *et al.*, 2000c[b] Zhong *et al.*, 2000a[b] Kumagai and Saino, 2001[b] Vartian *et al.*, 2001[c] Calvert and Evans, 2002[b] Von Kügelgen and Pelzer, 2002[d]
SCG satellite cells					P2X (G)		ATP increases $[Ca^{2+}]_i$	Kumagai and Saino, 2001[b]
Coeliac	$P2X_3$ (B) $P2X_4$ (B) $P2X_5$ (B)		$P2X_1$ (D) $P2X_2$ (D) $P2X_3$ (D)		$P2X_2$ (G)		ATP increases $[Ca^{2+}]_i$ P2X and nicotinic R do not act independently	Khakh *et al.*, 1995[b] Buell *et al.*, 1996[b] Collo *et al.*, 1996[b]

	$P2X_6$ (B)		$P2X_4$ (D) $P2X_6$ (D)				Evans and Surprenant, 1996[b] Xiang *et al.*, 1998[b] Searl *et al.*, 1998[b] Zhong *et al.*, 2000b[b]
Thoracolumbal	$P2X_2$ (B) $P2X_5$ (B)	$P2Y_2$ (B) $P2Y_4$ (B) $P2Y_6$ (B)	$P2X_2$ (D) $P2X_5$ (D)	$P2X_1$ (G) $P2X_2$ (G)	$P2Y_2$ (GH) or $P2Y_4$ (GH)	ATP induces NA release ATP induces inward currents via $P2X_2$ R	Von Kügelgen *et al.*, 1997, 1999[d] Nörenberg *et al.*, 2000, 2001[c] Schadlich *et al.*, 2001[b]
Nerve terminals							
Vas deferens					P2Y (G)	ATP inhibits NA release	Todorov *et al.*, 1994[c] Gonçalves and Queiroz, 1996[c]
Ear artery				P2X (G)		ATP inhibits NA release	Ishii *et al.*, 1995[b] Ishii-Nozawa *et al.*, 1999[b]
Atria	$P2X_2$ (B) $P2X_3$ (B)		$P2X_1$ (D) $P2X_3$ (D)	$P2X_3$ (G) $P2X_{2/3}$ (G)	P2Y (G)	ATP acting via P2X R enhances NA release ATP acting at postganglionic sympathetic P2Y R inhibits NA release	Von Kügelgen *et al.*, 1995a[d] Hansen *et al.*, 1999a[b] Sperlágh *et al.*, 2000[b] Sesti *et al.*, 2002[c]
Sympathetic							
Cotransmission							
Tail artery				$P2X_1$ (G)		ATP via P2X R mediates EJPs	Haniuda *et al.*, 1997[b]
Auricular artery				$P2X_1$ (G)			Brock and Cunnane, 1999[b]
Mesenteric vein				$P2X_1$ (G)			Smyth *et al.*, 2000[b]
Vas deferens			$P2X_1$ (D)	$P2X_1$ (G)			Knight *et al.*, 2003[b]

[a]See footnote *a* for Table III.
[b]References refer to P2X receptors.
[c]References refer to P2Y receptors.
[d]References refer to P2X and P2Y receptors.

3. Parasympathetic Neurons

Cultured neurons of guinea pig intramural ganglia of the bladder and intracardiac ganglia of guinea pig and rat responded to microapplication of ATP (Allen and Burnstock, 1990; Burnstock *et al.*, 1987; Fieber and Adams, 1991). ATP depressed cholinergic transmission in vesical parasympathetic ganglia of the cat and high concentrations of ATP also produced a direct excitatory effect on bladder ganglion cells (Theobald and de Groat, 1989). Exogenous ATP modulated the activity generated by canine *in situ* intrinsic cardiac neurons (Huang *et al.*, 1993a).

Table XLIII summarizes the receptor subtypes present in parasympathetic neurons based on mRNA, protein, and pharmacological and biochemical profiles. The functions claimed for the receptors together with key references are included.

ATP has been localized in a subpopulation of guinea pig neurons in bladder ganglia (Burnstock *et al.*, 1978a; Crowe *et al.*, 1986) and intrinsic cardiac neurons (Allen and Burnstock, 1990; Burnstock, 1980, 1989) using quinacrine. ATP release from rat pelvic ganglion in response to electrical stimulation has been measured by the luciferin/luciferase method (Liang and Vizi, 1998).

In summary, limited studies on the expression of mRNA for P2X and P2Y receptors in peripheral parasympathetic neurons have been carried out to date, and only mRNA for $P2X_2$, $P2X_4$, $P2Y_2$, and $P2Y_4$ receptor subunits has been identified. In contrast, parasympathetic neurons have been shown to express protein for multiple P2X receptor subtypes but no studies on the expression of P2Y receptor protein have been conducted; this may be a consequence of the antibodies to P2Y receptor protein becoming available only more recently. Functionally, responses of parasympathetic neurons reflect the presence of $P2X_2$ and $P2X_3$ subunits in varying proportions of homomeric and heteromeric receptors. $P2Y_1$, $P2Y_2$, and $P2Y_{11}$ receptor subunits have been identified by functional studies.

4. Enteric Nervous System

ATP (possibly via adenosine) was shown to inhibit peristaltic activity in guinea pig ileum elicited by distention (Okwuasaba *et al.*, 1977; Van Nueten *et al.*, 1977). Quinacrine-positive nerve cell bodies and fibers in the stomach and intestine of several mammalian species indicated the presence of nerves in the myenteric plexus containing high levels of ATP (Ålund and Olson, 1978, 1979; Crowe and Burnstock, 1981a,b; Olson *et al.*, 1976). ATP and adenosine inhibited release of ACh from synaptosomes derived from guinea pig ileum, partly via P1 receptors (Reese and Cooper, 1982). At the enteric plexus level $GABA_A$ receptors were shown to mediate GABA

TABLE XLIII
Parasympathetic Neurons[a]

Cellular component	Receptor mRNA	Receptor protein	Pharmacological and biochemical profile	Function	References
Cell bodies					
Vesical ganglia			P2X (G)	ATP modulates amplitude of fast EPSPs	Nishimura and Akasu, 1994[b] Nishimura and Tokimasa, 1996[b]
Intracardiac ganglia	$P2Y_2$ (B) $P2Y_4$ (B)	$P2X_4$ (D)	$P2Y_2$ (H)	ATP modulates myocyte contractility via intrinsic cardiac neurons ATP via P2Y R increases $[Ca^{2+}]_i$	Horackova *et al.*, 1994[c] Rubino *et al.*, 1996[c] Liu *et al.*, 2000[c] Bo *et al.*, 2003[b]
Submandibular ganglia					
Whole		$P2X_5$ (D)	$P2Y_1$ (G) or $P2Y_{11}$ (G)	ATP activates presynaptic P2 R to inhibit ACh release	Smith *et al.*, 2001a[d]
Dissociated		$P2X_2$ (D) $P2X_4$ (D) $P2X_5$ (D)	$P2X_2$ (G) $P2Y_2$ (G)		Liu and Adams, 2001[b] Abe *et al.*, 2003[c]
Pelvic ganglia	$P2X_2$ (C) $P2X_4$ (C)	$P2X_2$ (D) $P2X_3$ (D) $P2X_4$ (D)	$P2X_2$ (G) $P2X_3$ (G) $P2X_{2/3}$ (G)	ATP activates inward currents	Zhong *et al.*, 1998, 2000b, 2001[b] Bo *et al.*, 2003[b]
Ciliary ganglion			P2Y (G)	ATP operates nonselective cation channels with a role in the excitation of ciliary neurons	Abe *et al.*, 1995[c]
Nerve terminals					
Ciliary ganglion			P2X (G)	ATP induces short latency cation current	Sun and Stanley, 1996[b]

[a]See footnote *a* for Table III.
[b]References refer to P2X receptors.
[c]References refer to P2Y receptors.
[d]References refer to P2X and P2Y receptors.

activation of NANC inhibitory purinergic receptors of rat duodenum (Maggi *et al.*, 1984). Slow excitatory postsynaptic potentials (EPSPs) recorded in neurons of the submucous plexus of guinea pig caecum could be mimicked by ATP (Mihara *et al.*, 1985).

5′-Nucleotidase is abundantly localized in enteric ganglia of guinea pigs, consistent with the possibility of release of ATP within these ganglia (Andersson Forsman and Gustafsson, 1985).

ATP modulated membrane K^+ currents in guinea pig myenteric neurons (both AH and S neurons) (Katayama and Morita, 1989) and evoked rapidly desensitizing inward currents (Barajas-López *et al.*, 1993).

Table XLIV summarizes the receptor subtypes present in the enteric nervous system based on mRNA, protein, and pharmacological and biochemical profiles. The functions claimed for the receptors together with key references are included.

Release of purines following stimulation of NANC inhibitory nerves to the stomach and also from enteric nerves was first observed by Satchell and Burnstock (1971) and Su and colleagues (1971), respectively, and was confirmed in later studies (Belai *et al.*, 1991). ATP was released from nerve varicosities isolated from the myenteric plexus of guinea pig ileum by 5-HT, ACh, and nicotine (Al-Humayyd and White, 1985; Hammond *et al.*, 1988).

In summary, protein for multiple P2X receptor subtypes has been identified for both the myenteric and submucous plexuses, in addition to multiple functional receptors. In contrast, $P2Y_1$ receptors are the only P2Y receptor subtype mRNA, protein, and functional receptor that has been identified (see Fig. 2).

5. Sensory Neurons

In 1983, Jahr and Jessell demonstrated that ATP could excite cultured rat dorsal root ganglion (DRG) neurons and some neurons from the spinal cord and dorsal horn. The excitation was associated with an increase in membrane conductance suggesting P2X receptors, although not identified as such at the time. Similar results were also found in a study of isolated rat and cat nodose, vestibular, trigeminal, and spinal ganglia (Fyffe and Perl, 1984; Krishtal *et al.*, 1983; Mori *et al.*, 1985; Salt and Hill, 1983). Many subsequent studies using voltage-clamp recordings of dissociated sensory neurons followed (see Dunn *et al.*, 2001). Nonmammalian sensory neurons, such as bullfrog DRG neurons, were also activated by ATP (Bean *et al.*, 1990; Tokimasa and Akasu, 1990).

ATP had an excitatory effect on carotid body chemoreceptors (Anichkov and Belen'kii, 1963; Dontas, 1955; Jarisch *et al.*, 1952), although α,β-meATP depressed chemoreceptor discharge (McQueen and Ribeiro, 1983) implying

TABLE XLIV

Enteric Nervous System[a]

Cellular component	Receptor mRNA	Receptor protein		Pharmacological and biochemical profile		Function	References
Enteric plexuses							
Myenteric neurons							
Stomach		$P2X_4$ (D)					Bo *et al.*, 2003[b]
Ileum	$P2Y_1$ (C)	$P2X_3$ (D)	$P2Y_1$ (D)	$P2X_2$ (G)		Purinergic transmission is involved	Kamiji *et al.*, 1994[d]
		$P2X_7$ (D)		$P2X_7$ (G)		in the descending excitatory reflex	Clark *et al.*, 1996[b]
						ATP regulates fast synaptic	LePard and Galligan, 1999[b]
						transmission at both	Hu *et al.*, 2001b[b]
						pre- and postsynaptic sites	Bertrand and Bornstein, 2002[b]
						$P2X_7$ R are associated with nerve	Poole *et al.*, 2002[b]
						fibers on both myenteric and	Ren *et al.*, 2002[b]
						submucous plexuses	Van Nassauw *et al.*, 2002[b]
Colon				P2 (G)		Endogenous opioids inhibit purinergic pathways	Takahashi *et al.*, 1999[e]
Human colon		$P2X_3$ (D)				P2X immunoreactivity in subpopulation of myenteric neurons only	Yiangou *et al.*, 2000[b]
Cultured myenteric				$P2X_1$ (GH)	P2Y (G)	ATP produces membrane	
neurons				$P2X_2$ (GH)		hyperpolarization of Dogiel	Kimball and Mulholland, 1995[c]
				$P2X_4$ (G)		AH/type II neurons	Kimball *et al.*, 1996[c]
				$P2X_5$ (G)		expressing calbindin	Barajas-López *et al.*, 1996[b]
				$P2X_6$ (G)		P2X R mediate fast EPSCs	Christofi *et al.*, 1996, 1997[c]
						P2X and nicotinic R are linked	Zhou and Galligan, 1996, 1998[b]
						in a mutually inhibitory manner	
Submucous plexus	$P2Y_1$ (C)	$P2X_2$ (D)	$P2Y_1$ (D)	P2X (G)	$P2Y_1$ (G)	ATP closes a K^+ channel and opens	Barajas-López *et al.*, 1994,
		$P2X_3$ (D)		$P2X_7$ (G)		a cationic conductance	1995[c]
		$P2X_4$ (D)				through different P2 R	LePard *et al.*, 1997[b]
		$P2X_7$ (D)				$P2X_7$ R is associated with nerve fibers	Bo *et al.*, 2003[b]
						ATP inhibits synaptic ACh release	Hu *et al.*, 2003[c]
Freshly dissociated				$P2X_2$ (G)		ATP activates cation currents	Glushakov *et al.*, 1996, 1998[b]
neurons				$P2X_4$ (G)		unaffected by suramin	Barajas-López *et al.*, 1998, 2002[b]
						or α,β-me ATP	

(*continued*)

TABLE XLIV (*continued*)

Cellular component	Receptor mRNA	Receptor protein	Pharmacological and biochemical profile		Function	References
					P2X and 5-HT_3 channels directly inhibit each other	
Cultured neurons			P2X (GH)	P2Y (GH)	Fast and slow depolarizations are associated with P2X and P2Y R activation	Barajas-López *et al.*, 2000[d]
Myenteric ganglia		$P2X_2$ (D) $P2X_3$ (D)			$P2X_2$ R in NOS-containing neurons P2X R mediate fast synaptic transmission	Castelucci *et al.*, 2002[b] Nurgali *et al.*, 2003[b]
Isolated intestinal segments		$P2X_2$ (D)	P2X (G)	P2Y (G)	ATP acting via P2Y R mediates synaptic transmission between interneurons of the descending inhibitory reflex pathway P2X R are involved in synaptic transmission from descending interneurons to inhibitory motor neurons ATP inhibits peristalsis Mucosal stimulation releases ATP and ACh in both ascending and descending excitatory reflex pathways	Bian *et al.*, 2000[b] Spencer *et al.*, 2000[c] Bornstein *et al.*, 2002[c] Monro *et al.*, 2002[b] Castelucci *et al.*, 2003[b]
Sensory neurons						
Intestine			$P2X_2$ (G) $P2X_{2/3}$ (G)		ATP is involved in chemosensory transduction	Kirkup *et al.*, 1999[b] Holzer, 2001[b] Page *et al.*, 2001[b] Bertrand and Bornstein, 2002[b] Wynn *et al.*, 2003[b]
Abdominal wall			$P2X_3$ (G)			Honore *et al.*, 2002a[b]

[a]See footnote *a* for Table III.
[b]References refer to P2X receptors.
[c]References refer to P2Y receptors.
[d]References refer to P2X and P2Y receptors.
[e]References refer to uncharacterized P2 receptors.

the presence of different P2 receptors since it was shown that ATP was not exerting its effect following degradation to adenosine (Spergel and Lahiri, 1993).

