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REVIEW

The birth and postnatal development of purinergic signalling

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Abstract

The purinergic signalling system is one of the most ancient and arguably the most widespread intercellular signalling system in living tissues. In this review we present a detailed account of the early developments and current status of purinergic signalling. We summarize the current knowledge on purinoceptors, their distribution and role in signal transduction in various tissues in physiological and pathophysiological conditions.

Keywords adenosine, ATP, co-transmission, history, purinergic signalling, purinoceptors.

The history of purines and pyrimidines began in 1776 when the Swedish Pharmacist Carl Wilhelm Scheele isolated uric acid from bladder stones (Scheele, V. Q. Examen Chemicum Calculi Urinari, *Opuscula*, 1776, 2, 73). Half a century later, in 1844, guanine was isolated by Unger from the faeces of guano sea birds (B. Unger, *Ann.* 1846, 58, 18). At the end of the 19th century, several principal purines (adenine and xanthine) and pyrimidines (thymine, cytosine and uracil) were discovered by Ludwig Karl Martin Leonhard Albrecht Kossel (1853–1927; see Jones 1953, Bendich 1955). A particularly important role was played by the great Emil Fisher, who started a study of the structure of caffeine and related compounds (Fischer 1881). He solved the structures and confirmed them by synthesis. His elucidation of the structures of the group of compounds he denoted 'purines' (Fischer 1907) was an important reason for his Nobel prize in 1902. The term 'pyrimidines' was introduced by Pinner (1885). An arduous task of determining the sugar part of nucleosides (and nucleotides) followed and was finally solved by Phoebus Aaron Levene (Levene & Jacobs 1908, Levene & Tipson 1931).

In 1927, Gustav Embden and Margarete Zimmermann described adenosine monophosphate in skeletal muscle (Embden & Zimmermann 1927). Adenosine 5′-triphosphate (ATP) was discovered in 1929 independently by Karl Lohmann in Germany and by Cyrus Hartwell Fiske and Yellagaprada SubbaRow in the USA (Fiske & SubbaRow 1929, Lohmann 1929). Lohmann's publication appeared several months earlier than the paper by Fiske and SubbaRow, and yet the latter had obtained the first evidence for ATP probably as early as in 1926 (Fig. 1). Whether Fiske briefed Otto Meyerhof, who was Lohmann's director, about his discovery or not remains a matter of doubt (the dramatic history of ATP discovery is described in detail in Maruyama 1991). In the following decade the role of ATP in cell energetics was firmly established and the concept of the 'high-energy phosphate bond' was introduced by Fritz Lipman (Lipman 1941).

Early studies of the extracellular effects of purines

Adenine was detected in blood in 1914 (most probably in the form of the adenosine 5′-monophosphate, AMP; Bass 1914), and later it was suggested that it had inhibitory properties (Freund 1920). At about the same time, Thannhauser & Bommes (1914) claimed that, unlike adenosine, adenine injected subcutaneously in humans was not toxic. In 1926, IG Farben in Germany started to isolate potential cardio-stimulant substances from the heart and developed an extract that contained mostly AMP.

Extracellular signalling roles for purines were experimentally discovered by Drury & Szent-Györgyi (1929)

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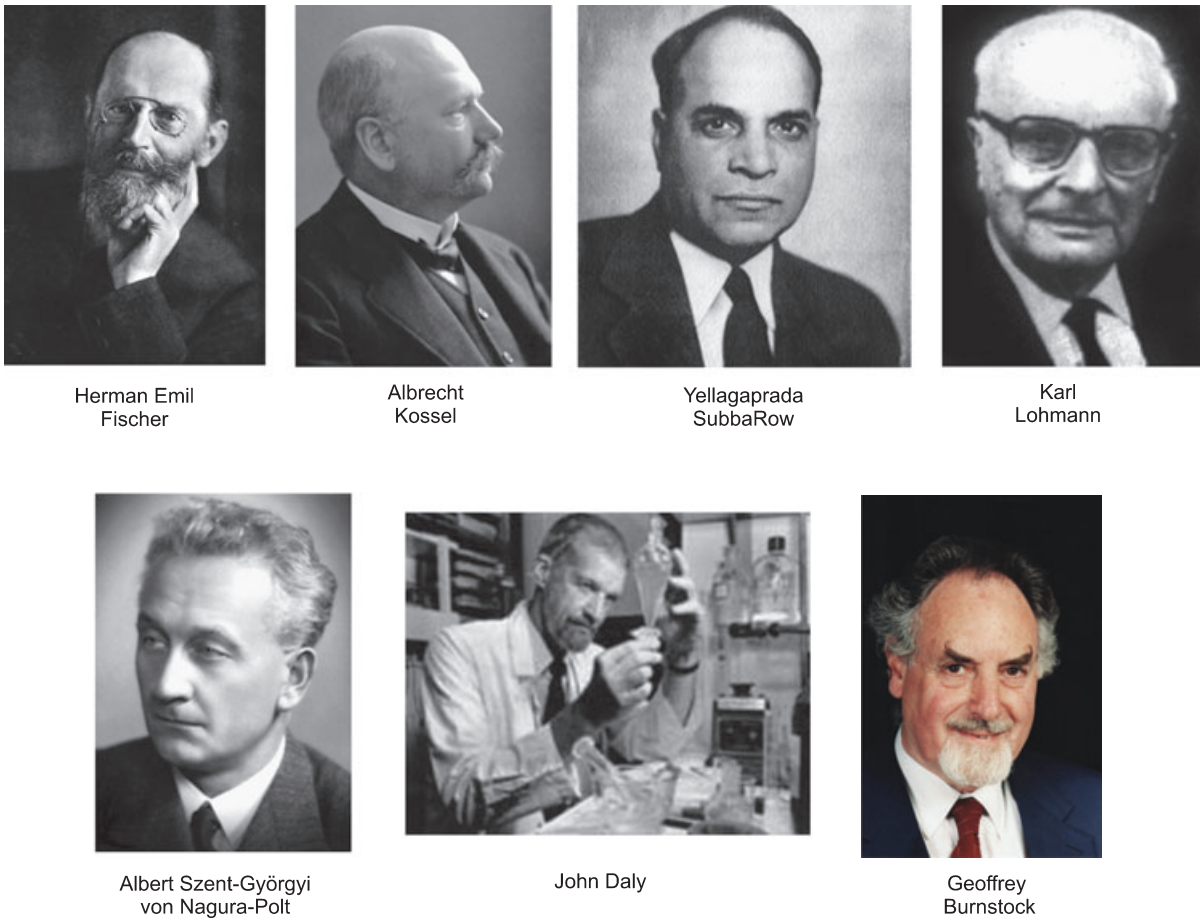

Figure 1 Discoverers of purinergic signalling.

when they found that crude extracts of bullock and sheep heart muscle, brain, kidney and spleen, when injected intravenously, exerted profound pharmacological effects, including a negative chronotropic effect (up to a complete cardiac arrest – Fig. 2) on the guinea-pig, rabbit, cat and dog heart, dilatation of coronary blood vessels that resulted in profound hypotensive actions and inhibition of spontaneously active intestinal smooth muscle. The active constituent in their extracts was identified as adenylic acid (adenosine-5′-monophosphate, 5′-AMP). Furthermore, they showed that intravenous injection of both adenosine and adenylic acid fully mimicked the effects of heart extracts causing sinus bradycardia and heart block, and that they were

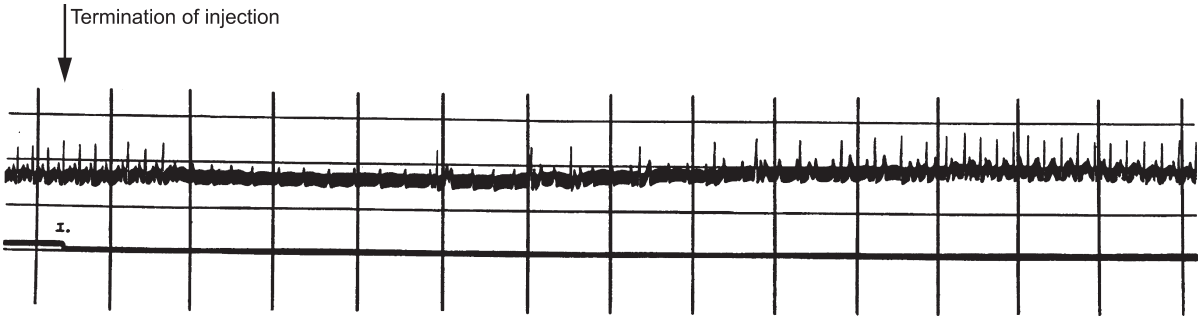

Figure 2 The first experimental recording of the action of purine-enriched tissue extract on heartbeat. The electrocardiogram shows the influence of intravenous injection of 1 c.c. of extract from heart muscle. Injection commenced 3 s before and terminated at point 'I' (also marked by an arrow). Time marker = 1 s. Figure reproduced with permission from Drury & Szent-Györgyi (1929).