When applied to, or injected intradermally, ATP induced intense pain in humans by stimulating sensory nerve endings in the skin (Bleehen *et al.*, 1976; Coutts *et al.*, 1981) and inducing an increase in sensory nerve discharge (Bleehen and Keele, 1977). Animal studies showed a similar action of ATP, activating nociceptors (Bean, 1990; Bleehen, 1978; Krishtal *et al.*, 1983).

Table XLV summarizes the receptor subtypes present in sensory neurons based on mRNA, protein, and pharmacological and biochemical profiles. The functions claimed for the receptors together with key references are included (cf. Table XLIV).

ATP release was shown from sensory nerve terminals in the rabbit ear following antidromic stimulation (Holton, 1959) and from SCG neurons of the rat following electrical stimulation (Liang and Vizi, 1999). In addition, there is considerable evidence that ATP is released from damaged tissue, such as skin cells (Cook and McCleskey, 2002), which then stimulates nociceptors to initiate pain. Tumor cells contain high concentrations of ATP, which may be released when the tumor reaches a critical size due to abrasive movement of the tumor resulting in leakage of ATP and activation of nociceptive nerve endings (Burnstock, 1996b). ATP is released from the rat carotid body during hypoxia (Xu *et al.*, 2003) and ATP and ACh are co-released during chemotransduction (Zhang *et al.*, 2000a).

In summary, peripheral sensory neurons express mRNA and protein for multiple P2X receptor subtypes. Functionally responses of sensory neurons are a mixture of $P2X_2$ and $P2X_3$ subunits as homomeric and heteromeric receptors. Few studies as to mRNA and protein expression have been carried out for P2Y receptors and only $P2Y_1$ and $P2Y_2$ receptor mRNA and protein have been identified in DRG cell bodies. Functionally $P2X_2$ and $P2X_3$ subunits have been identified as both homomeric and heteromeric receptors. For P2Y receptors, only $P2Y_1$ and $P2Y_2$ receptor subunits have been identified.

6. Glial Cells

a. Astrocytes ATP induced Ca^{2+} release (Kriegler and Chiu, 1993) and PGD_2 synthesis in rat astrocytes (Gebicke-Haerter *et al.*, 1988; Neary *et al.*, 1988, 1991), a process linked to phosphoinositide hydrolysis (Pearce *et al.*, 1989) and identified as a P2Y receptor based on agonist potencies (Bruner and Murphy, 1990; Kastritsis *et al.*, 1992; Seregi *et al.*, 1992). The presence of multiple receptors was shown; a P2U receptor in addition to a P2Y receptor (Bruner and Murphy, 1993) and both purines and pyrimidines induced astrocyte proliferation (Christjanson *et al.*, 1993).

TABLE XLV
Sensory Neurons[a]

Cellular component	Receptor mRNA		Receptor protein		Pharmacological and biochemical profile		Function	References
Cell bodies								
DRG—intact	$P2X_1$ (C) $P2X_2$ (C) $P2X_3$ (C) $P2X_4$ (C) $P2X_5$ (C) $P2X_6$ (C)	$P2Y_1$ (BC) $P2Y_2$ (BC) $P2Y_4$ (B) $P2Y_6$ (B)	$P2X_1$ (D) $P2X_2$ (D) $P2X_3$ (D) $P2X_4$ (D) $P2X_5$ (D) $P2X_6$ (D)	$P2Y_1$ (D) $P2Y_4$ (D)	$P2X_{2/3}$ (G) $P2X_3$ (G)	$P2Y_2$ (G)	$P2X_3$, $P2X_{2/3}$, and $P2Y_2$ R are involved in nociceptive signaling	Lewis *et al.*, 1995[b] Chen *et al.*, 1996a[b] Collo *et al.*, 1996[b] Garcia-Guzman *et al.*, 1997a[b] Bradbury *et al.*, 1998[b] Rae *et al.*, 1998[b] Xiang *et al.*, 1998[b] Moriyama *et al.*, 2003[c] Ruan and Burnstock, 2003[d]
DRG—dissociated	$P2X_2$ (C) $P2X_3$ (C)	$P2Y_1$ (B) $P2Y_2$ (BC)	$P2X_1$ (D) $P2X_2$ (D) $P2X_3$ (D)	$P2Y_1$ (D) $P2Y_2$ (D)	$P2X_{2/3}$ (G) $P2X_3$ (G)	$P2Y_1$ (GH) $P2Y_2$ (G)	ATP stimulates SP release ATP inhibits M-current in bullfrog DRG ATP currents are reversibly depressed by Mg^{2+} representing a negative feedback process to limit ATP-mediated nociception $P2X_3$ R are slowly inhibited via metabotropic $GABA_B$ R UTP stimulates CGRP release $P2Y_2$ R contribute to ATP-mediated sensory signaling	Robertson *et al.*, 1996[b] Svichar *et al.*, 1997[d] Burgard *et al.*, 1999[b] Ueno *et al.*, 1999[b] Li *et al.*, 1999[b] Petruska *et al.*, 2000[b] Piper and Docherty, 2000[b] Song *et al.*, 2000, 2001[b] Tsuda *et al.*, 2000[b] Lalo *et al.*, 2001[b] Nakatsuka *et al.*, 2001[b] Pankratov *et al.*, 2001[b] Tsuzuki *et al.*, 2001, 2003[b] Assis *et al.*, 2002[b] Molliver *et al.*, 2002[c] Sanada *et al.*, 2002[c] Borvendeg *et al.*, 2003[c] Choi *et al.*, 2003a[c] Giniatullin *et al.*, 2003[b]

								Huang *et al.*, 2003[c] Labrakakis *et al.*, 2003[b] Sokolova *et al.*, 2003[b]
Nodose ganglion	$P2X_1$ (CB) $P2X_2$ (CB) $P2X_3$ (C) $P2X_4$ (CB) $P2X_5$ (C) $P2X_6$ (C) $P2X_7$ (B)	$P2Y_1$ (B) $P2Y_2$ (B) $P2Y_4$ (B) $P2Y_6$ (B)	$P2X_1$ (D) $P2X_2$ (D) $P2X_3$ (D) $P2X_4$ (D) $P2X_7$ (D)	$P2Y_1$ (D) $P2Y_4$ (D)	$P2X_{2/3}$ (G) $P2X_3$ (G)		P2X R are involved in visceral sensory processing	Collo *et al.*, 1996[b] Li *et al.*, 1996[b] Garcia-Guzman *et al.*, 1997a[b] Thomas *et al.*, 1998[b] Virginio *et al.*, 1998[b] Xiang *et al.*, 1998[b] Atkinson and Deuchars, 2001[b] Hubscher *et al.*, 2001[b] Fong *et al.*, 2002[c] Ruan and Burnstock, 2003[d]
Trigeminal ganglion	$P2X_1$ (C) $P2X_2$ (C) $P2X_3$ (C) $P2X_4$ (C) $P2X_5$ (C) $P2X_6$ (C)	$P2Y_1$ (B) $P2Y_2$ (B) $P2Y_4$ (B) $P2Y_6$ (B)	$P2X_1$ (D) $P2X_2$ (D) $P2X_3$ (D) $P2X_4$ (D) $P2X_5$ (D) $P2X_6$ (D)	$P2Y_1$ (D) $P2Y_4$ (D)				Collo *et al.*, 1996[b] Garcia-Guzman *et al.*, 1997a[b] Llewellyn-Smith and Burnstock, 1998[b] Xiang *et al.*, 1998[b] Jiang and Gu, 2002[b] Ruan and Burnstock, 2003[d]
Petrosal ganglion	$P2X_2$ (B) $P2X_3$ (B)		$P2X_2$ (D) $P2X_3$ (D)		$P2X_{2/3}$ (G)		ATP activates carotid sinus nerves	Alcayaga *et al.*, 2000, 2003[b] Zhang *et al.*, 2000a[b] Prasad *et al.*, 2001[b]
Spinal (dorsal horn)			$P2X_1$ (D) $P2X_2$ (D) $P2X_3$ (D) $P2X_4$ (D) $P2X_6$ (D)		$P2X_3$ (G)			Collo *et al.*, 1996[b] Gu and MacDermott, 1997[b] Nörenberg and Illes, 2000[b] Zheng and Chen, 2000[b]
Vestibular ganglion					$P2X_2$ (D) $P2X_3$ (D)			Xiang *et al.*, 1999[b]
Spiral ganglion	$P2X_2$ (BC)		$P2X_1$ (D) $P2X_2$ (D) $P2X_3$ (D) $P2X_4$ (D) $P2X_7$ (D)		P2X (G) $P2X_2$ (G)	P2Y (G)		Cho *et al.*, 1997[c] Housley *et al.*, 1999, 2002[b] Salih *et al.*, 1998, 1999, 2002[c] Xiang *et al.*, 1999[b] Järlebark *et al.*, 2000[b]

(*continued*)

TABLE XLV (*continued*)

Cellular component	Receptor mRNA	Receptor protein	Pharmacological and biochemical profile		Function	References
						Ito and Dulon, 2002[b]
						Nikolic *et al.*, 2003[b]
Substantia gelatinosa			P2 (G)		ATP acts as a synaptic modulator	Li and Perl, 1995[e]
Peripheral terminals						
Skin (amphibian)			P2 (G)		ATP modulates touch R	Fallon *et al.*, 2002[e]
Skin (foot pad)	$P2X_3$ (B)		$P2X_3$ (G)	$P2Y_1$ (G)	P2X and $P2Y_2$ R are involved	Nakamura and Strittmatter, 1996[c]
				$P2Y_2$ (G)	in thermal hyperalgesia	Bland-Ward and Humphrey, 1997[b]
						Cockayne *et al.*, 2000[b]
						Hamilton *et al.*, 2000, 2001[b]
						Souslova *et al.*, 2000[b]
						Jarvis *et al.*, 2001[b]
						Cook and McCleskey, 2002[b]
						Honore *et al.*, 2002b[b]
						Moriyama *et al.*, 2003[c]
Sweat glands				$P2Y_2$ (H)		Rakhit *et al.*, 1995[c]
Knee joint			P2X (G)			Hurt *et al.*, 1994[b]
Tooth pulp		$P2X_3$ (D)	$P2X_3$ (G)		ATP initiates nociception	Dowd *et al.*, 1998[b]
						Cook *et al.*, 1997[b]
						Alavi *et al.*, 2001[b]
						Jiang and Gu, 2002[b]
						Renton *et al.*, 2003[b]
Vibrissae		$P2X_3$ (D)		P2Y (H)		Cheung and Burnstock, 2002[b]
						Takahashi-Iwanaga and Habara, 2002[c]
Tongue—taste		$P2X_2$ (D)	$P2X_3$ (G)	P2Y (GH)	ATP modulates taste	Bo *et al.*, 1999[b]
		$P2X_3$ (D)	$P2X_{2/3}$ (G)		ATP evokes discharge in lingual nerves	Kim *et al.*, 2000[c]
Tongue—nociception		$P2X_2$ (D)	$P2X_3$ (G)		ATP mediates nociception	Rong *et al.*, 2000[b]
		$P2X_3$ (D)				
Carotid body	$P2X_2$ (B)	$P2X_2$ (D)	$P2X_{2/3}$ (G)	$P2Y_2$ (H)	ATP is a cotransmitter	Zhang *et al.*, 2000a[b]

	$P2X_3$ (B)	$P2X_3$ (D)			ATP modulates O_2 sensing ATP and UTP increase $[Ca^{2+}]_i$ ATP triggers vagal reflexes ATP attenuates reflex increases in sympathetic nerve activity	Prasad *et al.*, 2001[b] Rong *et al.*, 2003[b] Xu *et al.*, 2003[c]
Heart			P2X (G)			Katchanov *et al.*, 1996, 1997[b] Taneyama *et al.*, 1997[b]
CNS terminals						
Dura mater				$P2Y_2$ (G)		Zimmermann *et al.*, 2002[c]
Spinal cord lammena II		$P2X_3$ (D)				Collo *et al.*, 1996[b]
Unmyelinated axons						
Vagus nerve			$P2X_3$ (G)		ATP is involved in sensory/ nociceptive transduction	Trezise *et al.*, 1994a,b[b] Burgstahler and Grafe, 2001[b]
Sural nerve			P2X (G)	$P2Y_2$ (H)		Wächtler *et al.*, 1996[c] Irnich *et al.*, 2002[b]
Sciatic nerve		$P2X_3$ (D)		P2Y (G)		Vulchanova *et al.*, 1998[b] Chen *et al.*, 2000c[c]
Viscera						
Urinary bladder		$P2X_3$ (D) $P2X_{2/3}$ (D)	$P2X_3$ (G) $P2X_{2/3}$ (G)		ATP is involved in visceral mechanosensory transduction—nociception and non-nociception	Namasivayam *et al.*, 1999[b] Sun *et al.*, 2001[b] Vlaskovska *et al.*, 2001[b] Rong *et al.*, 2002[b]
Ureter		$P2X_3$ (D) $P2X_{2/3}$ (D)				Knight *et al.*, 2002[b]
Gut	See Table XLIV					

[a]See footnote *a* for Table III.
[b]References refer to P2X receptors.
[c]References refer to P2Y receptors.
[d]References refer to P2X and P2Y receptors.
[e]References refer to uncharacterized P2 receptors.

b. Microglia Cultured rat and mouse microglial cells responded to ATP with an activation of a cation conductance and an accompanying increase in cytosolic Ca^{2+} (Kettenmann *et al.*, 1993; Walz *et al.*, 1993), although the receptor subtype for this action was not identified until later.

c. Schwann Cells In the frog, motor nerve stimulation elicited a rise in $[Ca^{2+}]_i$ of perisynaptic Schwann cells, which was mimicked by local application of ATP (Jahromi *et al.*, 1992). In addition, ATP inhibited Schwann cell proliferation in regenerating nerves (Edstrom *et al.*, 1992).

d. Oligodendrocytes ATP induced an increase in $[Ca^{2+}]_i$ in mature oligodendrocytes (Kastritsis and McCarthy, 1993).

Table XLVI summarizes the receptor subtypes present in glial cells based on mRNA, protein, and pharmacological and biochemical profiles. The functions claimed for the receptors together with key references are included (Fig. 10).

Astrocytes are the main cerebral source of extracellular ATP (Caciagli *et al.*, 1988, 1989; Ciccarelli *et al.*, 2001), which is released from astrocytes in response to various stimuli, including glutamate and bradykinin receptor stimulation (Coco *et al.*, 2003; Queiroz *et al.*, 1997, 1999; Verderio and Matteoli, 2001) and hypo-osmotic and mechanical stimulation (Darby *et al.*, 2003; Newman, 2003; Ueno *et al.*, 2000; Verderio and Matteoli, 2001). The propagation of Ca^{2+} signaling over large distances in the form of Ca^{2+} waves may involve ATP release (Guthrie *et al.*, 1999; Haydon, 2001) controlled by the gap junction proteins, connexins (Cotrina *et al.*, 1998).

ATP is released from microglia (Ciccarelli *et al.*, 2001; Shigemoto-Mogami *et al.*, 2001) independently of cell lysis (Di Iorio *et al.*, 2002). ABC protein inhibitors significantly reduce basal and electrically stimulated ATP release, implying that ABC proteins are not the sole mechanism of ATP release from microglia, which may also include vesicular release (Ballerini *et al.*, 2002).

The release of ATP from the retina has been visualized using luciferin/luciferase and it is thought that the Ca^{2+} waves are propagated from astrocytes to Müller cells and from Müller cells to other Müller cells by the release of ATP (Newman, 2003).

In summary, astrocytes express mRNA for multiple P2X and P2Y receptor subtypes and receptor protein for multiple P2X receptors, although only protein for $P2Y_1$ receptors has as yet been identified. Functionally astrocytes have been shown to express $P2X_2$ and $P2X_7$ receptor subunits in addition to several P2Y receptors. Less is known about the expression of P2X and P2Y receptor mRNA and protein in microglia, where $P2X_7$ receptors are prominent and $P2Y_1$, $P2Y_4$, and $P2Y_{12}$ receptors have been identified. Schwann cells have been shown to possess $P2X_7$ receptors by functional studies in addition to $P2Y_1$ and $P2Y_2$ receptors, however, there are no studies as to the

TABLE XLVI

Glial Cells[a]

Cellular component	Receptor mRNA		Receptor protein		Pharmacological and biochemical profile		Function	References
Astrocytes Type 1 astrocytes from Cerebellar Cortex Hippocampus Nucleus accumbens Neurohypophysis (pituicytes) Optic nerve Spinal cord Striatum	$P2X_1$ (B) $P2X_2$ (B) $P2X_3$ (B) $P2X_4$ (B) $P2X_5$ (B) $P2X_6$ (B) $P2X_7$ (B)	$P2Y_1$ (AB) $P2Y_2$ (AB) $P2Y_4$ (AB) $P2Y_6$ (AB)	$P2X_1$ (D) $P2X_2$ (D) $P2X_3$ (D) $P2X_4$ (D) $P2X_6$ (D) $P2X_7$ (D)	$P2Y_1$ (D)	$P2X_2$ (I) $P2X_7$ (G)	$P2Y_1$ (GH) or $P2Y_{12}$ (GH) $P2Y_2$ (GH) $P2Y_4$ (GH) $P2Y_6$ (G)	$P2Y_1$ (or $P2Y_{12}$) R mediate reactive astrogliosis via COX-2 (Astrogliosis *in vivo* may be associated with upregulation of P2X R) P2Y R mediates proliferation, prostanoid synthesis, propagation of Ca^{2+} waves between astrocytes, and between astrocytes and microglia P2Y R activation results in immediate early gene expression ATP activates $P2Y_1$ and $P2Y_2$ R stimulating AA release ATP modulates amino acid release ATP (and GTP) is involved in brain repair ATP stimulates glutamate release Astrocyte injury causes ATP-dependent astrocyte-endothelial Ca^{2+} signaling Synergistic action of ATP and NGF on DNA synthesis $P2Y_6$ R stimulation reduces cell death	Ciccarelli *et al.*, 1994[c] Pearce and Langley, 1994[b] Neary and Zhu, 1994[c] Neary *et al.*, 1994,[b] 1999,[c] 2001,[b] 2003[b] Salter and Hicks, 1994[c] Walz *et al.*, 1994[b] Ho *et al.*, 1995[c] Chen and Chen, 1996, 1998[c] King *et al.*, 1996[c] Bolego *et al.*, 1997, 2001[c] Ishimoto *et al.*, 1997[c] Lin and Murphy, 1997[c] Reetz *et al.*, 1997[c] Stella *et al.*, 1997[c] Bernstein *et al.*, 1998[c] Deng *et al.*, 1998[c] Idestrup and Salter, 1998[c] Loesch and Burnstock, 1998, 2001[b] Priller *et al.*, 1998[c] Scemes *et al.*, 1998[c] Webb *et al.*, 1998[c] Brambilla *et al.*, 1999, 2002, 2003[c] Franke *et al.*, 1999, 2001a,b, 2003b[b] Kanjhan *et al.*, 1999[b] Loesch *et al.*, 1999[b] Troadec *et al.*, 1999[c] Cotrina *et al.*, 2000[c] Fam *et al.*, 2000, 2003[c]

(*continued*)

TABLE XLVI (*continued*)

Cellular component	Receptor mRNA		Receptor protein	Pharmacological and biochemical profile		Function	References
							Jiménez *et al.*, 2000, 2002[c] Lenz *et al.*, 2000[c] Sergeeva *et al.*, 2000[c] Wang *et al.*, 2000b[c] Delicado *et al.*, 2001[c] James and Butt, 2001[d] Jeremic *et al.*, 2001[c] John *et al.*, 2001[c] Kukley *et al.*, 2001[b] Panenka *et al.*, 2001[b] Shiga *et al.*, 2001[c] Zhu and Kimelberg, 2001[c] Bal-Price *et al.*, 2002[c] Kaya *et al.*, 2002[b] Koizumi *et al.*, 2002[c] Mongin and Kimelberg, 2002[c] Yamakuni *et al.*, 2002[c] Bo *et al.*, 2003[b] Darby *et al.*, 2003[c] Gallagher and Salter, 2003[c] Kim *et al.*, 2003b[c] Murakami *et al.*, 2003a[c] Nobile *et al.*, 2003[b]
Fetal primary astrocyte cultures	$P2X_7$ (B)	$P2Y_1$ (B) $P2Y_2$ (B) $P2Y_4$ (B)		$P2X_7$ (G)	P2Y (G)	ATP regulates IL-1β signaling ATP stimulates mitogenic signaling	Ballerini *et al.*, 1996[b] Kimelberg *et al.*, 1997[b] Neary *et al.*, 1998[c] John *et al.*, 1999,[c] 2001[b] Zhu and Kimelberg, 2001[c] Wang *et al.*, 2002a[d]
Rat brain-derived type 2 astrocyte cell line RBA-2	$P2X_4$ (B) $P2X_7$ (B)		$P2X_4$ (E) $P2X_7$ (E)	$P2X_7$ (G)		$P2X_7$ R induce Ca^{2+} influx and PLD activation $P2X_{4\text{ and }7}$ R mediate GABA release	Sun *et al.*, 1999[b] Hung and Sun, 2002[b] Sun, 2002[b]

Microglia	$P2X_7$ (C)	$P2Y_1$ (B) $P2Y_4$ (B) $P2Y_6$ (B)	$P2X_4$ (D) $P2X_7$ (D)	$P2Y_4$ (D)	$P2X_7$ (H)	$P2Y_1$ (GH) $P2Y_2$ (GH) or $P2Y_4$ (GH) $P2Y_{12}$ (G)	ATP induces ramification of microglia *in vitro* ATP triggers TNF-α release ATP (probably via P2Y R) induces early gene formation ATP potentiates LPS-induced NO production ATP induces production of NO and inducible NOS mRNA ATP induces the release of plasminogen $P2X_4$ R are upregulated following nerve injury $P2X_7$ R mediate IL-1β release P2Y R mediate IL6 release P2Y R are involved in astrocytic–microglia signaling	Ilschner *et al.*, 1995[c] Priller *et al.*, 1995[c] Ferrari *et al.*, 1996[d], 1999a,b[b] Haas *et al.*, 1996[b] Illes *et al.*, 1996[d] Chessell *et al.*, 1997a[b] Collo *et al.*, 1997[c] Nörenberg *et al.*, 1997[c] Deng *et al.*, 1998[c] Inoue *et al.*, 1998[b] Toescu *et al.*, 1998[c] McLarnon *et al.*, 1999[c] Visentin *et al.*, 1999[b] Hide *et al.*, 2000[b] Möller *et al.*, 2000[c] Morigiwa *et al.*, 2000[d] Ohtani *et al.*, 2000[c] Wang *et al.*, 2000a[d] Honda *et al.*, 2001[c] Verderio and Matteoli, 2001[b] Wollmer *et al.*, 2001[c] Brough *et al.*, 2002[b] Chakfe *et al.*, 2002[b] Inoue, 2002[c] Bennett *et al.*, 2003[c] Boucsein *et al.*, 2003[d] Duan *et al.*, 2003[b] Tsuda *et al.*, 2003[b] Weick *et al.*, 2003[c]
Schwann cells								
Nonmyelinating					P2X (H)	$P2Y_1$ (H) $P2Y_2$ (H)	ATP mediates neuron–Schwann cell signaling	Ansselin *et al.*, 1997[c] Mayer *et al.*, 1998[c] Stevens and Fields, 2000[c] Fields and Stevens, 2000[c] Irnich *et al.*, 2001[c]

(*continued*)

TABLE XLVI (*continued*)

Cellular component	Receptor mRNA	Receptor protein	Pharmacological and biochemical profile		Function	References
Myelinating			$P2X_7$ (H)	$P2Y_2$ (H)	ATP arrests maturation and prevents the formation of myelin $P2X_7$ R may contribute to cell reactions in nerve injury	Lyons *et al.*, 1994[c] Mayer *et al.*, 1997[c] Grafe *et al.*, 1999[b]
Frog neuromuscular junction			P2X (H)			Robitaille, 1995[b]
DRG			P2X (G)			Vinogradova *et al.*, 1994[b]
Cultured Schwann cells		$P2X_7$ (D)	$P2X_7$ (GH)	$P2Y_2$ (H) or $P2Y_4$ (H)	ATP stimulates release of excitatory amino acids	Amédée and Deapeyroux, 1995[b] Ansselin *et al.*, 1997[c] Jeftinija and Jeftinija, 1998[c] Colomar and Amédée, 2001[b]
Skate electric organ				P2Y (H)		Green *et al.*, 1997[c]
Oligodendrocytes		$P2Y_1$ (D)	$P2X_7$ (H)	$P2Y_1$ (H) $P2Y_2$ (H) or $P2Y_4$ (H) $P2Y_{12}$ (H)	P2Y R may play a role in neuron–glial signal transfer	Salter and Hicks, 1994[c] Kirischuk *et al.*, 1995[c] Móran-Jiménéz and Matute, 2000[c] James and Butt, 2001[d] Laitinen *et al.*, 2001[c]
Enteric glial cells				$P2Y_2$ (G) or $P2Y_4$ (G)		Kimball and Mulholland, 1996[c] Sarosi *et al.*, 1998[c] Heinemann *et al.*, 1999[c]
Neural stem cells				P2Y (G)	ATP stimulates culture proliferation	Ryu *et al.*, 2003[c]
Müller glial cells	See Table XLVII					

[a]See footnote *a* for Table III.
[b]References refer to P2X receptors.
[c]References refer to P2Y receptors.
[d]References refer to P2X and P2Y receptors.

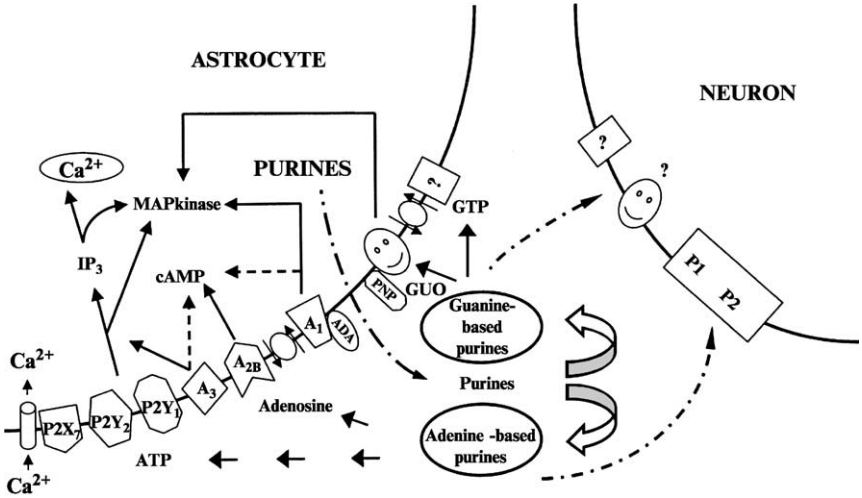

FIG. 10 Schematic representation of the purine receptors expressed by astrocytes and of the principal transduction pathways activated (solid lines) or inhibited (dashed lines) by the stimulation of such receptors. "?" refers to the possible existence of receptors for guanine-based purines, for which studies are currently in development. Once released from astrocytes (dot-dashed line) purines can interact with the respective receptors on astrocytes or on neurons, exerting trophic effects as reported in different sections of the review. Adenosine released as such or derived from ATP metabolism may be taken up from cells by specific transport systems (represented by ↑O↓). (Reproduced, with permission, from Ciccarelli *et al.*, 2001.) Since this was presented in 2001, additional evidence has been presented for the expression of $P2Y_6$ and $P2Y_{12}$ mRNA in cortical astrocytes (Franke *et al.*, 2001a; Kim *et al.*, 2003b).

expression of P2X and P2Y receptor mRNA and protein in Schwann cells with the exception of $P2X_7$ receptor protein, which has been identified on cultured Schwann cells. Similarly, functional studies have identified $P2X_7$ receptors on oligodendrocytes and Müller cells, both of which express $P2Y_1$ and $P2Y_2$ receptors. mRNA for multiple P2X receptor subtypes has also been shown for Müller cells.