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approximately equiactive. In addition, Drury and Szent-Györgyi also found that the purines could normalize supraventricular tachyarrhythmia.

This study prompted further work on the IG Farben preparation, called Lacarnol, which was readily available. Many studies followed, confirming that purine nucleosides and nucleotides were able to exert potent actions as vasodilators of coronary (Bennett & Drury 1931, Lindner & Rigler 1931, Wedd 1931, Wedd & Drury 1934, Winbury *et al.* 1953, Wolf & Berne 1956), renal (Houck *et al.* 1948) and pulmonary vessels (Gaddum & Holtz 1933), and produce blood pressure changes if administered systemically (Gillespie 1934, Emmelin & Feldberg 1948, Folkow 1949, Davies *et al.* 1951, Duff *et al.* 1954). There were also early reports using the IG Farben extract of actions in humans. The first was largely positive and suggested therapeutic usefulness (Rothman 1930), but later reports in humans found little therapeutic benefit, perhaps because the patients treated had chronic atrial fibrillation which is not amenable to normalization by adenosine (Honey *et al.* 1930). At the same time the depressing effects of purines on heart muscle were demonstrated on perfused frog heart (Lindner & Rigler 1931, Ostern & Parnas 1932, Loewi 1949). When studying the guinea-pig heart, Drury (1936) noted that ATP was more effective than adenosine at producing heart block. During the war there was much interest in traumatic shock, and one hypothesis is particularly relevant, namely that crushed tissues, especially muscle, would release ATP and other adenylates and then they would contribute to vasodilatation (Green 1943, Bielschowsky & Green 1944). Harry Norman Green and H.B. Stoner, who during World War II were given the job of studying the role of ATP in wound shock, published a book on the *Biological Actions of Adenine Nucleotides* in 1950 (Green & Stoner 1950), in which they correlated activity with the length of the phosphate chain, such that adenosine was the least active and ATP the most active of the purine compounds. The hypothesis that circulating adenine compounds were responsible for the blood pressure fall was refuted by cross-transfusion experiments (Green & Stoner 1950) and, particularly, by the careful measurements of adenine levels made by Herman Kalckar (which were many times too low; Kalckar & Lowry 1947), using his new enzymatic detection methods (Kalckar 1947a,b). These results also demonstrated the very rapid degradation of these compounds in blood.

Extracellular effects of purines were also identified in non-cardiovascular preparations, including adenosine- and ATP-induced contraction of the uterus (Deuticke 1932, Watts 1953) and intestine (Gillespie 1934, Ewing *et al.* 1949, Mihich *et al.* 1954). From the very early studies it had already become apparent that the presence of additional phosphates conferred differences in activity, although these differences were not to be resolved until purinoceptors were discovered more than half a century later. In retrospect, a major problem in the interpretation of the early data was the impurity of the compounds available (Gillespie 1934) as well as the extremely rapid metabolism of extracellular adenine nucleotides and nucleosides (Kalckar & Lowry 1947).

Studies of the actions of purine nucleosides and nucleotides were continued in the 1960s on a variety of tissues. In the guinea-pig taenia coli, exogenously applied adenylate compounds were shown to suppress spontaneous electrical activity and hyperpolarize the membrane (Axelsson *et al.* 1965, Axelsson & Holmberg 1969). In these experiments adenosine 5′-diphosphate (ADP), AMP and adenosine were found to be much less effective than ATP (Axelsson & Holmberg 1969). Purines were shown to alter systemic blood pressure (Flesher *et al.* 1960, Gordon & Hesse 1961, Rowe *et al.* 1962, Haddy & Scott 1968) and change the tone of isolated arteries from the mesentery, kidney and skeletal muscle (Hashimoto & Kumukura 1965, Scott *et al.* 1965, Walter & Bassenge 1968). Further experiments confirmed the effects of purines on heart rhythm; in particular, it was demonstrated that ATP, ADP, AMP and adenosine all have strong negative chronotropic effects when acting on the whole heart or directly on the sino-atrial node (Angelakos & Glassman 1965, James 1965, Stafford 1966). At the same time, ATP-induced stimulation of insulin secretion was also demonstrated (Rodriguez Candela & Garcia-Fernandez 1963).

The effects of administration of purines in humans were widely explored in the 1930s and l940s, especially in geriatric patients with cardiovascular disorders. Richards (1934) found that, in striking contrast to animals, injection of adenosine and AMP invariably induced tachycardia and did not affect blood pressure. During this time, clinical studies were initiated for the use of adenosine to treat cardiac arrhythmias (Honey *et al.* 1930). However, large boluses of adenosine triggered heart arrest and the short half-life of adenosine further confounded attempts to utilize this nucleoside as an antihypertensive agent (Honey *et al.* 1930, Jezer *et al.* 1933). In other studies, the effect of ATP on the heart was found to be dose dependent; although small doses of ATP produced transient tachycardia, its usual effect was to slow the heart and to produce atrioventricular block, probably following breakdown to adenosine (Stoner & Green 1945, Wayne *et al.* 1949, Johnson & McKinnon 1956, Hollander & Webb 1957). In their monograph Green & Stoner (1950) drew attention to the similarity of shock induced by low blood pressure or by ATP. An extensive review was published by Boettge *et al.* (1957), describing the

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physiological significance, pharmacological action and therapeutic use of adenylyl compounds in humans.

An important and influential hypothesis was developed by Berne (1963) and Gerlach *et al.* (1963), who elaborated on the earlier proposal by Lindner & Rigler (1931). This hypothesis postulated that adenosine was the physiological mediator of the coronary vasodilatation associated with myocardial hypoxia; intracellular ATP in myocardial cells was suggested to be degraded to adenosine that then left the cells and induced vasodilatation of the coronary resistance vessels acting through adenosine receptors. This suggestion was based largely on the observation that adenosine and its degradation products were found in the effluent from isolated perfused cat hearts and in the coronary sinus blood of dog hearts, following severe coronary hypoxia, and on the correspondence between the levels of measured adenosine (Olsson & Pearson 1990). This hypothesis was later questioned for the following reasons: (1) ATP is more potent than adenosine in inducing coronary vasodilatation (Winbury *et al.* 1953, Wolf & Berne 1956, Walter & Bassenge 1968, Moir & Downs 1972); (2) methylxanthines block adenosine-induced coronary vasodilatation, but have very little effect on that produced by ischaemia or ATP (Eikens & Wilcken 1973, Olsson *et al.* 1978); and (3) an increased level of ATP in the effluent from perfused hypoxic hearts was detected by a sensitive and specific assay system (Paddle & Burnstock 1974). An alternative hypothesis has been put forward (see Burnstock 1982, 1993a), namely that hypoxia and shear stress induce the release of ATP from endothelial cells that regulate coronary vascular resistance by acting on endothelial ATP receptors, resulting in the release of nitric oxide (NO) and subsequent vasodilatation, whereas adenosine controls the longer-lasting component of reactive hyperaemia. This is not the appropriate place to critically assess the current data on coronary vasodilatation, but a comparative study showed that several factors including adenosine receptors, NO and K_{ATP} channels contribute, and may act synergistically (Tune *et al.* 2004).

Early studies of the effects of purines on the nervous system

In 1947, Buhthal, Engback, Sten-Knudsen and Thomasen reported to the Physiological Society (Buhthal *et al.* 1947) that arterial injection of ATP to the cervical segments of the spinal cord of cats resulted in tetanus-like contractions of muscles of the upper extremities. The authors attributed this action to the direct excitation of anterior horn cells of the spinal cord. This initial finding of central effects of ATP was soon to be corroborated by 'an incidental observation made in decerebrated cats when adenosine triphosphate (ATP) was injected into the artery supplying a leg muscle, the *tibialis anticus*' (Emmelin & Feldberg 1948). The ATP injection led to a 'complex symptomatology' which involved bradycardia, obstruction of the pulmonary circulation, peristalsis, micturition, vomiting, defaecation and generalized muscular contraction. This broad response, was, at least in part, mediated by nervous centres. Subsequently, several reports appeared which demonstrated that injections of ATP into the ventricles or into the brain resulted in ataxia, sleepiness and motor weakness, and triggered electrophysiological or biochemical responses (Babskii & Malkiman 1950, Feldberg & Sherwod 1954, Galindo *et al.* 1967, Shneour & Hansen 1971).