N. Special Senses

1. Eye

In the late 1950s, the injection of exogenous ATP into the carotid artery of the rabbit caused a rise in intraocular pressure in addition to an increase in the permeability of the blood–aqueous barrier (Perkins, 1959). These experiments were designed to test the hypothesis that antidromic stimulation of the first division of the trigeminal nerve, which results in pupil contraction,

vasodilatation of ocular vessels, and an increase in capillary permeability resulting in a rise in intraocular pressure, released ATP, which was responsible for these effects. ATP mimicked some of the effects of antidromic stimulation, and as such it was concluded that ATP accounted for some of the consequences of trigeminal stimulation. This research was carried further and it was shown that ATP was released upon antidromic stimulation of the trigeminal nerve (Maul and Sears, 1979).

It has been shown that with aging, there is a decrease in ATP content of the bovine lens (Hockwin *et al.*, 1973/74); this was thought to have implications in the aging and opacity of the lens. In contrast, the ATP content of the human lens was found to differ very little with age from normal subjects (Nordmann and Klethi, 1978), although the ATP content of older human cataract lenses was significantly less than age-matched clear lenses (Harding and Crabbe, 1984; Iwata and Takehana, 1982).

ATP was thought to be a cotransmitter with NA in the neurally mediated contractile response of the cat nictitating membrane, as α,β-meATP induced a contraction and could inhibit the residual responses evoked by sympathetic nerve stimulation in reserpinized cats (Duval *et al.*, 1985).

There is evidence that ATP has a role in iris muscle contraction. α,β-meATP reduced the tonic phase of neurogenic contractions of rabbit iris sphincter muscles (Onisile and Westfall, 1990). This prejunctional effect has been investigated further. ATP inhibited field stimulation-evoked NA release from the rat iris (Funder *et al.*, 1992); the receptor subtype was identified subsequently as a P2Y receptor (Fuder and Muth, 1993).

The two epithelial cell types of the ocular ciliary body, the pigmented and nonpigmented epithelia, both possess P2 receptors, originally classified as belonging to the P2U subtype (Wax *et al.*, 1993). The activity of these receptors is thought to be of importance since the ciliary epithelium regulates secretion of proteins and ions resulting in the formation of aqueous humor, the continuous and balanced formation of which determines the intraocular pressure.

A subpopulation of rat corneal nerve fibers fluoresces when stained with the dye quinacrine (Cavallotti *et al.*, 1982).

As found with other blood vessels, the endothelium of the microvasculature of the retina was shown to possess P2 receptors, the activity of which is important in the maintenance of normal retinal vascular tone. Both ATP and ADP stimulated the accumulation of inositol phosphates within the endothelium and prostacyclin formation (Robertson *et al.*, 1990). Further studies identified the receptor as belonging to the P2Y subtype based on agonist activity (Tao *et al.*, 1992).

Other structures within the eye also respond to ATP via P2 receptors. Exogenously applied ATP to the mouse and rat lacrimal acinar cells augmented ionic permeability and elevated $[Ca^{2+}]_i$ (Sasaki and Gallacher,

1990; Vincent, 1992). ATP directly activated receptor-operated cation channels and is therefore acting via a P2X receptor (Sasaki and Gallacher, 1992).

Table XLVII summarizes the receptor subtypes present in the eye based on mRNA, protein, and pharmacological and biochemical profiles. The functions claimed for the receptors together with key references are included (cf. Tables XXIV and XLVI; see Fig. 11).

Increased ATP levels in aqueous humor were observed following antidromic stimulation of the trigeminal nerve, and it was thought that stimulation of sensory nerves caused the release of ATP (Maul and Sears, 1979). The fluorescent ATP marker quinacrine was shown to stain rabbit and bovine ciliary epithelia but not the nerve fibers in the ciliary bodies and ATP release from cultured bovine ocular ciliary epithelial cells when hypotonically stimulated (Mitchell *et al.*, 1998). The highly secretory epithelial cells of the ciliary processes of the ciliary body responsible for the continuous secretion of aqueous humor also release ATP (Mitchell, 2001). Release of ATP from the cornea was also induced by shear stress (Srinivas *et al.*, 2002). ATP (ADP and AMP) together with Ap_4A and Ap_5A is present in aqueous humor (Pintor and Peral, 2001; Pintor *et al.*, 2002b, 2003) and tears (Pintor *et al.*, 2002a).

In summary, structures within the eye have been shown to express mRNA and protein for multiple P2X receptor subtypes and mRNA for multiple P2Y receptor subtypes, although the expression of protein for P2Y receptors is lacking. Functionally, although P2X receptors have been identified in structures of the eye, few have been characterized, with the exception of $P2X_7$ receptors in structures of the retina. $P2Y_1$ and $P2Y_2$ receptors are the only P2Y receptors identified functionally in the eye.

2. Inner Ear

The first report of the effect of extracellular ATP on inner ear function resulted from a screening study by Bobbin and Thompson in 1978, during a search for neurotransmitter substances by perfusing potential neurotransmitter substances into the perilymph at low to moderate sound levels. They found that ATP was one of the more potent substances to reduce activity of the cochlear nerve. ATP was later found to directly activate both P2X and P2Y receptors on sensory hair cells of both the chick and guinea pig (Ashmore and Ohmori, 1990; Nakagawa *et al.*, 1990; Shigemoto and Ohmori, 1990). The inhibitory effects of ATP and analogues on electrocochleography were largely attributable to stimulation of P2Y receptors acting on several sites. These include the organ of Corti, where ATP induced inositol phosphate release (Niedzielski and Schacht, 1992), probably by an action on the outer hair cell. The localization of P2Y receptors on outer hair

TABLE XLVII
Eye[a]

Cellular components	Receptor mRNA		Receptor protein	Pharmacological and biochemical profile		Function	References
Iris smooth muscle				P2X (G)	P2Y (G)	ATP contracts iris muscle	Muramatsu *et al.*, 1994[d]
Retina							
Whole retina				P2X (G)		ATP modulates ACh release	Neal and Cunningham, 1994[b] Neal *et al.*, 1995[b]
Retinal slice				$P2X_7$ (G)		$P2X_7$ R stimulation enhances IL-1β, and TNF-α release	Pintor, 1998[d]
Retinal microglia				$P2X_7$ (H)	$P2Y_2$ (H)		Greenwood *et al.*, 1997[b]
Retinal ganglion cells	$P2X_2$ (BC) $P2X_3$ (B) $P2X_4$ (B) $P2X_5$ (B) $P2X_7$ (B)	$P2Y_1$ (BC) $P2Y_2$ (BC) $P2Y_4$ (BC) $P2Y_6$ (BC)	$P2X_1$ (D) $P2X_2$ (D) $P2X_3$ (D) $P2X_4$ (D) $P2X_7$ (D)	$P2X_7$ (G)		$P2Y_2$ R stimulation may underlie mitotic response	Brändle *et al.*, 1998a,b[b] Morigiwa *et al.*, 2000[d] Davis and Baldridge, 2000[b] Innocenti *et al.*, 2001[b] Wheeler-Schilling *et al.*, 2001[b] Ishii *et al.*, 2003[b]
Retinal ganglion cells in culture				P2X (G)		ATP increases $[Ca^{2+}]i$	Taschenberger *et al.*, 1999[b]
Bipolar neurones	$P2X_3$ (B) $P2X_4$ (B) $P2X_5$ (B)					Neuromodulation of visual processing	Wheeler-Schilling *et al.*, 2000[b]
Inner nuclear layer	$P2X_2$ (BC)	$P2Y_1$ (C) $P2Y_2$ (C) $P2Y_4$ (C) $P2Y_6$ (BC)	$P2X_1$ (D) $P2X_2$ (D) $P2X_3$ (D) $P2X_4$ (D) $P2X_7$ (D)				Greenwood *et al.*, 1997[b] Brändle *et al.*, 1998a,b[b] Davis and Baldridge, 2000[b] Wheeler-Schilling *et al.*, 2001[b] Cowlen *et al.*, 2003[c] Ishii *et al.*, 2003[b]
Inner plexiform layer	$P2X_2$ (C)		$P2X_1$ (D) $P2X_2$ (D) $P2X_7$ (D)				Greenwood *et al.*, 1997[b] Ishii *et al.*, 2003[b]
Outer plexiform layer			$P2X_4$ (D) $P2X_7$ (D)				Davis and Baldridge, 2000[b]
Photoreceptors	$P2X_2$ (BC)		$P2X_2$ (D)				Greenwood *et al.*, 1997[b] Peral and Pintor, 1998[b]

Müller cells	$P2X_3$ (B) $P2X_4$ (B) $P2X_5$ (B) $P2X_7$ (B)	$P2X_7$ (D)	P2X (G) $P2X_7$ (H)	$P2Y_1$ (GH) $P2Y_2$ (GH) $P2Y_4$? (H) $P2Y_6$ (H) $P2Y_{11}$ (H) $P2Y_{13}$? (H)	ATP and UTP increase $[Ca^{2+}]i$ ATP involved in neuronal–glial signaling ATP modulates GABA release from retina P2Y R stimulate proliferation $P2Y_1$ R mediate Ca^{2+} waves, K^+, and cation currents $P2Y_2$ R mediate glial DNA synthesis	Liu and Wakakura, 1998[c] Neal *et al.*, 1998[d] Jabs *et al.*, 2000[b] Pannicke *et al.*, 2000[b] Bringmann *et al.*, 2001[b] Li *et al.*, 2001a,b[c] Newman, 2001[c] Wheeler-Schilling *et al.*, 2001[b] Bringmann *et al.*, 2002a,b[c] Moll *et al.*, 2002[c] Milenkovic *et al.*, 2003[c] Reifel Saltzberg *et al.*, 2003[c]
Pigmented epithelial cells		$P2Y_2$ (BC)	P2X (GH)	$P2Y_2$ (GH)	ATP increases $[Ca^{2+}]_i$ UTP increases fluid absorption	Peterson *et al.*, 1997[c] Sullivan *et al.*, 1997[c] Ryan *et al.*, 1999[d] Maminishkis *et al.*, 2002[c] Cowlen *et al.*, 2003[c]
Ciliary body						
Pigmented ciliary epithelia		$P2Y_2$ (C)		$P2Y_1$ (G) $P2Y_2$ (GH)	ATP involved in autocrine regulation of secretion ATP increases $[Ca^{2+}]_i$	Shahidullah and Wilson, 1997[c] Fleischhauer *et al.*, 2001[c] Cowlen *et al.*, 2003[c]
Nonpigmented epithelia		$P2Y_2$ (C)		$P2Y_1$ (H) $P2Y_2$ (H)	ATP and UTP regulate aqueous humor secretion ATP increases $[Ca^{2+}]_i$	Cullinane *et al.*, 1995[c] Farahbakhsh and Cilluffo, 2002[c] Cowlen *et al.*, 2003[c]
Conjunctiva epithelial cells		$P2Y_2$ (C)		$P2Y_2$ (G)	ATP and UTP stimulate Cl^- and fluid secretion	Hosoya *et al.*, 1999[c] Murakami *et al.*, 2000, 2003b[c] Shiue *et al.*, 2000[c] Li *et al.*, 2001c[c] Pintor *et al.*, 2002b[c] Cowlen *et al.*, 2003[c] Kulkarni *et al.*, 2003[c]

(*continued*)

TABLE XLVII (*continued*)

Cellular components	Receptor mRNA	Receptor protein	Pharmacological and biochemical profile	Function	References
Lens epithelial cells	$P2Y_2$ (C)		$P2Y_2$ (GH)	ATP regulates fluid transport ATP increases $[Ca^{2+}]_i$	Zhang and Jacob, 1994[c] Riach *et al.*, 1995[c] Churchill and Louis, 1997[c] Cowlen *et al.*, 2003[c]
Cornea					
Epithelial cells	$P2Y_2$ (C)	$P2X_5$ (D) $P2X_7$ (D)	$P2Y_1$ (H) $P2Y_2$ (H)	ATP and UTP increase $[Ca^{2+}]_i$ P2Y R regulate proliferation	Gröschel-Stewart *et al.*, 1999a[b] Kimura *et al.*, 1999[c] Klepeis *et al.*, 2001[d] Kubo-Watanabe *et al.*, 2002[c] Cowlen *et al.*, 2003[c]
Endothelial cells			P2X (GH)	$P2Y_1$ (GH) $P2Y_2$ (GH)	ATP induces endothelial proliferation ATP and UTP increase $[Ca^{2+}]_i$	Rae and Watsky, 1996[b] Srinivas *et al.*, 1998[b] Cha *et al.*, 2000[c]
Choroid	$P2X_2$ (B) $P2X_4$ (B)	$P2Y_2$ (C)			ATP involved in visual processing	Brändle *et al.*, 1998a,b[b] Meyer *et al.*, 2002[c] Cowlen *et al.*, 2003[c]
Lacrimal gland acinar cells			$P2Y_2$ (G)		ATP and UTP stimulate tear secretion	Pintor *et al.*, 2002b[c]
Optic nerve	$P2Y_2$ (C)					Cowlen *et al.*, 2003[c]
Glial cells	See Table XLVI					
Eye vasculature	See Table XXIV					

[a]See footnote *a* for Table III.
[b]References refer to P2X receptors.
[c]References refer to P2Y receptors.
[d]References refer to P2X and P2Y receptors.

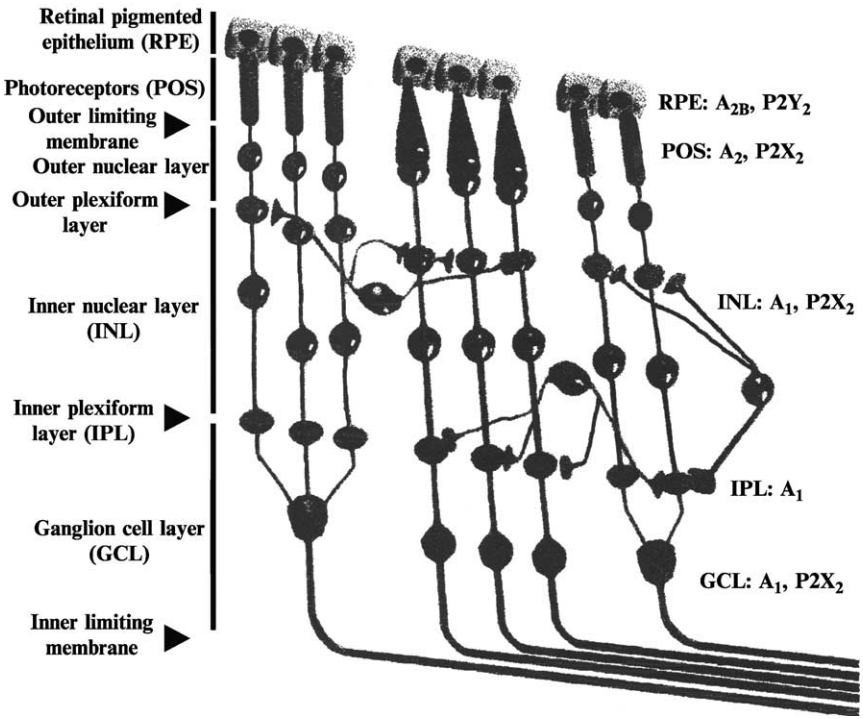

FIG. 11 Schematic representation of the retina and the purinergic receptors present in the different cell types. (Reproduced, with permission, from Peral and Pintor, 1998.)

cells suggested that ATP was mediating a humoral modulation of the mechano-electrical transduction processes of the cochlea (Heilbronn *et al.*, 1993; Housley *et al.*, 1992). Both Deiters' and Hensen cells, support cells of the organ of Corti, respond to submicromolar concentrations of ATP (Dulon *et al.*, 1993).