There was early recognition for a physiological role for ATP at the neuromuscular junction. Buchthal & Folkow (1948) found that acetylcholine (ACh)-evoked contraction of skeletal muscle fibres was potentiated by exposure to ATP. The first indication that ATP might act as a neurotransmitter in the peripheral nervous system arose when Holton & Holton (1954) proposed that ATP released from sensory nerves during antidromic nerve stimulation of the great auricular nerve caused vasodilatation in the rabbit ear artery. Some years later Pamela Holton, using the firefly luminescence method for ATP detection (Strehler & Totter 1952, 1954), found that electrical stimulation of great auricular nerves of rabbits resulted in transient elevation of extracellular ATP (Fig. 3). She then concluded that 'when noradrenalin is liberated from sympathetic nerve endings ATP may also be liberated in to the tissue spaces' (Holton 1959), thus providing the first hint for the concept of purinergic co-transmission (Burnstock 1976).

Subsequently, the presynaptic modulation of ACh release from the neuromuscular junction by purines was reported by Ginsborg & Hirst (1972) and Ribeiro & Walker (1975). ATP was found in vesicular fractions of synaptosomes of neuromuscular junctions (Dowdall *et al.* 1974) and ATP release following electrical stimulation of the presynaptic nerve was identified (Zimmermann 1978). It was also demonstrated that ATP increased ACh sensitivity of both rat diaphragm and the frog skeletal muscle endplate (Ewald 1976, Akasu *et al.* 1981).

The effects of ATP on physiological activity in the autonomic ganglia were initially reported in 1948 when Feldberg & Hebb (1948) demonstrated that intra-arterial ATP injection excited neurones in the cat superior cervical ganglia (SCG). Subsequent experiments performed in de Groat's laboratory demonstrated that in rat SCG and in the cat vesical parasympathetic ganglia, purines suppressed synaptic transmission through adenosine receptors; at the same time high

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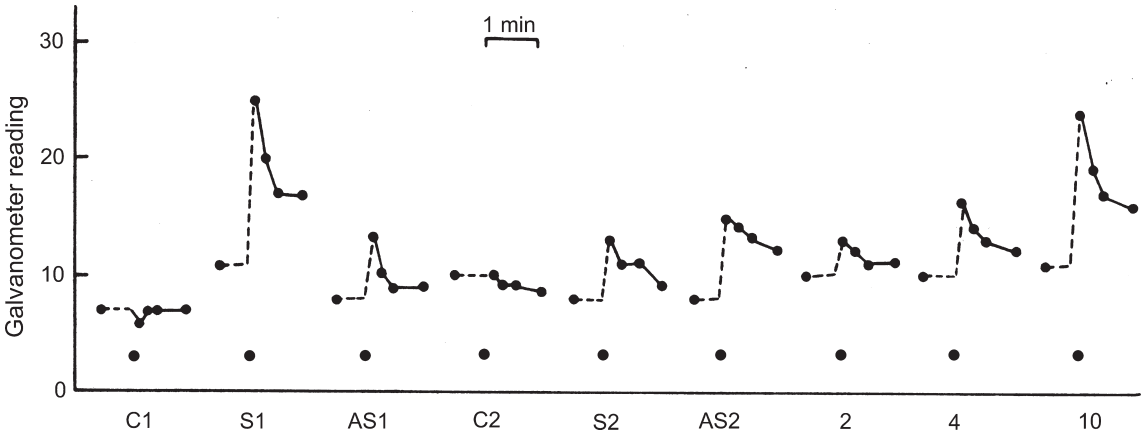

Figure 3 Discovery of ATP release from sensory nerve terminals. Galvanometer readings before and at 10, 20, 30 and 60 s after adding 0.5 mL test solution to the firefly enzyme. C1, C2 perfusate collected during control period, S1 and S2 during stimulation and AS1 and AS2 immediately after stimulation. The last three deflexions were caused by adding 2, 4 and 10 pmol ATP to the control perfusate (C2). Figure reproduced with permission from Holton (1959).

concentrations of ATP excited the postganglionic neurones (Theobald & De Groat 1977). The earliest intracellular recordings of the action of ATP on neurones were obtained in frog sympathetic ganglia where ATP produced a depolarization through a reduction in K^+ conductance (Siggins *et al.* 1977, Akasu *et al.* 1983).

The initial discoveries of peripheral purinergic transmission (Burnstock 1972) stimulated an increase in the interest in purinergic mechanisms in the central nervous systems (CNS). In the early 1970s, Pull & McIlwain (1972a,b, 1973) described the release of adenine nucleotides and their derivatives from superfused guinea-pig neocortex that had been electrically stimulated *in vitro*. Subsequently, Heller & McIlwain (1973) showed release of labelled nucleotides from isolated superior colliculus and lateral geniculate body incubated in [^{14}C]adenine and stimulated through an incoming optic tract, but not from preparations of piriform cortex stimulated through the lateral olfactory tract. McIlwain and his colleagues discussed their results in terms of a neurohumoral role for adenine derivatives in the brain.

Another major stimulus to the interest in purines in the CNS was the finding from Ted Rall's group that the accumulation of cyclic 3′,5′-AMP (cAMP) was not increased by theophylline, despite it being an inhibitor of phosphodiesterase inhibitor and therefore able to reduce cAMP breakdown. The finding was resolved when it became apparent that theophylline antagonized the effects of endogenous (and exogenous) adenosine, which provided a major stimulus for cAMP production in brain slices (Sattin & Rall 1970). These results were soon confirmed and extended in a series of papers from John Daly's laboratory, which also provided an explanation for an earlier finding that electrical field stimulation caused an increase in cAMP in the stimulated slice (Kakiuchi *et al.* 1969).

These *in vitro* experiments were soon extended to the intact cerebral cortex (Sulakhe & Phillis 1975). It was shown that iontophoretic application of adenosine and several adenine nucleotides depressed the excitability of cerebral cortical neurones, including identified Betz cells; cAMP, adenine and inosine were less effective, whereas ATP caused an initial excitation followed by a depression (Phillis *et al.* 1974, 1975). Adenosine and ATP also depressed firing in cerebellar Purkinje cells (Kostopoulos *et al.* 1975). ATP was shown to activate units of the emetic chemoreceptor trigger zone of the area postrema of cat brain (Borison *et al.* 1975). Premature arousal of squirrels from periods of hibernation was evoked by adenosine nucleotides, but not by other purine nucleotides, and it was suggested that this effect was due to their direct action on central neurones (Twente *et al.* 1970). The infusion of cAMP into the hypothalamus of fowl induced behavioural and electrophysiological sleep, whereas dibutyryl cAMP produced arousal (Marley & Nistico 1972). Local or systemic administration of adenosine in normal animals produced EEG and behavioural alterations in the hypnogenic type (Haulica *et al.* 1973).

Two groups demonstrated that low concentrations of adenosine caused a rise in the levels of cAMP in slices of guinea-pig cerebral cortex (Shimizu *et al.* 1969, Sattin & Rall 1970, Shimizu & Daly 1970) and that this rise was antagonized by the methylxanthines, theophylline and caffeine (Sattin & Rall 1970). Other investigators showed that adenosine and 2-chloroadenosine stimulated cAMP production in membrane fractions of

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human platelets (Mills & Smith 1971) and that this action was antagonized by aminophylline (Haslam & Lynham 1972). Subsequently, adenosine was shown to stimulate adenylate cyclase in a variety of membrane preparations, including those from adipocytes (Fain *et al.* 1972), turkey erythrocytes (Sevilla *et al.* 1977), liver (Londos & Wolff 1977) and a glioma cell line (Clark & Seney 1976).

At the same time Cornford & Oldendorf (1975) described two independent transport systems across the rat blood–brain barrier, one for adenine and the other for adenosine, guanosine, inosine and uridine, thus showing that purine homeostasis in the brain parenchyma is tightly controlled. High levels of 5′-nucleotidase were demonstrated histochemically in the substantia gelatinosa of mouse spinal cord (Suran 1974).

Observations of mentally ill patients suggested that purines may play a role in the cognitive and emotional functions of the human brain. Thus, adenine nucleotides have been implicated in depressive illness (Abdulla & McFarlane 1972, Hansen 1972). Abdulla & McFarlane (1972) suggested that indirect effects of adenine nucleotides on prostaglandin biosynthesis mediated development of depression. Blood levels of ATP and/or adenosine and urinary cAMP excretion were found to be significantly elevated in patients diagnosed with schizophrenia or in psychotic and neurotic depression (Abdulla & Hamadah 1970, Paul *et al.* 1970, Brown *et al.* 1972, Hansen & Dimitrakoudi 1974); however, these results were not reproduced in the study of Jenner *et al.* (1975). Inherited disorders of purine metabolism in the brain have been related to psychomotor retardation, athetosis and self-mutilation (Lesch-Nyhan syndrome) (Lesch & Nyhan 1964, Rosenbloom *et al.* 1967, Seegmiller *et al.* 1967, Berman *et al.* 1969). Adenine therapy has been used for Lesch-Nyhan syndrome (Schulman *et al.* 1971) and therapeutic effects of ATP in the treatment of nerve deafness were also claimed (Ohsawa *et al.* 1961).