Purinergic signaling in the vestibular system has been proposed. A P2Y receptor-mediated effect in vestibular sensory epithelium has been shown (Ogawa and Schacht, 1993). In addition, ATP applied to hair cells of the guinea pig cochlea induced membrane currents (Dulon *et al.*, 1991; Rennie and Ashmore, 1993); the receptor subtype responsible was tentatively identified as a P2z receptor.

Table XLVIII summarizes the receptor subtypes present in the inner ear based on mRNA, protein, and pharmacological and biochemical profiles. The functions claimed for the receptors together with key references are included (cf. Tables XXIV and XLV; see Fig. 12).

TABLE XLVIII
Inner Ear[a]

Cellular component	Receptor mRNA	Receptor protein	Pharmacological and biochemical profile		Function	References
Cochlea—whole	$P2X_1$ (C) $P2X_{2\text{-}1}$ (C) $P2X_{2\text{-}2}$ (C) $P2X_{2\text{-}3}$ (C)	$P2X_1$ (D)	$P2X_2$ (G)	P2Y (G)	ATP influences cochlear function ATP increases $[Ca^{2+}]_i$	Kujawa *et al.*, 1994[c] Housley *et al.*, 1999[b] Chen *et al.*, 2000a[b] Nikolic *et al.*, 2001[b]
Outer sulcus cells		$P2X_2$ (D)	$P2X_2$ (G)		P2X R regulate endolymph concentrations	Järlebark *et al.*, 2000[b] Lee *et al.*, 2001b[b]
Pillar cells	$P2X_2$ (C)			P2Y (H)	ATP increases $[Ca^{2+}]_i$	Chung and Schacht, 2001[c]
Cochlea hair cells						
Inner	$P2X_2$ (C)	$P2X_1$ (D) $P2X_2$ (D) $P2X_7$ (D)	P2X (G)	P2Y (G)	ATP increases $[Ca^{2+}]_i$ ATP via $P2X_2$ R regulates excitability of primary afferent dendrites	Sugasawa *et al.*, 1996a[b] Järlebark *et al.*, 2000, 2002[b] Nikolic *et al.*, 2001, 2003[b] Robertson and Paki, 2002[b]
Outer	$P2X_2$ (C)	$P2X_1$ (D) $P2X_2$ (D) $P2X_7$ (D)	P2X (G)	P2Y (GH)	ATP increases $[Ca^{2+}]_i$ ATP via P2X R regulates cochlear function	Nilles *et al.*, 1994[c] Chen *et al.*, 1995a,b[b] Van Den Abbeele *et al.*, 1996[d] Raybould and Housley, 1997[b] Spreadbury and Ashmore, 1997[b] Kirk and Yeats, 1998[b] Wikström *et al.*, 1998[b] Järlebark *et al.*, 2000, 2002[b] Nikolic *et al.*, 2001, 2003[b]
Stereocilia		$P2X_2$ (D)		P2Y (GH)	ATP increases $[Ca^{2+}]_i$	Housley *et al.*, 1999[b] Mammano *et al.*, 1999[c] Järlebark *et al.*, 2000, 2002[b]

Otoconial membrane						P2Y (H)	ATP increases $[Ca^{2+}]_i$	Suzuki *et al.*, 1997[c]
Epithelial cells								
Endolymphatic compartment	$P2X_2$ (C)		$P2X_2$ (D)		P2X (GH)		ATP has suppressive effect on endocochlear potential and cochlear microphonic	Muñoz *et al.*, 1995b[b] Housley *et al.*, 1998[b] Wu and Mori, 1999[c] Järlebark *et al.*, 2000, 2002[b]
Reissner's membrane cells	$P2X_2$ (B)		$P2X_1$ (D) $P2X_2$ (D)		$P2X_{1/3}$ (G) $P2X_2$ (G)		ATP decreases sound transduction	King *et al.*, 1998b[b] Nikolic *et al.*, 2001[b]
Lateral wall					$P2X_7$ (H)	P2Y (GH)	ATP increases $[Ca^{2+}]_i$	Ikeda *et al.*, 1995[d] Ogawa and Schacht, 1995[c]
Vestibular dark cells		$P2Y_2$ (B) $P2Y_4$ (B)		$P2Y_2$ (DE) $P2Y_4$ (DE)		$P2Y_2$ (G) $P2Y_4$ (G)	ATP via $P2Y_4$ R regulates K^+ secretion	Marcus *et al.*, 1997[c] Marcus and Scofield, 2001[c] Sage and Marcus, 2002[c]
Cochlear blood flow	See Table XXIV							
Stria vascularis marginal cells		$P2Y_2$ (B) $P2Y_4$ (B)	$P2X_1$ (D)	$P2Y_2$ (DE) $P2Y_4$ (DE)		$P2Y_2$ (G) $P2Y_4$ (G)	ATP increases $[Ca^{2+}]_i$ ATP inhibits K^+ secretion	Suzuki *et al.*, 1995b[c] Marcus *et al.*, 1998, 1999[c] Sage and Marcus, 2002[c]
Spiral ligament	$P2X_1$ (D)			$P2Y_2$ (D)				Nikolic *et al.*, 2001[b] Sage and Marcus, 2002[c]
Organ of Corti	$P2X_2$ (BC)							Housley *et al.*, 1998, 1999[b]
Hensen cells	$P2X_2$ (C)		$P2X_2$ (D)		P2X (GH)	P2Y (GH)	ATP regulates ions and H_2O balance of cochlear fluid	Sugasawa *et al.*, 1996b[b] Housley *et al.*, 1999[d] Järlebark *et al.*, 2000, 2002[b]
Deiters' cells	$P2X_2$ (C)		$P2X_2$ (D)		$P2X_2$ (G)	P2Y (G)	Purinergic modulation of cochlear micromechanisms	Lagostena *et al.*, 2001[d] Chen and Bobbin, 1998[b] Housley *et al.*, 1998[b] Nenov *et al.*, 1998[b] Parker *et al.*, 1998[b] Bobbin, 2001[d] Järlebark *et al.*, 2000, 2002[b]

(*continued*)

TABLE XLVIII (*continued*)

Cellular component	Receptor mRNA	Receptor protein	Pharmacological and biochemical profile	Function	References
Vestibular labyrinth					
Transitional cells	$P2X_2$ (BC)		$P2X_2$ (G)	P2X R regulate endolymph concentrations	Housley *et al.*, 1998[b] Lee *et al.*, 2001b[b]
End organs	$P2X_2$ (C)				Troyanovskaya and Wackym, 1998[b]
Cell lines					
Middle ear epithelial cell line (MESV)			P2Y (G)		Yen *et al.*, 1997[c]
Spiral ganglion	See Table XLV				
Cochlear vasculature	See Table XXIV				

[a]See footnote *a* for Table III.
[b]References refer to P2X receptors.
[c]References refer to P2Y receptors.
[d]References refer to P2X and P2Y receptors.

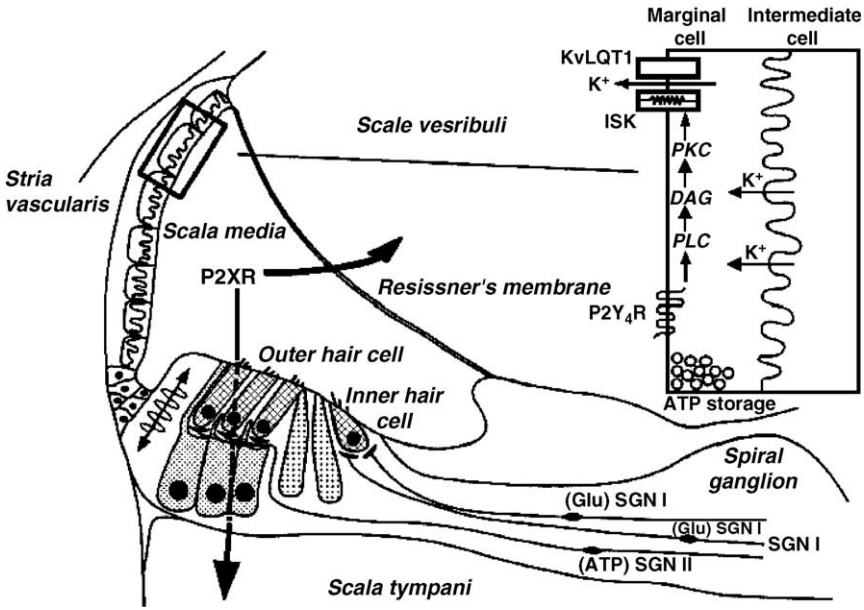

FIG. 12 Diagram indicating major actions of ATP mediated by P2X and P2Y receptors (R) in the cochlea. These include (1) regulation of the cochlear partition resistance (ATP induces a shunt conductance with efflux of K^+ from scala media); (2) ATP-induced inhibition of K^+ flux from the stria vascularis (inset); (3) altered micromechanics; and (4) putative neurotransmission at the hair cell-spiral ganglion neuron (SGN) synapses for outer hair cells and inner hair cells. Glu, L-glutamate: PKC, protein kinase C; DAG, diacylglycerol; PLC, phospholipase C. (Reproduced, with permission, from Housley, *Clin. Exp. Pharmacol. Physiol.* **27,** 575–580, 2000.)

A baseline level of ATP has been identified as being in the low nanomolar range within the perilymph and endolymph of the guinea pig cochlea (Muñoz *et al.*, 1995a, 1999b), although following noise stress, these levels were found to increase (Muñoz *et al.*, 2001; Thorne *et al.*, 1999). This level of ATP is maintained by the activity of ectonucleotidases present in both perilymphatic and endolymphatic compartments (Vlajkovic *et al.*, 1998a,b). These levels are thought to be insufficient to stimulate the ATP-gated ion channels that are expressed on the hair cells (Mockett *et al.*, 1994) without a further source of ATP.

Fluorescence labeling using quinacrine and biochemical analysis has revealed that ATP is stored in vesicles in the marginal cells of the stria vascularis in the lateral wall of the cochlea (Thorne *et al.*, 1999; White *et al.*, 1995). Sensory epithelium of the organ of Corti releases ATP in a Ca^{2+}-dependent manner (Wangemann, 1996). It has been suggested that ATP is

actively secreted from cochlear stria vascularis during noise exposure and implicated in the process of sound transduction during normal function (Muñoz *et al.*, 2001).

In summary, structures within the inner ear have been shown to express mRNA and protein for multiple P2X receptor subtypes. Functionally, the expression of $P2X_2$ has been shown to be particularly significant within structures of the inner ear, although $P2X_1$ and $P2X_7$ receptor subtypes have also been identified. With the exception of $P2Y_2$ and $P2Y_4$ receptor mRNA and protein shown to be expressed in vestibular dark cells and stria vascularis marginal cells, the expression of P2Y receptor mRNA and protein is lacking for structures within the inner ear. Functionally, P2Y receptors have been identified in many structures of the inner ear, but these have not been characterized, except for vestibular dark cells where $P2Y_2$ and $P2Y_4$ receptors have been identified.

3. Olfactory Organ

Table XLIX summarizes the receptor subtypes present in the olfactory organ based on mRNA, protein, and pharmacological and biochemical profiles. The functions claimed for the receptors together with key references are included.

In summary, $P2X_2$, $P2X_4$, and $P2Y_2$ mRNA has been identified in the olfactory bulb, and protein for multiple P2X receptor subunits and protein for $P2Y_2$ receptors have been identified. Although functional P2X and P2Y receptors have been identified in olfactory receptor neurons, the subtypes have not been characterized.

4. Tongue

A possible role for purines in taste sensation has been proposed based on activation of extracellular ATP-dependent membrane conductances (Barry, 1992), the immunohistochemical identification of stored adenosine in taste buds (Borisy *et al.*, 1993), and the presence of ecto-ATPase sites on fungiform taste buds (Barry, 1992).

Table L summarizes the receptor subtypes present in the tongue based on mRNA, protein, and pharmacological and biochemical profiles. The functions claimed for the receptors together with key references are included (cf. Tables XXIV and XLV).

In summary, to date there are no studies showing the expression of mRNA for either P2X or P2Y receptors from structures of the tongue. The expression of protein for $P2X_2$ and $P2X_3$ receptor subtypes has been shown on taste buds and functionally $P2X_1$, $P2X_2$, and $P2X_{2/3}$ receptors have been identified in addition to an uncharacterized P2Y receptor.

TABLE XLIX
Olfactory Organ[a]

Cellular component	Receptor mRNA		Receptor protein		Pharmacological and biochemical profile		Function	References
Olfactory receptor neurons (ORN)			$P2X_1$ (D) $P2X_4$ (D)	$P2Y_2$ (D)				Hegg *et al.*, 2003[d]
Cultured ORNs					P2X (GH)	P2Y (GH)	ATP evokes inward currents ATP increases $[Ca^{2+}]_i$	Hegg *et al.*, 2003[d]
Olfactory bulb	$P2X_2$ (BC) $P2X_4$ (B)	$P2Y_2$ (B)	$P2X_1$ (D) $P2X_2$(D) $P2X_4$ (D)	$P2Y_2$ (D)				Bo *et al.*, 1995[b] Kidd *et al.*, 1995[b] Kanjhan *et al.*, 1999[b] Hegg *et al.*, 2003[d]
Cultured olfactory bulb neurons			$P2X_2$ (D) $P2X_4$ (D)				$P2X_4$ R activation may modulate synaptic transmission.	Bobanovic *et al.*, 2002[b]
Olfactory epithelium	$P2X_2$ (B)	$P2Y_2$(B)	$P2X_2$ (D)	$P2Y_2$ (D)				Hegg *et al.*, 2003[d]

[a]See footnote *a* for Table III.
[b]References refer to P2X receptors.
[d]References refer to P2X and P2Y receptors.