Early studies of peripheral effects of purines

The first experiments demonstrating that ADP causes aggregation of blood platelets were performed almost 50 years ago. Initially it was found that a small molecule derived from red blood cells stimulated platelet adhesion (Hellem 1960). Subsequently, the same compound was found to induce platelet aggregation (Ollgaard 1961) and was finally identified as ADP (Gaarder *et al.* 1961, Born 1962). Later, adenosine was found to inhibit ADP-induced platelet aggregation (Born & Cross 1963); a similar inhibitory potency was found for ATP (Macfarlane & Mills 1975), adenosine tetraphosphate (Harrison & Brossmer 1976) and β,γ-methylene ATP (β,γ-meATP; Born & Foulks 1977). For full reviews of developments in this field, see e.g. Haslam & Cusack (1981), Gachet & Cazenave (1991) and Hourani & Cusack 1991).

ATP has been known to induce the release of histamine from mast cells for some time (Diamant & Kruger 1967, Sugiyama 1971). As close apposition of autonomic and sensory nerve varicosities with mast cells has been described (Heine & Forster 1975, Wiesner-Menzel *et al.* 1981, Newson *et al.* 1983, Bienenstock *et al.* 1991), it seems likely that ATP released as a neural co-transmitter is involved in the physiological control of histamine release from mast cells. Adenosine has been shown to modulate ADP-induced release of histamine (Marquardt *et al.* 1978, Lohse *et al.* 1987). The receptor for ATP on mast cells was studied in depth by Cockcroft & Gomperts (1980) and was designated a P_{2Z}-purinoceptor by Gordon (1986). About 15 years later, this P_{2Z} receptor was cloned and found to belong to the ATP-gated P2X receptor family and designated $P2X_7$ (Surprenant *et al.* 1996).

During the last two decades, purinoceptors of one or another variety have been detected virtually in every type of cell in every type of tissue (Table 1; for a detailed account of the tissue distribution of purinoceptors, see also Burnstock & Knight 2004).

Early comparative studies

Comparative studies of the actions of purines in invertebrates and lower vertebrates were scanty before 1972. Exceptions include: the depolarizing actions of ATP on amoeba (Nachmias 1968), the ATP-mediated increase in ciliary beat and locomotion in paramecium (Organ *et al.* 1968), adenosine actions on the oyster heart (Aikawa & Ishida 1966) and the initiation of feeding behaviour in blood sucking insects by ATP (Galun 1966, 1967). Reviews of the developments concerned with the comparative physiology and evolution of purinergic actions in the animal kingdom are available (Burnstock 1975a, 1979b, 1996a, Burnstock & Verkhratsky 2009, Fountain & Burnstock 2009).

Birth and development of the theory of purinergic neurotransmission

Non-adrenergic, non-cholinergic (NANC) nerves

There was early recognition of atropine-resistant responses of the gastrointestinal tract to parasympathetic nerve stimulation (Langley 1898, McSwiney & Robson 1929, Ambache 1951, Paton & Vane 1963); however, it was not until the early l960s that autonomic nerves other than adrenergic and cholinergic were suggested. In 1963, Burnstock, Campbell, Bennett and

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Table 1 Identification of purinoceptors in mammalian tissues

Tissue	Purinoceptors	Main functional role	References
Central nervous system			
Neurones	A_1	Inhibition of transmitter release; inhibition of firing; decreased seizures; neuroprotection; reduction in pain	Hedqvist & Fredholm (1976), Vizi & Knoll (1976), Harms *et al.* (1978), Ribeiro & Dominguez (1978), Harms *et al.* (1979), Dunwiddie (1980), Dunwiddie & Hoffer (1980), Dolphin & Archer (1983), Proctor & Dunwiddie (1983), Dunwiddie & Fredholm (1984), Fastbom & Fredholm (1985), Trussell & Jackson (1985), Evans *et al.* (1987), Trussell & Jackson (1987), Goldberg *et al.* (1988), von Lubitz *et al.* (1988), Arvin *et al.* (1989), Fastbom *et al.* (1990), Sawynok *et al.* (1991)
	A_{2A}	Stimulation of indirect pathway in striatum; increased transmitter release; neurodegeneration	Sebastiao & Ribeiro (1992), Cunha *et al.* (1995), Svenningsson *et al.* (1995), Sebastiao & Ribeiro (1996), Svenningsson *et al.* (1997a,b, 2000), Huang *et al.* (2005)
	A_{2B}, A_3	Unknown	
	$P2X_1$, $P2X_2$, $P2X_3$, $P2X_4$, $P2X_5$, $P2X_6$, $P2X_7$	Fast and slow neurotransmission in central synapses; pre-synaptic modulation; synaptic plasticity	Jahr & Jessell (1983), Wieraszko & Seyfried (1989), Edwards *et al.* (1992), Bo & Burnstock (1994), Ergene *et al.* (1994), Furukawa *et al.* (1994), Balcar *et al.* (1995), Li & Perl (1995), Sperlagh *et al.* (1995), Collo *et al.* (1996), Soto *et al.* (1996a,b), Vulchanova *et al.* (1996, 1997), Funk *et al.* (1997), Nieber *et al.* (1997), Scislo *et al.* (1997), Le *et al.* (1998), Li *et al.* (1998), Pankratov *et al.* (1998), Kanjhan *et al.* (1999), Jang *et al.* (2001), Nakatsuka & Gu (2001), Pankratov *et al.* (2002)
	$P2Y_1$, $P2Y_6$, $P2Y_{12}$	Regulation of growth and development; metabolic regulation	Mironov (1994), Salter & Hicks (1994), Ikeuchi *et al.* (1995), Ikeuchi & Nishizaki (1996), Kirischuk *et al.* (1996), Chessell *et al.* (1997a), Lalo *et al.* (1998), Ralevic *et al.* (1999), Brown & Dale (2002), Vasiljev *et al.* (2003)
Astroglia	A_1, A_{2A}, A_{2B}, A_3	Trophic effects; Ca^{2+} signalling; inhibition of glutamate uptake; regulation of growth and development; regulation of astrogliosis and cell death	Bourke *et al.* (1978), Hosli *et al.* (1987), Woods *et al.* (1989), Friedman *et al.* (1992), Fredholm & Altiok (1994), Hindley *et al.* (1994), Ogata *et al.* (1994), Peakman & Hill (1994, 1995), Porter & McCarthy (1995), Ogata *et al.* (1996), Abbracchio *et al.* (1997, 1998), Pilitsis & Kimelberg (1998), Jimenez *et al.* (1999), Brambilla *et al.* (2003), Bjorklund *et al.* (2008), Boison *et al.* (2010)
	$P2X_{1/5}$, $P2X_7$ (in pathological conditions?)	Fast neuronal–glial transmission(?); regulation of astrogliosis in pathological conditions	Magoski & Walz (1992), Walz *et al.* (1994), Ballerini *et al.* (1996), Pannicke *et al.* (2000), Kukley *et al.* (2001), Panenka *et al.* (2001), Duan *et al.* (2003), Lalo *et al.* (2008)
	$P2Y_1$, $P2Y_2$, $P2Y_4$, $P2Y_6$	Ca^{2+} signalling; propagating Ca^{2+} waves; release of glio-transmitters; regulation of gap junctions; neuronal–glial and glial–glial signalling	Pearce *et al.* (1989), Kastritsis *et al.* (1992), Bruner & Murphy (1993), Pearce & Langley (1994), Salter & Hicks (1994), Kirischuk *et al.* (1995b), Salter & Hicks (1995), Chen & Chen (1996), Centemeri *et al.* (1997), Ishimoto *et al.* (1997), Bernstein *et al.* (1998), Troadec *et al.* (1999), Cotrina *et al.* (2000), Fam *et al.* (2000), Jimenez *et al.* (2000), Wang *et al.* (2000), Zhu & Kimelberg (2001), Franke *et al.* (2004), Meme *et al.* (2004), Fries *et al.* (2005), Haas *et al.* (2006)

Table 1 (Continued)

Tissue	Purinoceptors	Main functional role	References
Oligodendroglia	A_1, A_{2A}, A_{2B}, A_3	Control of myelination; may be involved in demyelinating disorders	Stevens *et al.* (2002), Turner *et al.* (2002), Tsutsui *et al.* (2004)
	$P2X_7$ $P2Y_1$, $P2Y_2$, $P2Y_4$, $P2Y_{12}$	Ca^{2+} signalling; axonal-oligodendroglial signalling; development and maturation	Kirischuk *et al.* (1995a), Deng *et al.* (1998), James & Butt (1999), Moran-Jimenez & Matute (2000), James & Butt (2001), Laitinen *et al.* (2001), Matute *et al.* (2007)
Microglia	A_1, A_{2A}, A_{2B}, A_3	MAP kinase signaling; cytokine production; neuronal survival; microglial proliferation	Gebicke-Haerter *et al.* (1996), Hammarberg *et al.* (2003, 2004), Tsutsui *et al.* (2004), Synowitz *et al.* (2006), Min *et al.* (2008), Maggi *et al.* (2009)
	$P2X_4$, $P2X_7$	Ca^{2+} signalling; control of microglial activation; regulation of the production and release of inflammatory mediators	Ferrari *et al.* (1996), Haas *et al.* (1996), Illes *et al.* (1996), Chessell *et al.* (1997b), Collo *et al.* (1997), Visentin *et al.* (1999)
	$P2Y_1$, $P2Y_2$, $P2Y_4$, $P2Y_6$, $P2Y_{12}$	Ca^{2+} signalling; control of microglial activation; induction of early gene expression; regulation of K^+ channels	Ilschner *et al.* (1995), Priller *et al.* (1995, 1998), Norenberg *et al.* (1997), Inoue *et al.* (1998), Toescu *et al.* (1998), McLarnon *et al.* (1999), Moller *et al.* (2000)
Peripheral nervous system			
Sensory neurones	A_1, A_{2A}	Antinociception; sensitization	Sawynok *et al.* (1986), DeLander & Wahl (1988), Sosnowski *et al.* (1989), Karlsten *et al.* (1992), Sylven (1993), Reeve & Dickenson (1995), Abo-Salem *et al.* (2004)
	$P2X_2$, $P2X_3$, $P2X_{2/3}$ $P2Y_4$	Nociception; thermal sensitivity	Krishtal *et al.* (1983), Salt & Hill (1983), Fyffe & Perl (1984), Mori *et al.* (1985), Bean *et al.* (1990), Tokimasa & Akasu (1990), Collo *et al.* (1996), Svichar *et al.* (1997a,b), Xiang *et al.* (1998), Souslova *et al.* (2000), Boldogkoi *et al.* (2002), Khmyz *et al.* (2008)
Sympathetic neurones	A_1 $P2X_1$, $P2X_2$, $P2X_3$, $P2X_5$, $P2X_{2/3}$ $P2Y_1$, $P2Y_6$,	Neuronal-effector transmission; presynaptic modulation; regulation of neurotransmitter (noradrenaline) release; Ca^{2+} signalling	Hedqvist & Fredholm (1976), Connolly & Harrison (1994), Reekie & Burnstock (1994), Todorov *et al.* (1994), Boehm *et al.* (1995), Cloues (1995), Connolly & Harrison (1995), Ishii *et al.* (1995), Khakh *et al.* (1995), Haniuda *et al.* (1997), Simon *et al.* (1997), Searl *et al.* (1998), Xiang *et al.* (1998)
Parasympathetic neurones	A_1 $P2X_2$, $P2X_3$, $P2X_4$, $P2Y_1$, $P2Y_2$, $P2Y_4$, $P2Y_{11}$	Neuronal-effector transmission; pre- and postsynaptic modulation; Ca^{2+} signalling; control of excitability via opening of ion channels	Ginsborg & Hirst (1972), Hayashi *et al.* (1978), Horackova *et al.* (1994), Nishimura & Tokimasa (1996), Sun & Stanley (1996), Zhong *et al.* (1998, 2000), Liu *et al.* (2000), Liu & Adams (2001), Smith *et al.* (2001), Zhong *et al.* (2001)
Enteric neurones	A_1, A_{2A}, A_{2B} $P2X_3$, $P2X_4$, $P2X_7$, $P2Y_1$, $P2Y_6$, $P2Y_{12}$	Modulation of neurotransmitter release; regulation of neurotransmission; Ca^{2+} signalling; control of excitability via induction of inward current and modulation of K^+ channels	Gustafsson *et al.* (1978), Hayashi *et al.* (1978), Kamiji *et al.* (1994), Barajas-Lopez *et al.* (1995, 1996), Kimball & Mulholland (1995), Kimball *et al.* (1996), LePard & Galligan (1999), Bian *et al.* (2000)

Table 1 (Continued)

Tissue	Purinoceptors	Main functional role	References
Cardiovascular system			
Heart	A_1, A_3 $P2X_1$, $P2X_3$, $P2X_4$, $P2X_5$ $P2Y_1$, $P2Y_2$, $P2Y_4$, $P2Y_6$	Chronotoropic effects (both negative and positive); preconditioning; regulation of Ca^{2+} signalling; control of pacemaking activity; regulation of excitability of cardiomyocytes; modulation of Ca^{2+} channels; activation of Cl^- currents; activation of muscarinic K^+ channel in atrial cells	Collis (1983), Liu *et al.* (1991), Thornton *et al.* (1992), Auchampach & Gross (1993), Froldi *et al.* (1994), Kaneda *et al.* (1994), Liu *et al.* (1994), Parr *et al.* (1994), Scamps & Vassort (1994), Stark *et al.* (1994), Levesque & Hume (1995), Garcia-Guzman *et al.* (1996), Matsuura *et al.* (1996), Pelleg *et al.* (1996), Qi & Kwan (1996), Babenko & Vassort (1997), Carr *et al.* (1997), Froldi *et al.* (1997), Shoda *et al.* (1997), Blouse *et al.* (1998), Bogdanov *et al.* (1998), Soto *et al.* (2003), Lankford *et al.* (2006), Eckle *et al.* (2007)
Blood vessels/muscle cells	$P2X_1$, $P2X_2$, $P2X_4$ $P2Y_1$, $P2Y_2$, $P2Y_4$, $P2Y_6$	Regulation of blood flow by inducing contraction or relaxation of smooth muscle depending on the vessel type; Ca^{2+} signalling. Angiogenesis. Control of myocyte excitability via Ca^{2+}-dependent currents. Regulation of gene expression, proliferation and migration of smooth muscle cells	Fredholm (1974), Sollevi & Fredholm (1981), Winn *et al.* (1981), Jonzon *et al.* (1985), Li & Fredholm (1985), Proctor & Stojanov (1991), Corr & Burnstock (1994), Vials & Burnstock (1994), Windscheif *et al.* (1994), Ziganshin *et al.* (1994), Erlinge *et al.* (1995, 1996), Kohno *et al.* (1995), Pacaud *et al.* (1995), Malam-Souley *et al.* (1996), Miyagi *et al.* (1996), Orre *et al.* (1996), Harper *et al.* (1998), Muraki *et al.* (1998), Abebe & Mustafa (2002), Fiser *et al.* (2002), Nayeem & Mustafa (2002), Yaar *et al.* (2002)
Blood vessels/endothelial cells	A_1, A_{2A}, A_{2B}, A_3 $P2X_1$, $P2X_2$, $P2X_3$, $P2X_4$, $P2X_5$, $P2X_7$ $P2Y_1$, $P2Y_2$, $P2Y_4$	Induction of the release of NO and vasodilatation; Ca^{2+} signalling. Angiogenesis. Stimulation of prostacyclin release; activation of MAPK; control of cell proliferation	Corr & Burnstock (1994), Wilkinson *et al.* (1994), Zahler *et al.* (1994), Communi *et al.* (1995a), Ikeuchi & Nishizaki (1995), Brown *et al.* (1996), Graham *et al.* (1996), Miyagi *et al.* (1996), Patel *et al.* (1996)
Blood			
Erythrocytes	$P2X_2$ (?) $P2Y_2$ (?)	Potentiation of regulatory volume decrease	Sohn & Kim (1991), Light *et al.* (1999), Sak (2000)
Platelets	$P2X_1$ $P2Y_1$, $P2Y_{12}$	Ca^{2+} signalling; platelet aggregation; shape changes; formation of thrombin	Haslam & Cusack (1981), Paul *et al.* (1990), Lohse *et al.* (1991), Cristalli *et al.* (1994), Gachet *et al.* (1995), Soslau *et al.* (1995), MacKenzie *et al.* (1996), Leon *et al.* (1997), Savi *et al.* (1997), Vial *et al.* (1997)
Megakaryocytes	$P2X_1$ $P2Y_1$, $P2Y_{12}$	Ca^{2+} signalling and $[Ca^{2+}]_i$ oscillations; cytoskeletal remodelling	Somasundaram & Mahaut-Smith (1994), Uneyama *et al.* (1994a,b), Kawa (1996)
Immune system			
Macrophages	A_1, A_{2A}, A_{2B}, A_3 $P2X_7$ $P2Y_2$, $P2Y_6$	Ca^{2+} signalling; macrophage activation; regulation of release of cytokines, NO and other pro-inflammatory factors; cytotoxicity; cell death	Cronstein *et al.* (1985), Hasday & Sitrin (1987), Steinberg & Silverstein (1987), Hickman *et al.* (1994), Nuttle & Dubyak (1994), Perregaux & Gabel (1994), Tonetti *et al.* (1994), Zambon *et al.* (1994), Alonso-Torre & Trautmann (1995), Blanchard *et al.* (1995), Falzoni *et al.* (1995), Griffiths *et al.* (1995), Ichinose (1995), Naumov *et al.* (1995), Chiozzi *et al.* (1996), Coutinho-Silva *et al.* (1996), Denlinger *et al.* (1996), Lin & Lee (1996), Ferrari *et al.* (1997), Knight *et al.* (1997), Sperlagh *et al.* (1998), Xaus *et al.* (1999), Reiss *et al.* (2004), Zidek *et al.* (2004)