TABLE L
Tongue[a]

Cellular component	Receptor mRNA	Receptor protein	Pharmacological and biochemical profile	Function	References
Taste receptors					
Embryonic		$P2X_2$ (D) $P2X_3$ (D)			Cheung and Burnstock, 2002[b]
Adult			P2Y (G)	ATP increases $[Ca^{2+}]_i$ and modulates ionic currents	Kim *et al.*, 2000[c]
Epithelial cells		$P2X_5$ (D) $P2X_7$ (D)			Gröschel-Stewart *et al.*, 1999a[b]
Hypoglossal motoneurons (XII) innervating tongue			P2 (G)	ATP produces tonic excitation during first 2 weeks postnatal development	Funk *et al.*, 1997[e]
Sensory nerves supplying taste buds	See Table XLV				
Lingual artery	See Table XXIV				

[a]See footnote *a* for Table III.
[b]References refer to P2X receptors.
[c]References refer to P2Y receptors.
[e]References refer to uncharacterized P2 receptors.

O. Cancer Cells

Elevated extracellular ATP has been shown to inhibit tumor growth *in vivo* and *in vitro* (Chahwala and Cantley, 1984; Correale *et al.*, 1993; Fang *et al.*, 1992; Heppel *et al.*, 1985; Hosoi *et al.*, 1992; Mure *et al.*, 1992; Rapaport, 1983; Rapaport and Fontaine, 1989; Rapaport *et al.*, 1983; Ueno *et al.*, 1984). Studies through the years have been concerned with whether the development of tumors correlates with the high levels of ATP in tumor cells (Maehara *et al.*, 1987; Martin *et al.*, 2000, 2001; Ray and Ray, 1997, 1998). There were also early reports that extracellular ATP modulates TNF-induced cytolysis of tumor cells (Bronte *et al.*, 1993; Kinzer and Lehmann, 1991). P2 receptors on leukemia cells were implicated in chemotactic effects (Seifert *et al.*, 1989a; Xie *et al.*, 1991).

More recently attempts have been made to identify the receptor subtypes and mechanisms involved. In general, inhibition of tumor growth appears to be a combination of inhibition of cell proliferation (via P2Y receptors) (Cowen *et al.*, 1990a; Dubyak and De Young, 1985; Flezar and Heisler, 1993; Lin *et al.*, 1993; Schwaner *et al.*, 1992; Smit *et al.*, 1993; Spungin and Friedberg, 1993), stimulation of differentiation (with subsequent inhibition of proliferation, via $P2X_5$ receptors) (Cowen *et al.*, 1991; Popper and Batra, 1993), and induction of cell death (via $P2X_7$ receptors) (Chueh and Kao, 1993).

There have been several clinical trials for the beneficial use of ATP against cancer (Agteresch *et al.*, 2000a,b, 2002; Cree and Kurbacher, 1999; Froio *et al.*, 1995; Haskell *et al.*, 1996, 1998; Jatoi and Loprinzi, 2001; Jatoi *et al.*, 2000).

Table LI summarizes the receptor subtypes present in cancer cells based on mRNA, protein, and pharmacological and biochemical profiles. The functions claimed for the receptors together with key references are included.

Nucleoside transporters have been identified in rat C6 glioma cells (Sinclair *et al.*, 2000) and oxidative-induced acute ATP depletion was found to correlate with delayed cell death in human neuroblastoma cells (Aito *et al.*, 1999). Human breast cancer cells have been shown to generate extracellular ATP in the presence of ADP (Satterwhite *et al.*, 1998) and high K^+-stimulated Ca^{2+} influx and ATP release from pheochromocytoma PC12 cells was also shown (Kasai *et al.*, 2001; Ogura and Takahashi, 1984; Reynolds *et al.*, 1982; Shoji-Kasai *et al.*, 1992). ATP release rates from erythrocytes in blood samples from patients with prostate or breast cancer receiving external beam ionizing radiation treatment were found to be significantly reduced compared to control subjects, implying a synergistic effect between *in vivo* ATP cancer therapy and radiation therapy (Abraham *et al.*, 2001).

In summary, the expression of mRNA for multiple P2X and P2Y receptor subtypes has been demonstrated, although corresponding protein for these

TABLE LI
Cancer Cells[a]

Cellular component	Receptor mRNA	Receptor protein	Pharmacological and biochemical profile	Function	References
Astrocytoma					
1321N1 cell line		$P2Y_1$ (DE)	$P2Y_1$ (G)	$P2Y_1$ R mediate proliferation and regulate apoptosis	Sellers *et al.*, 2001[c]
Pheochromocytoma (PC12 cells)	$P2X_2$ (AB) $P2X_4$ (AB) undifferentiated cells: $P2X_1$ (B) $P2Y_1$ (B) $P2X_2$ (B) $P2Y_2$ (B) $P2X_3$ (B) $P2Y_6$ (B) $P2X_4$ (B) $P2Y_{12}$ (B) $P2X_5$ (B) NGF-differentiated cells: $P2X_1$ (B) $P2Y_1$ (B) $P2X_2$ (AB) $P2Y_2$ (B) $P2X_3$ (B) $P2Y_6$ (B) $P2X_4$ (B) $P2Y_{12}$ (B) $P2X_5$ (B) $P2X_6$ (B)		$P2X_2$ (GH) $P2Y_1$? (G) $P2X_2$ (G)—possibly in undifferentiated cells $P2Y_2$ (G) $P2Y_{12}$ (G) —in differentiated cells	ATP stimulates Ca^{2+} influx ATP evokes CA uptake and release ATP increases AA release ATP induces mitogenesis ATP acting via $P2X_2$ R inhibits starvation-induced apoptosis ATP induces focal adhesion kinase activity ATP mediates $[Ca^{2+}]_i$ wave propagation ATP enhances lipid peroxidation ATP activates transcription factor AP-1, contributing to cell death $P2X_2$ R participate in growth cone arrest $P2X_2$ and $P2Y_2$ R mediate activation of MAPK Antagonists of P2 R prevent NGF-induced neuritogenesis UTP (and GTP) synergistically enhance NGF-induced neurite outgrowth	Barry and Cheek, 1994[c] Nikodijevic *et al.*, 1994[c] Kim and Rabin, 1994[c] de Souza *et al.*, 1995[c] Koizumi *et al.*, 1995[c] Murayama *et al.*, 1995[c] Cheng *et al.*, 1996[c] Gysbers and Rathbone, 1996[c] Michel *et al.*, 1996b[b] Yakushi *et al.*, 1996[b] Khiroug *et al.*, 1997[b] Soltoff *et al.*, 1998[c] Swanson *et al.*, 1998[b] Arslan *et al.*, 2000[c] D'Ambrosi *et al.*, 2000[b] Fujita *et al.*, 2000[b] Schindelholz and Reber, 2000[b] Bae and Ryu, 2001[c] Hur *et al.*, 2001[b] Lee *et al.*, 2001a[c] Liu *et al.*, 2001[b] Vartian and Boehm, 2001[c] Kulick and Von Kügelgen, 2002[c] Kubista *et al.*, 2003[c] Moskvina *et al.*, 2003[c]
Leukemia					
Myelomonocytic M1 cells			P2Y (G)	ATP enhances differentiation	Yamaguchi *et al.*, 1994[c]

Promyelocytic NB4 cells		$P2Y_{11}$ (AB)	$P2X_1$ (D)	$P2X_1$ (G)	$P2Y_{11}$ (G)	ATP promotes cell differentiation Slight reduction in proliferation rate	Van der Weyden *et al.*, 2000b,c[c] Buell *et al.*, 1996[b]
Myeloblastic HL-60 cells		$P2Y_{11}$ (AB)		P2X (G)	$P2Y_2$ (G) $P2Y_{11}$ (G) $P2Y_{12}$? (G)	ATP increases $[Ca^{2+}]_i$ ATPγS reduces cell size and decreases the nuclear/cytoplasm ratio Reduces percentage cells expressing transferrin R Increases percentage cells expressing type 1 complement R (CR1) Promotes cell differentiation toward mature phagocyte leukocytes	Choi and Kim, 1997[c] Communi *et al.*, 1997[c] Seetulsingh-Goorah and Stewart, 1998[b] Boeynaems *et al.*, 2000[c] Conigrave *et al.*, 2000[c]
T-acute lymphoblastic CB1 cells					$P2Y_1$ (H) $P2Y_2$ (H)	ATP increases $[Ca^{2+}]_i$	Biffen and Alexander, 1994[c]
Erythroleukemia HEL cells		$P2Y_2$ (AB)			$P2Y_1$ (H) $P2Y_2$ (H)		Akbar *et al.*, 1996[c] Baltensperger and Porzig, 1997[c]
Glioma cells C6 cells C6-2B cells		$P2Y_1$ (B) $P2Y_2$ (B) $P2Y_{12}$ (B)			$P2Y_1$ (GH) $P2Y_2$ (GH) $P2Y_{12}$ (HI)	$P2Y_1$ and $P2Y_2$ R mediate cell proliferation ATP induces c-*fos* expression via P2Y R ATP and ADP via $P2Y_{12}$ R stimulate an increase in MAPK activation	Boyer *et al.*, 1994[c] Lazarowski and Harden, 1994[c] Lin and Chuang, 1994[c] Schachter *et al.*, 1996, 1997[c] Sabala *et al.*, 1997, 2001[c] Lin, 1995[c] Tu *et al.*, 2000[c] Wójcik *et al.*, 2000[c] Zhang *et al.*, 2000b[c] Claes *et al.*, 2001[c] Jin *et al.*, 2001[c] Grobben *et al.*, 2001[c] Czajkowski *et al.*, 2002[c]
Neuroblastoma cells							
Neuro-2A cells					$P2Y_2$ (G)	ATP and UTP increase inositol phosphate accumulation	Chen and Chen, 1997[c]
N1E-115 cells	$P2X_7$ (B)		$P2X_7$ (DE)	$P2X_7$ (G)		ATP induces apoptosis	Schrier *et al.*, 2002[b]
NG108-15 cells and parent N18TG-2 cells	$P2X_7$ (B)	$P2Y_2$ (B) $P2Y_6$ (B)		$P2X_7$ (GH)	$P2Y_2$ (GH) $P2Y_6$ (G)	ATP increases $[Ca^{2+}]_i$ ATP and UTP induce formation of NO UTP and UDP activate PLC	Chueh *et al.*, 1994[b] Lin, 1994[c] Filippov *et al.*, 1995[c] Matsuoka *et al.*, 1995[c]

(*continued*)

TABLE LI (*continued*)

Cellular component	Receptor mRNA		Receptor protein	Pharmacological and biochemical profile		Function	References
						$P2Y_2$ R stimulation inhibits M-type K^+ current	Reiser, 1995[c] Czubayko and Reiser, 1996[c] Filippov and Brown, 1996[c] Kaiho *et al.*, 1996, 1998[b] Song and Chueh, 1996a,[b] 1996b[c] Bräter *et al.*, 1999[d] Ohkubo *et al.*, 2000[c] Sak *et al.*, 2001[c] Watano *et al.*, 2002[b]
SH-SY5Y cells			$P2X_7$ (E)	$P2X_7$ (H)		Bz-ATP increases $[Ca^{2+}]_i$	Larsson *et al.*, 2002[b]
SK-N-BE(2)C cells		$P2Y_1$ (AB) $P2Y_4$ (AB) $P2Y_6$ (AB)			$P2Y_6$ (H)	UDP increases $[Ca^{2+}]_i$	Lee *et al.*, 2003[c]
NH2 cells				$P2X_7$ (G)			El-Sherif *et al.*, 2001[b]
Laryngeal carcinoma							
Hep-2 cells					$P2Y_2$ (H)	ATP and UTP modulate cytosolic Ca^{2+} oscillations	Visegrády *et al.*, 2000[c]
Lung cancer							
A549 cells (small-cell adenocarcinoma)	$P2X_4$ (B)	$P2Y_2$ (B) $P2Y_4$ (B) $P2Y_6$ (B)		$P2X_4$ (G)	$P2Y_2$ (GH) $P2Y_4$ (G)	ATP increases $[Ca^{2+}]_i$ ATP via $P2Y_2$ R stimulates proliferation	Clunes and Kemp, 1996[c] Zhao *et al.*, 2000b[d] Schäfer *et al.*, 2003[c]
Esophageal cancer cells					$P2Y_2$ (G)	Nucleotides inhibit proliferation	Maaser *et al.*, 2002[c]
Colo-rectal tumours							
HT29 cells		$P2Y_2$ (B)			$P2Y_2$ (GH)	ATP and UTP activate Cl^- secretion ATP stimulates granule fusion $P2Y_2$ R mediate growth inhibition and apoptosis	Richards *et al.*, 1997[c] Zhang and Roomans, 1997[c] Cummins *et al.*, 2000[c]
Primary cultures		$P2Y_2$ (B)			$P2Y_2$ (H)	ATP increases $[Ca^{2+}]_i$	Höpfner *et al.*, 1998, 2001[c]
Human colonic adenocarcinoma cells:							

Caco-2 cells		$P2Y_2$ (B) $P2Y_4$ (B) $P2Y_6$ (B)		$P2Y_2$ (H)	ATP and UTP activate Cl^- secretion ADP evokes a rise in $[Ca^{2+}]_i$	McAlroy *et al.*, 2000[c]
Goblet cell line						
HT-29-Cl.16E			P2 (GH)		Apical P2 R mediate granule exocytosis	Guo *et al.*, 1995, 1997[e] Bertrand *et al.*, 1999[e]
Endometrial carcinoma						
HEC-1A cells		$P2Y_2$ (B)		$P2Y_2$ (H)	ATP controls cell cycle	Katzur *et al.*, 1999[c]
Ishikawa cells		$P2Y_2$ (B)		$P2Y_2$ (H)		
Ovarian cancer cells:						
Of epithelial origin						
OC-109		$P2Y_2$ (B)		$P2Y_2$ (G)	ATP increases $[Ca^{2+}]_i$	Batra and Fadeel, 1994[c]
OC-238					ATP improves the penetration of adriamycin	Maymon *et al.*, 1994[c]
OC-7-NU					Low concentrations of ATP cause cellular proliferation	Schultze-Mosgau *et al.*, 2000[c]
EFO-21						
EFO-27						
SKOV-3					High concentrations of ATP reduce cell numbers	
Cervical carcinoma						
HeLa cells		$P2Y_2$ (B) $P2Y_4$ (B) $P2Y_6$ (B)		$P2Y_2$ (HI) $P2Y_4$ (H) $P2Y_6$ (H)	ATP and UTP increase $[Ca^{2+}]_i$ $P2Y_2$ R constant; $P2Y_4$ and $P2Y_6$ R vary with culture nutrients	Muscella *et al.*, 2002[c] Okuda *et al.*, 2003[c]
Breast cancer cell lines						
WRK-1 cells			P2X (G)		ATP increases $[Ca^{2+}]_i$	Pubill *et al.*, 2001[b]
CD8F1 cells			P2 (I)			Colofiore *et al.*, 1995[e]
MCF-7 cells		$P2Y_2$ (B)		$P2Y_2$ (G)	ATP potentiates growth factor-induced c-*fos* gene expression	Vandewalle *et al.*, 1994[c]
Hs578T		$P2Y_2$ (B)				Dixon *et al.*, 1997b[c]
SK-Br3		$P2Y_2$ (B)				Wagstaff *et al.*, 2000[c]
T47-D		$P2Y_2$ (B)				
Prostate cancer cell lines						
PC3 cells	$P2X_4$ (B) $P2X_5$ (B) $P2X_6$ (B) $P2X_7$ (B)	$P2Y_2$ (A) $P2Y_6$ (A) $P2Y_{11}$ (A)	$P2X_7$ (H)	$P2Y_2$ (HI)	ATP increases $[Ca^{2+}]_i$ ATP (probably via P2X R) reduces cell numbers, probably by inducing cell death	Dainty *et al.*, 1995[c] Wasilenko *et al.*, 1997[c] Janssens and Boeynaems, 2001[d]
LNCaP		$P2Y_2$ (A) $P2Y_6$ (A)				Janssens and Boeynaems, 2001[c]