Table 1 (Continued)

Tissue	Purinoceptors	Main functional role	References
Leucocytes	A_1, A_{2A}, A_{2B}, A_3 $P2X_1$, $P2X_4$, $P2X_5$, $P2X_7$ $P2Y_2$, $P2Y_4$, $P2Y_6$, $P2Y_{11}$	Ca^{2+} signalling; promotion of adhesion to endothelial cells; stimulation of the oxidative burst; secretion of allergic and pro-inflammatory mediators	Marone *et al.* (1985), Roberts *et al.* (1985), Cronstein *et al.* (1992), Wollner *et al.* (1993), Ludowyke & Scurr (1994), O'Flaherty & Cordes (1994), Dawicki *et al.* (1995), Susztak *et al.* (1995), Fredholm *et al.* (1996), Zalavary *et al.* (1996), Zhang *et al.* (1996), Gessi *et al.* (2005), Chen *et al.* (2006), Inoue *et al.* (2008)
Lymphocytes	A_{2A}, A_{2B} $P2X_1$, $P2X_2$, $P2X_4$, $P2X_7$ $P2Y_{11}$	Regulation of proliferation, differentiation and cell death; regulation of secretion of IL-2 and IFN-γ	Miles *et al.* (1977), Fredholm *et al.* (1978), Marone *et al.* (1978), Schwartz *et al.* (1978), Sandberg & Fredholm (1981), Wiley *et al.* (1994), Bretschneider *et al.* (1995), Baricordi *et al.* (1996), Chused *et al.* (1996), Macino *et al.* (1996), Huang *et al.* (1997), Markwardt *et al.* (1997), Varani *et al.* (1997), Mirabet *et al.* (1999)
Monocytes	A_1, A_{2A}, A_{2B}, A_3 $P2X_7$ $P2Y_1$, $P2Y_2$, $P2Y_4$, $P2Y_6$	Adenosine controls differentiation and cytokine production; ATP acts as a potent chemoattractant	Najar *et al.* (1990), Salmon *et al.* (1993), Akbar *et al.* (1997), Rassendren *et al.* (1997), Jin *et al.* (1998), Mayne *et al.* (1999), Landells *et al.* (2000), Link *et al.* (2000), Broussas *et al.* (2002), Zhang *et al.* (2005)
Mast cells	A_{2B}, A_3 $P2Y_1$, $P2Y_2$	Adenosine and ATP release histamine and cause degranulation	Diamant & Kruger (1967), Ramkumar *et al.* (1993), Jin *et al.* (1997), McCloskey *et al.* (1999), Schulman *et al.* (1999), Hua *et al.* (2007)
Lung			
Airway smooth muscle	A_1 $P2Y_2$, $P2Y_6$	Ca^{2+} signalling; regulation of proliferation	Bjorck *et al.* (1992), Michoud *et al.* (1997), Bergner & Sanderson (2002), Brown *et al.* (2008)
Tracheal smooth muscle	$P2X_1$, $P2Y_1$, $P2Y_2$	Ca^{2+} signalling	Michoud *et al.* (1997), Sawai *et al.* (1997)
Tracheal epithelial cells	A_1 $P2X_4$, $P2X_7$, $P2Y_1$, $P2Y_2$	Ca^{2+} signalling; regulation of ciliary function; activation of Ca^{2+}-dependent Cl^- channels	Aksoy *et al.* (1995), Satoh *et al.* (1995), Hwang *et al.* (1996), Kim *et al.* (1996), Evans & Sanderson (1999), Gabriel *et al.* (2000), Nlend *et al.* (2002), Ma *et al.* (2006), Brown *et al.* (2008)
Tracheal goblet cells	$P2X_4$, $P2X_7$ $P2Y_1$, $P2Y_2$	Stimulation of mucin secretion	Marino *et al.* (1999)
Acinar cells from submucosal gland	P2Y	Ca^{2+} signalling; stimulation of protein secretion	Shimura *et al.* (1994)
Lung goblet cells	$P2Y_2$	Increase in mucin secretion	Conway *et al.* (2003)
Alveolar type II cells	$P2X_4$ $P2Y_2$, $P2Y_5$	Facilitation of mucociliary clearance; activation of Cl^- currents	Gobran *et al.* (1994), Rice *et al.* (1995), Buell *et al.* (1996)
Ciliated epithelium	$P2X_4$, $P2Y_2$	Potentiation of surfactant release; increase in ciliary beat frequency	Stutts *et al.* (1994), Ma *et al.* (1999)
Non-ciliated epithelium (Clara cells)	$P2Y_2$	Stimulation of Cl^- and HCO_3^- secretion	Van Scott *et al.* (1995), Kishore *et al.* (2000)
Neuroepithelial bodies	$P2X_3$	Mechanosensory transduction and O_2 sensing	Brouns *et al.* (2000)

Table 1 (Continued)

Tissue	Purinoceptors	Main functional role	References
Gastrointestinal tract			
Stomach	$P2X_1$, $P2X_7$ $P2Y_1$, $P2Y_2$	Stimulation of contraction/relaxation; Ca^{2+} signalling; prostaglandin production	Soediono & Burnstock (1994), Baccari *et al.* (1996), Blottiere *et al.* (1996), Mashimo *et al.* (1996), Otsuguro *et al.* (1996), Curro & Preziosi (1998)
Duodenum	P2X(?) $P2Y_1$, $P2Y_2$, P2Y(?)	ATP [acting through P2Y(?)] induces relaxation whereas UTP (acting through $P2Y_2$) stimulates contraction	Irie *et al.* (1994), Johnson & Hourani (1994), Zagorodnyuk *et al.* (1995)
Ileum	A_1 $P2X_1$, $P2X_7$, $P2Y_1$, $P2Y_2$, P2Y(?)	Regulation of ACh release and muscle relaxation process	Gustafsson *et al.* (1978), Hayashi *et al.* (1978), Kennedy & Humphrey (1994), Nitahara *et al.* (1995), Longhurst *et al.* (1996), Smits & Lefebvre (1996)
Colon	$P2X_1$, $P2X_7$ $P2Y_1$, $P2Y_2$	ATP induces contraction of circular muscle and relaxation of longitudinal muscle; Ca^{2+} signalling; modulation of Cl^- currents	Venkova *et al.* (1994), Zagorodnyuk & Maggi (1994), Briejer *et al.* (1995), Qian & Jones (1995), Maggi & Giuliani (1996)
Liver	A_1, A_{2A}, A_{2B} P2X(?) $P2Y_1$, $P2Y_2$, $P2Y_{13}$	Regulation of gluconeogenesis, stimulation of glycogen breakdown and inhibition of glycolysis and fatty acid synthesis; Ca^{2+} signalling	Cooper & Londos (1979), Carmichael *et al.* (1988), Ohigashi *et al.* (1993), Nagy (1994), Guzman *et al.* (1996), Capiod (1998), Dixon *et al.* (2000, 2003), Che *et al.* (2007)
Urinary system			
Kidney/glomerulus	A_1 $P2X_1$, $P2X_3$, $P2X_4$, $P2X_5$, $P2X_7$ $P2Y_1$, $P2Y_2$, $P2Y_4$, $P2Y_6$, $P2Y_{11}$, $P2Y_{12}$	Urine production; renal constriction; tubuloglomerular feedback; Ca^{2+} signalling; stimulation of mitogenesis; induction of apoptosis and necrosis via $P2X_7$ receptors in development	Hedqvist *et al.* (1978), Murray & Churchill (1984), Schnermann (1988), Schnermann *et al.* (1990), Briner & Kern (1994), Ishikawa *et al.* (1994), Takeda *et al.* (1996), Huwiler *et al.* (1997), Schulze-Lohoff *et al.* (1998), Brown *et al.* (2001)
Kidney/loop of Henle	$P2Y_1$, $P2Y_2$, $P2Y_6$	Ca^{2+} signalling	Paulais *et al.* (1995), Bailey *et al.* (2000)
Bladder/smooth muscle	$P2X_1$, $P2X_2$, $P2X_4$, $P2X_5$, $P2X_6$, $P2X_7$ P2Y	ATP is a main parasympathetic co-transmitter; ATP induces contraction via P2X receptors and relaxation via P2Y; triggers micturition reflex	Bo *et al.* (1994, 1995), Suzuki & Kokubun (1994), Bolego *et al.* (1995), Evans *et al.* (1995), Michel *et al.* (1996), Zhao *et al.* (1996)
Bladder/urothelium	$P2X_3$, $P2X_5$, $P2X_6$, $P2X_7$	?	Lee *et al.* (2000a)
Urethra	P2X P2Y	ATP acts as a co-transmitter; induces relaxation via P2Y receptors	Pinna *et al.* (1996), Ohnishi *et al.* (1997)