(*continued*)

TABLE LI (*continued*)

Cellular component	Receptor mRNA	Receptor protein	Pharmacological and biochemical profile	Function	References
	$P2Y_{11}$ (A)				
DU145	$P2X_4$ (B) $P2X_5$ (B)	$P2Y_1$ (A) $P2Y_2$ (A) $P2Y_6$ (A) $P2Y_{11}$ (A)		$P2Y_2$ (HI)	ATP elicits a Ca^{2+} wave	Janssens and Boeynaems, 2001[d] Sauer *et al.*, 2002[c] Vanoverberghe *et al.*, 2003[c]
Pancreatic cancer cells					
CRI-G1 cells			P2 (G)	Inhibition of proliferation ATP induces apoptosis (possibly via adenosine) ADP activates a cation channel (possibly via adenosine)	Reale *et al.*, 1994[e] Yamada *et al.*, 1999[e]
Liver/bile duct carcinoma					
Novikoff hepatoma cells			P2Y (H)	ATP increases $[Ca^{2+}]_i$	Lazrak *et al.*, 1994[c]
HTC cells			P2Y (GH)	ATP and UTP regulate hepatocellular swelling	Fitz *et al.*, 1994[c] Roe *et al.*, 2001[c]
N1S1-67 cells			$P2Y_2$ (G)	ATP modulates cation channels	Peres and Giovannardi, 1995[c]
HuH-7 cells	$P2Y_1$ (B) $P2Y_2$ (B) $P2Y_4$ (B) $P2Y_6$ (B)		$P2Y_2$ (G) or $P2Y_4$ (G)	ATP increases $[Ca^{2+}]_i$	Schöfl *et al.*, 1999[c]
Hep G2 cells	$P2Y_1$ (B) $P2Y_2$ (B) $P2Y_4$ (B) $P2Y_6$ (B)		$P2Y_2$ (G) or $P2Y_4$ (G)	ATP increases $[Ca^{2+}]_i$	Schöfl *et al.*, 1999[c]
Biliary adenocarcinoma					
Mz-ChA-1 cells (human)			$P2Y_2$ (H)	ATP and UTP promote Cl^- secretion	McGill *et al.*, 1994[c]
NRC-1 cells (rat)			$P2Y_2$ (H)		Zsembery *et al.*, 1998[c] Zsembery *et al.*, 1998[c]
Ehrlich ascites tumour			$P2Y_1$ (G) $P2Y_2$ (G)	ATP *in vivo* inhibits tumor growth ATP and UTP increase $[Ca^{2+}]_i$	Lasso de la Vega *et al.*, 1994[c] Estrela *et al.*, 1995[c] Pedersen *et al.*, 1998[c]

Epidermal carcinoma								
Basal cell carcinoma			$P2X_5$ (D) $P2X_7$ (D)	$P2Y_1$ (D) $P2Y_2$ (D) $P2Y_4$ (D)				Greig *et al.*, 2003b[d]
Squamous cell carcinoma			$P2X_5$ (D) $P2X_7$ (D)	$P2Y_1$ (D) $P2Y_2$ (D)				Greig *et al.*, 2003b[d]
A-431 cells			$P2X_5$ (D) $P2X_7$ (D)	$P2Y_1$ (D) $P2Y_2$ (D)	$P2X_7$ (G)	$P2Y_2$ (G)	$P2X_7$ R inhibit proliferation and $P2Y_2$ R induce proliferation	Sugita *et al.*, 1994[c] Greig *et al.*, 2003b[d]
B16F10 cells						P2 (G)	ATP reduces proliferation	Palomares *et al.*, 1999[e]
Thyroid cancer								
Follicular carcinoma cells						P2Y (H)	ATP increases $[Ca^{2+}]_i$	Schöfl *et al.*, 1997[c]
Papillary carcinoma cells						P2Y (H)	ATP increases $[Ca^{2+}]_i$	Schöfl *et al.*, 1997[c]
Pineal gland tumour cells (PGT-β)						$P2Y_1$ (H) $P2Y_2$ (H)	ATP and UTP increase $[Ca^{2+}]_i$	Suh *et al.*, 1997, 2001b[c]
Bone cancer								
Osteosarcoma cells		$P2Y_2$ (B)						Bowler *et al.*, 1995[c]
Osteosarcoma cell lines								
UMR-106 cells						$P2Y_1$ (H) $P2Y_2$ (H)	ATP and UTP increase $[Ca^{2+}]_i$ PTH potentiates nucleotide-induced Ca^{2+} release ATP modulates acid production by osteoblasts	Sistare *et al.*, 1994, 1995[c] Gallinaro *et al.*, 1995[c] Kaplan *et al.*, 1995[c] Kaplan and Dixon, 1996[c] Jørgensen *et al.*, 1997[c] Buckley *et al.*, 2001[c]
Saos2	$P2X_7$ (B)	$P2Y_1$ (B) $P2Y_2$ (B)	$P2X_7$ (D)		$P2X_7$ (I)	$P2Y_1$ (H)	ATP and UTP increase $[Ca^{2+}]_i$ ATP and PTH have synergistic actions ATP potentiates induction of c-*fos* by PTH	Bowler *et al.*, 1999[c] Gartland *et al.*, 2001[b]
Te85	$P2X_7$ (B)	$P2Y_2$ (B)						Bowler *et al.*, 1999[c]
ROS 17/2.8 cells						P2Y (H)	ATP increases $[Ca^{2+}]_i$	Roldán *et al.*, 2001[c]
Osteoclastoma cells	$P2X_7$ (B)	$P2Y_2$ (C)					$P2X_7$ R activation modulates resorption	Bowler *et al.*, 1998b[c] Gartland *et al.*, 1999[b]

[a]See footnote *a* for Table III.
[b]References refer to P2X receptors.
[c]References refer to P2Y receptors.
[d]References refer to P2X and P2Y receptors.
[e]References refer to uncharacterized P2 receptors.

receptors has generally not been studied, with the exception of epidermal carcinoma cells and the presence of $P2X_7$ receptors in some cancer cells. Functionally, $P2X_7$ receptors have been demonstrated widely on different cancer cells, in addition to several P2Y receptor subtypes, predominately $P2Y_1$, $P2Y_2$, $P2Y_6$, $P2Y_{11}$, and $P2Y_{12}$.

III. Plasticity of Purinergic Receptor Expression

There are a growing number of reports of changing expression of purinoceptors in cells and organs during development and disease (Abbracchio and Burnstock, 1998; Burnstock, 1990b, 2001a; Hourani, 1999).

A. Organs and Tissues

1. Urinary Bladder

Increased responses of the human bladder to P2X agonists in interstitial cystitis have been described (Palea *et al.*, 1993). There is also an increase in the purinergic component of parasympathetic nerve-mediated contraction of the human obstructed bladder (see Burnstock, 2001b) and $P2X_1$ receptor expression on smooth muscle increases considerably in the symptomatically obstructed bladder (O'Reilly *et al.*, 2001a). Another possible explanation for the increased potency of ATP in generating contractions in detrusor from unstable bladders may be reduced extracellular ATP hydrolysis (Harvey *et al.*, 2002).

ATP released from urothelial cells has been shown to act on $P2X_3$ receptors on suburothelial nociceptive sensory nerve terminals in the bladder (Vlaskovska *et al.*, 2001). Purinergic $P2X_3$-mediated nociceptive signaling is increased in the cyclophosphonate model of interstitial cystitis (Rong and Burnstock, unpublished observations); this may be due to upgrading of $P2X_3$ receptors, reduced ATPase activity, and/or increased urothelial release of ATP. Augmented stretch-activated ATP release from bladder uroepithelial cells in patients with interstitial cystitis (Sun and Chai, 2002; Sun *et al.*, 2001), as well as with benign prostatic hyperplasia (Sun *et al.*, 2002), has been demonstrated. Reduction of $P2X_3$ and $P2X_5$ receptors in human detrusor from adults with urge incontinence has been claimed (Moore *et al.*, 2001).

2. Heart

Increased sensitivity of platelets from unstable angina patients to ADP-induced aggregation (probably via $P2Y_1$ receptors) has been reported (Viswanathan and Nair, 1994). An increase in cardiac $P2X_1$ and $P2Y_1$

receptor mRNA levels in congestive heart failure has been reported (Hou *et al.*, 1999b). A later study from this group also reported selective downregulation of P2X receptor-mediated pressor effects in congestive heart failure (Zhao *et al.*, 2000a). P2 receptors were strongly expressed in the fetal heart, including $P2X_1$ and $P2Y_4$ receptor subtypes as well as $P2X_3$, $P2X_4$, $P2Y_2$, and $P2Y_6$ known to be present in adult human heart, suggesting that there may be a contribution of ATP to differentiation in the embryo as well as control of cardiovascular function (Bogdanov *et al.*, 1998a).

3. Blood Vessels

Phenotype changes of the vascular smooth muscle cells regulate P2 receptor expression (Erlinge, 1998). RT-PCR studies showed that $P2X_1$ receptor mRNA is dominant in the contractile smooth muscle phenotype, although P2Y receptor mRNA subtypes are also present. In the synthetic phenotype, the mitogenic $P2Y_1$ and $P2Y_2$ receptors are upregulated, while the $P2X_1$ receptor is totally downregulated. The same group later showed that MAPKK-dependent growth factor can induce upregulation of $P2Y_2$ receptors in vascular smooth muscle cells (Hou *et al.*, 1999a) and speculated that this may be of importance in atherosclerosis and neointima formation after balloon angioplasty. The inflammatory cytokine IL-1β induced a time- and dose-dependent upregulation of $P2Y_2$ receptor mRNA in vascular smooth muscle cells, which was greatly enhanced when combined with interferin-γ or TNF-α; lipopolysaccharide also significantly increased the expression of $P2Y_2$ receptor mRNA (Hou *et al.*, 2000). The upregulation of $P2Y_2$ receptor mRNA was paralleled by an increase in UTP-stimulated DNA synthesis and release of $[Ca^{2+}]_i$. Functional upregulation of UTP-sensitive ($P2Y_2$) receptors is also a feature of dedifferentiated coronary smooth muscle cells (Hill *et al.*, 2001). Transient reduction in expression of $P2X_1$ mRNA and an increase in $P2Y_1$ and $P2Y_2$ mRNA were observed in basilar artery in a rat double hemorrhage model, perhaps reflecting changes in subarachnoid hemorrhage (Carpenter *et al.*, 2001).

Age-related changes in P2 receptor mRNA have been observed in rat arteries (Miao *et al.*, 2001). In basilar artery from 19-month compared to 2-month-old rats, $P2X_1$ receptor mRNA was reduced, but $P2Y_1$ and $P2Y_2$ receptor mRNA increased. In the aorta and carotid arteries, $P2Y_1$ receptor mRNA was decreased in the 19-month-old rats, but there were no significant changes in $P2X_1$ and $P2Y_2$ mRNA. It was concluded that downregulation of $P2X_1$ and upregulation of $P2Y_1$ and $P2Y_2$ receptor mRNA in smooth muscle cells and downregulation of $P2Y_1$ and $P2Y_2$ receptor mRNA in endothelial cells might underlie changes in cerebral vascular tone in aging.

Aortic vasodilatation is mediated by P2 receptors on vascular smooth muscle in young rats and rabbits but is gradually changed to P2 receptor endothelial-mediated vasodilatation during later development (Chinellato *et al.*, 1991; Koga *et al.*, 1992).

When human umbilical vein endothelial cells (HUVEC) were subjected to shear stress of 15 dyn/cm^2, $P2X_4$ mRNA levels began to decrease with time, reaching 60% at 24 h (Korenaga *et al.*, 2001). The Sp1 transcription factor was critical for this shear stress-induced change in $P2X_4$ receptor mRNA expression. Prolonged shear stress (for 6 h) of segments of human umbilical vein led to decreased expression of $P2X_1$ receptors and upregulation of $P2Y_2$ and $P2Y_6$ receptors on smooth muscle cells (Wang *et al.*, 2003a). Since $P2Y_2$ and $P2Y_6$ receptors mediate stimulation of growth and migration of smooth muscle cells it was speculated that they could be involved in the vascular remodeling induced by shear stress.

Posttransplantation thrombosis may occur in donor segments of iliac artery and liver following surgical removal and storage in University of Wisconsin (UW) solution for transplantation. A recent study has shown that cold storage of rabbit thoracic aorta in UW solution decreases $P2Y_2$ receptor-mediated vasodilatation via endothelial cells (Payne *et al.*, 2002).

ATP produced dose-related vasoconstriction of the renal vasculature, which was increased in hyperthyroid kidneys and was severely attenuated in kidneys from hypothyroid rats (Vargas *et al.*, 1996). There is upregulation of $P2Y_2$ receptors during ischemic reperfusion injury (Kishore *et al.*, 1998). Infusion of ATP-MgCl has a protective effect on postischemic renal failure (Osias *et al.*, 1977; Paller *et al.*, 1998; Siegel *et al.*, 1980; Sumpio *et al.*, 1987; Wang *et al.*, 1992).