Table 1 (Continued)

Tissue	Purinoceptors	Main functional role	References
Genital system			
Penis	$P2X_1$, $P2X_2$ $P2Y_1$	Relaxation of corpus cavernosum via NO-dependent (humans) and NO-independent pathways; role in priapism	Broderick *et al.* (1994), Levin *et al.* (1995), Ragazzi *et al.* (1996), Kaya *et al.* (1998), Shalev *et al.* (1999)
Testis	A_1, A_3 $P2X_2$, $P2X_3$, $P2X_7$ $P2Y_2$	Ca^{2+} signalling; regulation of secretion of fluids, oestradiol and testosterone	Nakata (1990), Zhou *et al.* (1992), Filippini *et al.* (1994), Foresta *et al.* (1995, 1996b), Rudge *et al.* (1995), Meroni *et al.* (1998)
Sperm	A_1 $P2X_2$, $P2X_3$, $P2X_5$, $P2X_7$ P2Y(?)	Modulation of spermatogenesis and stimulation of acrosomal exocytosis; capacitation	Tomiyama *et al.* (1995), Foresta *et al.* (1996a), Loir (1999), Glass *et al.* (2001), Minelli *et al.* (2004)
Vas deferens	$P2X_1$, $P2X_2$, $P2X_4$, $P2X_7$ $P2Y_1$, $P2Y_2$, P2Y(?)	ATP is a main sympathetic co-transmitter (with NA); triggers contraction and regulates muscle tone	Bultmann & Starke (1994b), Michel & Humphrey (1994), Bo *et al.* (1995), Westfall *et al.* (1997), Mulryan *et al.* (2000)
Prostate gland	$P2X_1$	ATP is a main sympathetic co-transmitter (with NA); regulation of excitability of epithelial cells	Janssens *et al.* (1996), Longhurst *et al.* (1996), Lee *et al.* (2000b)
Vagina and cervix	$P2X_2$, $P2X_4$, $P2X_5$, $P2X_7$ $P2Y_2$, P2Y(?)	Regulation of relaxation; stimulation of mucus and Cl^- secretion; regulation of transepithelial electrical conductance; regulation of cell turnover	Gorodeski & Hopfer (1995), Gorodeski *et al.* (1996), Gorodeski & Goldfarb (1997), Groschel-Stewart *et al.* (1999), Bardini *et al.* (2000), Min *et al.* (2003)
Uterus	A_1, A_{2A}, A_{2B} $P2X_1$, $P2X_2$, $P2X_3$, $P2X_4$, $P2X_5$, $P2X_6$, $P2X_7$ $P2Y_2$, $P2Y_4$, $P2Y_6$	Ca^{2+} signalling; stimulation of contraction; regulation of Na^+ transport in endometrial endothelial cells	Schiemann & Buxton (1991), Schiemann *et al.* (1991), Haynes & Pennefather (1993), Piper & Hollingsworth (1996), Gillman & Pennefather (1998), Blackburn *et al.* (1999), Bardini *et al.* (2000), Tassell *et al.* (2000), Aitken *et al.* (2001), Shmigol *et al.* (2001)
Ovary	$P2X_1$, $P2X_2$ $P2Y_2$	Ca^{2+} signalling; increase in ciliary beat frequency; regulation of fluid formation	Cox & Leese (1995), Dickens *et al.* (1996), Bardini *et al.* (2000)
Placenta	$P2X_1$, $P2X_2$, $P2X_4$, $P2X_7$ $P2Y_2$, $P2Y_6$, $P2Y_{11}$	Stimulation of PLC/$InsP_3$ production; Ca^{2+} signalling	Petit & Belisle (1995), Karl *et al.* (1997), Somers *et al.* (1999)
Exocrine glands			
Salivary glands	$P2X_4$, $P2X_7$ $P2Y_2$	Ca^{2+} signalling; regulation of ion balance; regulation of Zn^{2+} uptake; ATP acts as a co-transmitter in excitation–secretion coupling	Hurley *et al.* (1994), Dehaye (1995), Jorgensen *et al.* (1995), Amsallem *et al.* (1996), Lachish *et al.* (1996), Fukushi *et al.* (1997), Park *et al.* (1997), Tojyo *et al.* (1997), Zeng *et al.* (1997), Mizuno-Kamiya *et al.* (1998), Tenneti *et al.* (1998)

Table 1 (Continued)

Tissue	Purinoceptors	Main functional role	References
Exocrine pancreas	A_{2A} $P2X_1$, $P2X_4$, $P2X_7$ $P2Y_1$, $P2Y_2$, $P2Y_4$	Ca^{2+} signalling; stimulation of mucin and anion secretion	Chan *et al.* (1996), Christoffersen *et al.* (1998), Nguyen *et al.* (1998), Dubyak (1999), Hede *et al.* (1999), Luo *et al.* (1999), Iwatsuki (2000)
Endocrine glands			
Adrenal gland	$P2X_1$, $P2X_2$, $P2X_3$, $P2X_4$, $P2X_5$, $P2X_6$, $P2X_7$ $P2Y_2$, P2Y(?)	Ca^{2+} signalling; modulation of secretion of catecholamines; modulation of aldosterone production and secretion; modulation of exocytosis; control of excitability	Castro *et al.* (1995), Lin *et al.* (1995), Reichsman *et al.* (1995), Lim *et al.* (1997), Szalay *et al.* (1998), Afework & Burnstock (1999), Xu & Enyeart (1999)
Pituitary gland	$P2X_2$, $P2X_3$, $P2X_4$, $P2X_7$ $P2Y_2$	Ca^{2+} signalling; regulation of the release of vasopressin and prolactin	Carew *et al.* (1994), Chen *et al.* (1994, 1995), Tomic *et al.* (1996), Nunez *et al.* (1997), Troadec *et al.* (1998), Sperlagh *et al.* (1999)
Thyroid	A_1, A_{2A} $P2X_3$, $P2X_4$, $P2X_5$ $P2Y_2$	Ca^{2+} signalling; increase and decrease in cAMP; inhibition of Na^+ absorbtion	Fradkin *et al.* (1982), Frauman & Moses (1989), Okajima *et al.* (1989), Schofl *et al.* (1995), Bourke *et al.* (1999), Harii *et al.* (1999)
Endocrine pancreas	A_1, A_{2A} $P2X_1$, $P2X_7$ $P2Y_2$, $P2Y_4$	Inhibition or stimulation of insulin and glucagon release; regulation of pulsatility	Hillaire-Buys *et al.* (1987), Squires *et al.* (1994), Petit *et al.* (1998), Coutinho-Silva *et al.* (2001), Johansson *et al.* (2007), Salehi *et al.* (2009)
Musculoskeletal system			
Bone: osteoblasts	$P2X_2$, $P2X_4$, $P2X_5$, $P2X_7$ $P2Y_1$, $P2Y_2$	Ca^{2+} signalling; stimulation of osteoclast formation; regulation of proliferation; control of cell death	Dixon *et al.* (1997), Jones *et al.* (1997), Bowler *et al.* (1999), Hoebertz *et al.* (2000, 2001, 2002)
Bone: osteoclasts	A_1 $P2X_2$, $P2X_4$, $P2X_7$ $P2Y_1$, $P2Y_2$	Stimulation of osteoclast activity; stimulation of resorption pit formation; regulation of acid transport; regulation of intercellular communications via Ca^{2+} waves; inhibition of bone resorption ($P2X_7$?)	Modderman *et al.* (1994), Yu & Ferrier (1995), Weidema *et al.* (1997), Morrison *et al.* (1998), Hoebertz *et al.* (2000, 2001), Kara *et al.* (2009)
Cartilage	$P2X_2$, $P2X_5$ $P2Y_1$, $P2Y_2$, $P2Y_4$	Ca^{2+} signalling; stimulation of cartilage resorption and production of prostaglandins	Leong *et al.* (1994), Bulman *et al.* (1995), Kaplan *et al.* (1996), Hung *et al.* (1997), Koolpe & Benton (1997)
Skeletal muscle	A_1 $P2X_1$, $P2X_2$, $P2X_3$, $P2X_5$, $P2X_7$ $P2Y_1$, P2Y(?)	Modulation of neuromuscular junction transmission; Ca^{2+} signalling; inhibition of proliferation and stimulation of differentiation; glucose metabolism	Ayyanathan *et al.* (1996), Henning (1997), Urano *et al.* (1997), Cheng *et al.* (2000)