4. Uterus

Expression of P2 receptor subtypes in rat uterine epithelial cells changes during pregnancy (Slater *et al.*, 2000). P2X receptor subtype labeling was altered both spatially (apical, lateral, and basal membranes) and temporally during early pregnancy until the time of implantation. A later study from this group (Slater *et al.*, 2002) showed that there was no expression of $P2X_7$, $P2Y_2$, and $P2Y_4$ receptors in uterine epithelium on Day 1 of pregnancy, but at Day 3 $P2X_7$ and $P2Y_2$ receptors were expressed in lateral plasma membranes, but there was still no appearance of $P2Y_4$ receptors. At time of implantation (Day 6), there was a strong presence of $P2X_7$ receptors. P2Y receptor label was present along the entire surface of the apical epithelium. It was suggested that both P2X and P2Y receptors play a role in conditioning the entire uterine epithelium for blastocyst implantation regardless of the site of attachment.

5. Salivary Gland

Upregulation of $P2Y_2$ receptors in rat salivary glands during short-term culture has been demonstrated (Turner *et al.*, 1997). It was suggested that the changes in expression and activity of $P2Y_2$ receptors in salivary gland cells may be related to pathological challenges to the gland *in vivo*. In a later study of duct-ligated rat submandibular gland, it was shown that during the tissue damage produced, there was upregulation of $P2Y_2$ receptor mRNA, while after ligature removal the receptor mRNA level reverted to normal levels; responses to the $P2Y_2$ receptor agonist UTP increased and decreased in keeping with these findings (Ahn *et al.*, 2000).

$P2Y_1$ receptor activity is present in the submandibular gland in immature rats, but decreases over the first 4 weeks following birth, although mRNA levels remain relatively constant (Turner *et al.*, 1998b).

6. Gut

The number and intensity of $P2X_3$ immunoreactive neurons were significantly increased in the myenteric plexus in human inflammatory bowel disease (Yiangou *et al.*, 2001). $P2Y_6$ receptors are highly expressed in T cell infiltrating inflammatory bowel, whereas $P2Y_6$ receptor expression was absent from T cells in unaffected bowel (Somers *et al.*, 1998). Functional expression of the $P2X_7$ receptor in colonic macrophages and T lymphocytes in inflammatory bowel disease mucosa suggests they may play a role in the immunopathology of the disease (Li *et al.*, 2001a).

In aganglionic intestine in Hirschsprung's disease there was only weak $P2X_3$ immunostaining in the myenteric and submucous plexuses compared to normal intestine (Facer *et al.*, 2001). This finding is consistent with experimental studies that reported that no IJPs could be evoked in smooth muscle by intramural nerve stimulation of the rectosigmoidal part of the large intestine of Hirschsprung's patients, and ATP caused contraction of the muscle (Zagorodnyuk *et al.*, 1989).

In Chagas' disease, enhancement of $P2X_7$ receptor-associated cell permeabilization during the acute phase of the disease was reported (Coutinho *et al.*, 1998), although purinergic signaling through other P2X receptor subtypes and P2Y receptors seems to be impaired, perhaps because the parasite protozoan that causes the disease contains high levels of ATPases (Cooke *et al.*, 2003).

7. Liver

Abnormalities in hepatic glucose metabolism have been recognized as one of the major metabolic alterations after hemorrhagic shock and purinergic receptors have been shown to play a role in the control of liver glucose

metabolism (Keppens and De Wulf, 1986). Downregulation of hepatocyte P2 purinoceptor binding capacity in hepatocytes after trauma hemorrhage has been reported (Mahmoud *et al.*, 1994).

8. Pancreas

In the streptozotocin-induced diabetic rat, $P2X_7$ receptors, normally located on the outer periphery of pancreatic islets, were increased and relocated inside the islets on glycogen-containing α-cells (Coutinho-Silva *et al.*, 2003).

9. Skeletal Muscle

Transient changes in responsiveness to ATP (Thomas *et al.*, 1991; Wells *et al.*, 1995) and in P2 receptor expression have been described in developing skeletal muscle (Meyer *et al.*, 1999a; Ryten *et al.*, 2001, 2002). In particular, $P2X_5$, $P2X_6$, and $P2X_2$ receptors were expressed in a sequential manner, $P2X_5$ and $P2X_6$ receptors associated in the development of the myotube, while $P2X_2$ and $P2Y_1$ receptors appear to be involved in the formation of the skeletal neuromuscular junction (Choi *et al.*, 2003b; Ryten *et al.*, 2001).

B. Cells

1. Immune Cells

There is plasticity in $P2Y_2$ receptor expression during myeloid leukocyte differentiation (Clifford *et al.*, 1997). KG-1 myeloblasts express $P2Y_1$, but not $P2Y_2$ receptors, whereas later myeloid progenitors, including HL-60 promyelocytes and THP-1 monocytes, express $P2Y_2$, but not $P2Y_1$ receptors.

$P2X_7$ receptor expression can be positively modulated by diverse-proinflammatory stimuli and negatively modulated by cAMP, a classic antiinflammatory second messenger (Humphreys and Dubyak, 1998).

2. Brain Neurons

In a whole-cell patch clamp study of pontine slice preparations of rat brain containing the nucleus locus coeruleus (LC) 2-MeSATP was shown to cause a relatively small inward current in young animals (10–14 days of age), while inward current responses were much larger in most older animals, suggesting that P2 receptor function increases with age in the LC (Wirkner *et al.*, 1998). $P2X_3$ receptors are widely distributed in the embryonic rat brain, appearing first at E11, while the $P2X_2$ receptor was present in E16.5 embryonic brain; the $P2X_3$ receptor was downregulated in early postnatal brain stem (Cheung and Burnstock, 2002).

In contrast to normal human brain, $P2Y_1$ receptors were localized to a number of characteristic Alzheimer's disease structures, such as neurofibrillary tangles, neuritic plaques, and neuropil threads (Moore *et al.*, 2000a). $P2Y_1$ receptors were upregulated in both astrocytes and neurons in the striatum and nucleus accumbens of rats treated for 5 days with amphetamine (Franke *et al.*, 2003a). Chronic food restriction alters $P2Y_1$ receptor mRNA expression in the nucleus accumbens of the rat (Krügel *et al.*, 2003b).

Cerebellar lesion upregulates $P2X_1$ and $P2X_2$ receptors in the precerebellar nuclei of the rat, perhaps related to the survival of injured neurons (Florenzano *et al.*, 2002).

In vitro studies of organotypic cultures and *in vivo* experiments on hippocampus from gerbils subjected to bilateral common carotid occlusion from hippocampus showed that $P2X_2$ and $P2X_4$ receptors were upregulated by glucose/oxygen deprivation (Cavaliere *et al.*, 2002, 2003). It was speculated that the changes in P2X receptor expression might be associated with ischemic cell death.

Chronic ethanol exposure inhibits calcium influx through voltage-independent cationic channels associated with purinergic receptors on PC12 cells (Kim *et al.*, 1993b). Noise exposure alters the response of outer hair cells in the inner ear to ATP (Chen *et al.*, 1995a).

It is interesting that the amount of extracellular ATP detected in hippocampal slices following electrical stimulation of Schiffer collaterals was significantly greater in D2 mice that have an inherited susceptibility to audiogenic seizures, in contrast to B6 mice that are resistant to these seizures (Wieraszko and Seyfried, 1989b). It was suggested that the increased levels of extracellular ATP in D2 mice are associated with reduced brain Ca^{2+} ATPase activity.

3. Glial Cells

Astrocytes acutely isolated from rat cerebral cortex cultured in horse serum showed increased responses to ATP, but not to glutamate (Kimelberg *et al.*, 1997).

There was a marked decrease in mRNA to $P2Y_1$ receptors and upregulation of mRNA for $P2Y_2$ receptors on freshly isolated astrocytes during development of rat hippocampus (Zhu and Kimelberg, 2001).

Astrogliosis *in vivo* appears to be associated with an upregulation of P2X receptors in rat nucleus accumbens (Franke *et al.*, 2001a).

Upregulation of $P2X_7$ and $P2Y_2$ (and/or $P2Y_4$) receptor-mediated responses has been demonstrated in Müller glial cells during proliferative vitreoretinopathy (Bringmann *et al.*, 2001; Francke *et al.*, 2002). Upregulation of P2Y receptors in retinal glial Müller cells from rats infected with Borna disease virus has also been described (Pannicke *et al.*, 2001). During

the differentiation of immature radial glia into mature Müller cells there is a decrease in responses to ATP (Uckermann *et al.*, 2002).

After nerve injury, $P2X_4$ receptor expression increased strikingly in hyperactive microglia, but not in neurons or astrocytes, in the ipsilateral spinal cord; this appears to be associated with tactile allodynia (Tsuda *et al.*, 2003).

Propagation of intercellular Ca^{2+} waves between astrocytes depends on the diffusion of signaling molecules through gap junction channels. Deletion of the main gap junction protein connexin 43 (Cx43) by homologous recombination results in a switch in mode of intercellular Ca^{2+} wave propagation to a purinoceptor-dependent mechanism. This compensatory mechanism in Cx43 knockout mice for intercellular Ca^{2+} wave propagation is related to a switch from $P2Y_1$ to a UTP-sensitive $P2Y_4$ receptor in spinal cord astrocytes (Suadicani *et al.*, 2003).

4. Nociceptive Sensory Nerves

Following chronic constriction injury to the sciatic nerve, the number of $P2X_3$ receptor-positive small and medium diameter neurons increased in DRG, compared to sham-operated animals (Novakovic *et al.*, 1999; Tsuzuki *et al.*, 2001). In addition, spinal cord immunoreactivity increased on the side ipsilateral to the ligated nerve, consistent with upregulation of purinergic receptors on presynaptic terminals of the primary sensory nerves. Novel ectopic purinergic sensitivity mediated by P2 receptors developed at sites of chronic nerve constrictive injury in rats (Chen *et al.*, 1999). A decrease in $P2X_3$ immunoreactivity in DRG of animals with L5–L6 ligations was reported (Kage *et al.*, 2002). Changes in gene expression of multiple subtypes of P2X receptors on DRG neurons (L5) after spinal nerve ligation have been reported recently (Kim *et al.*, 2003a). The relative amounts of mRNA for P2X receptor subtypes were in the order of $P2X_3 \gg P2X_4 > P2X_6 > P2X_5 = P2X_2 > P2X_1$ in normal lumbar DRG. After nerve injury, the mRNA for $P2X_5$ receptors was increased, those for $P2X_3$ and $P2X_6$ receptors were decreased, and those for $P2X_2$ and $P2X_4$ receptors were unchanged. However, immunostaining for receptor protein showed an increase from 23% to 73% $P2X_2$-positive DRG neurons after nerve ligation. It was suggested that these changes in receptor expression might be associated with the enhancement of purinergic sensitivity in injured sensory neurons. Two days following unilateral section of the cervical vagus nerve there was a dramatic ipsilateral increase in $P2X_1$, $P2X_2$, and $P2X_4$ receptor immunoreactivity in the cell soma of vagal efferent neurons in the dorsal vagal motor nucleus, but not in the nucleus ambiguous (Atkinson *et al.*, 2003). Following surgical sympathectomy, 28% of the spontaneously active afferent fibers in sciatic nerve responded to ATP, compared to none in intact rats (Chen *et al.*, 2000c). Upregulated homomeric $P2X_3$ and heteromeric $P2X_{2/3}$ receptors augmented thermal

hyperalgesia and mechanical allodynia, respectively, at the spinal level in the acute stage of chronic constriction injury; at the chronic stage (>40 days), thermal hyperalgesia disappeared, but mechanical allodynia persisted (Ueno *et al.*, 2003).

In a study of the behavioral effects of intraplanter injections of ATP in freely moving rats, evidence was presented that ATP was more effective in exciting nociceptors in inflamed versus normal skin (Hamilton *et al.*, 1999). This was reported to be due to upregulation of $P2X_2$ and $P2X_3$ receptors on DRG neurons (De Roo *et al.*, 2003; Xu and Huang, 2002). $P2X_3$ receptors were also transiently upregulated in rat trigeminal ganglia following ligation or chronic constriction of the mandibular inferior alveolar nerve (Eriksson *et al.*, 1998). In the A/J inbred mouse strain, which is known to be resistant to tissue injury pain caused by formalin, downregulation of $P2X_3$ receptor-dependent sensory function was demonstrated (Tsuda *et al.*, 2002). Tactile allodynia caused by peripheral nerve injury was associated with a striking increase in $P2X_4$ receptor expression in microglia in the ipsilateral spinal cord (Tsuda *et al.*, 2003).

5. Cancer Cells

Evidence was presented that undifferentiated pheochromocytoma (PC12) cells mainly express $P2X_4$ receptors, but after treatment with NGF, the dominant P2 receptor subtype was $P2Y_2$ (Arslan *et al.*, 2000). $P2X_6$ and/or $P2Y_4$ receptors appear to increase with cell proliferation in the cervical carcinoma HeLa cell line (Okuda *et al.*, 2003).

IV. Conclusions and Future Directions

Clearly functional purinoceptors are widely distributed in both neuronal and non-neuronal tissues, probably because it is a primitive (perhaps the earliest) molecular messenger. In the nervous system ATP is recognized as a cotransmitter in all peripheral and central nerve types, although its relative importance varies in different sites and with age and under pathophysiological conditions.

It seems likely that all the P2X receptor subtypes ($P2X_1$–$P2X_7$) have now been cloned and characterized, but more P2Y receptor subtypes still seem likely to be identified. The purinergic signaling field awaits, in particular, the development of specific agonists and antagonists for the different P2 receptor subtypes, and especially compounds, that will not be degraded when used *in vivo*. So far, selective agonists and/or antagonists are available only for the $P2X_1$, $P2X_3$, and $P2X_7$ receptors, and for $P2Y_1$, $P2Y_2$, $P2Y_4$, $P2Y_6$,

and $P2Y_{12}$ receptors. Transgenic mice—for example knockout mice for $P2X_1$, $P2X_2$, $P2X_3$, $P2X_7$, $P2Y_1$, and $P2Y_2$ receptors and double knockout of $P2X_2$ and $P2X_3$ receptors—are currently being employed to examine the functional roles of these P2 receptor subtypes, although care must be taken in interpretation because of the remarkable compensatory changes that can occur, We can expect transgenic mice to be developed for the remaining P2 receptor subtypes in the future. Gene array analysis appears to be a powerful tool for identification of changes in gene expression due to purinergic receptor activation. RNA interference studies for P2 protein functions affecting cell shape, mitosis, and cytokinesis may also offer advances in the future.

We hope this review will provide a useful reference background for the current status of purinoceptors in the cells, organs, or systems of various special interests and provide a beginning for incorporating the new information that is rapidly emerging in this expanding field. We apologize if we have missed any important references—it has been a formidable task!

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