Table 1 (Continued)

Tissue	Purinoceptors	Main functional role	References
Connective tissue			
Fibroblasts	$P2X_7$, P2X(?) $P2Y_1$, $P2Y_2$, P2Y(?)	Ca^{2+} signalling; regulation of proliferation; activation of volume-sensitive Cl^- channels	Grierson & Meldolesi (1995), Arav & Friedberg (1996), Hofer *et al.* (1996), Tepel *et al.* (1996), Zheng *et al.* (1998)
Adipose tissue	A_1 P2X(?) $P2Y_1$, $P2Y_2$, $P2Y_4$	Antilipolysis; regulation of secretion, proliferation, growth, development, stimulation of lipogenesis and oestrogen synthesis in preadipocytes	Fain *et al.* (1972), Ebert & Schwabe (1973), Fain (1973), Hjemdahl & Fredholm (1976), Sollevi *et al.* (1981), Ukena & Schwabe (1985), Pappone & Lee (1996), Lee & Pappone (1997), Schmidt & Loffler (1998), Omatsu-Kanbe & Matsuura (1999), Yegutkin & Burnstock (1999), Johansson *et al.* (2008)

This table is compiled from Burnstock & Knight (2004), Burnstock (2007a), Burnstock & Verkhratsky (2009) and Verkhratsky *et al.* (2009) where readers are advised to find the full list of references; here we present mostly early works, and we apologize in advance for inevitable omissions.

Holman (Burnstock *et al.* 1963) were recording electrical and mechanical activity of the guinea-pig taenia coli using the sucrose-gap technique. After stimulation of the intramural nerves in the presence of adrenergic and cholinergic blocking agents, an inhibitory hyperpolarizing potential was observed (Burnstock *et al.* 1963, 1964) and this work was extended to an analysis of the mechanical response (Burnstock *et al.* 1966). NANC responses were blocked by tetrodotoxin, a neurotoxin that prevents the action potential in nerves without affecting the excitability of smooth muscle cells, indicating the neurogenic nature of the inhibitory junction potentials (IJPs; Bulbring & Tomita 1967; Fig. 4b). A comparable demonstration of NANC mechanical responses was made by Martinson and colleagues in the stomach upon stimulation of the vagus nerve (Martinson & Muren 1963, Martinson 1965).

As for the gastrointestinal tract, at the end of the 19th century, it was demonstrated that the excitatory response of the mammalian urinary bladder to parasympathetic nerve stimulation was only partially antagonized by anti-muscarinic agents (Langley & Anderson 1895). It was postulated that the atropine-resistant response was due to the release of a non-cholinergic excitatory transmitter (Henderson & Roepke 1934, Chesher & James 1966, Ambache & Zar 1970). However, it was also postulated that atropine was unable to block the subjunctional receptors at which the endogenous ACh acts (Dale & Gaddum 1930) or that it was displaced from these receptors by the high local concentration of ACh released upon parasympathetic stimulation (Hukovic *et al.* 1965).

By the end of the 1960s, evidence had accumulated for NANC nerves in the respiratory, cardiovascular and urinogenital systems as well as in the gastrointestinal tract (Burnstock 1969). Hughes & Vane (1967, 1970) also demonstrated the presence of a NANC inhibitory innervation of the rabbit portal vein. The existence of NANC neurotransmission is now firmly established in a wide range of peripheral and central nerves and fuller accounts of the development of this concept and the people involved are available (see Burnstock 1981, 2006a,c for comprehensive reviews) (Fig. 5).

ATP as a principal transmitter

In the late 1970s, systematic studies were undertaken in an attempt to identify the transmitter utilized by the NANC nerves of the gut and urinary bladder. Several criteria, which must be satisfied prior to establishing a substance as a neurotransmitter, were identified (Eccles 1964, Burnstock 1971). First, a putative transmitter must be synthesized and stored within the nerve terminals from which it is released. It must be shown to be released upon nerve stimulation. Once released, it

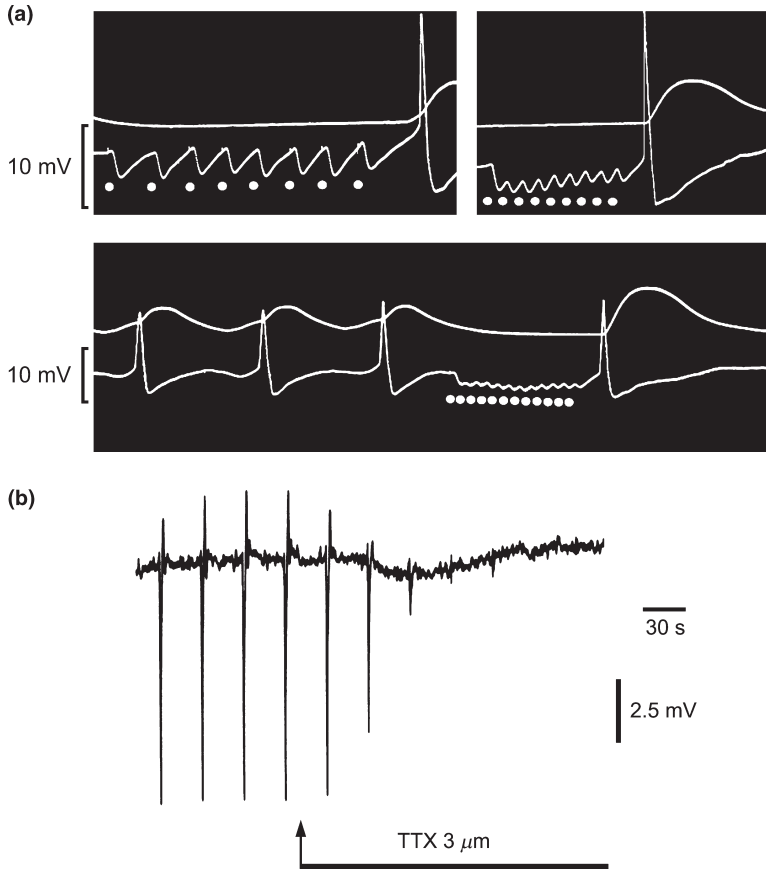

Figure 4 Non-adrenergic, non-cholinergic (NANC) neurotransmission. (a) Sucrose gap records from smooth muscle of guinea-pig taenia coli showing hyperpolarizations in response to different stimulation frequencies (1, 3 and 5 Hz) of intrinsic nerves in the presence of atropine and guanethidine. (b) Sucrose gap recording of membrane potential changes in smooth muscle of guinea-pig taenia coli in the presence of atropine (0.3 μM) and guanethidine (4 μM). Transmural field stimulation (0.5 ms, 0.033 Hz, 8 V) evoked transient hyperpolarizations, which were followed by rebound depolarizations. Tetrodotoxin (TTX, 3 μM) added to the superfusing Kreb's solution (applied at arrow) rapidly abolished the response to transmural field stimulation establishing these as inhibitory junction potentials in response to NANC neurotransmission. Figure reproduced with permission from Burnstock (1986b).

must interact with specific postjunctional receptors and the resultant nerve-mediated response must be mimicked by the exogenous application of the transmitter substance. Also, enzymes that inactivate the transmitter and/or uptake systems for the neurotransmitter or its derivatives must also be operational and, finally, drugs that affect the nerve-mediated response must be shown to modify the response to exogenous transmitter in a similar manner.

An early study, before ATP was identified as the principal transmitter mediated by NANC nerves, was inspired by Loewi's experiments establishing ACh as a neurotransmitter (Loewi 1921). In this study, Burnstock showed that stimulation of NANC nerves to the taenia coli in a top chamber produced the typical nerve-mediated response (fast relaxation, followed by rebound contraction), while the perfusate produced a slower relaxation (without rebound contraction) when reaching a lower taenia coli preparation (Fig. 6). Only later was it shown that the response in the top chamber was mimicked by ATP, while the response in the lower chamber was mediated by adenosine (after rapid breakdown of ATP, released from the top preparation, by ectonucleotidases).

Many substances were examined as putative transmitters in the NANC nerves of the gastrointestinal tract and bladder, but the substance that best satisfied the above criteria was the purine nucleotide, ATP (Burnstock *et al.* 1970, Burnstock 1972). Nerves utilizing ATP as their principal transmitter were subsequently named 'purinergic' (and a tentative model of storage, release, and inactivation of ATP for purinergic nerves was proposed; Burnstock 1971, 1972). Since then a great deal of evidence has followed in support of the purinergic hypothesis (see Burnstock 1975b,a, 1979a, 1993b, 2007a, Su 1983, Gordon 1986, White 1988,

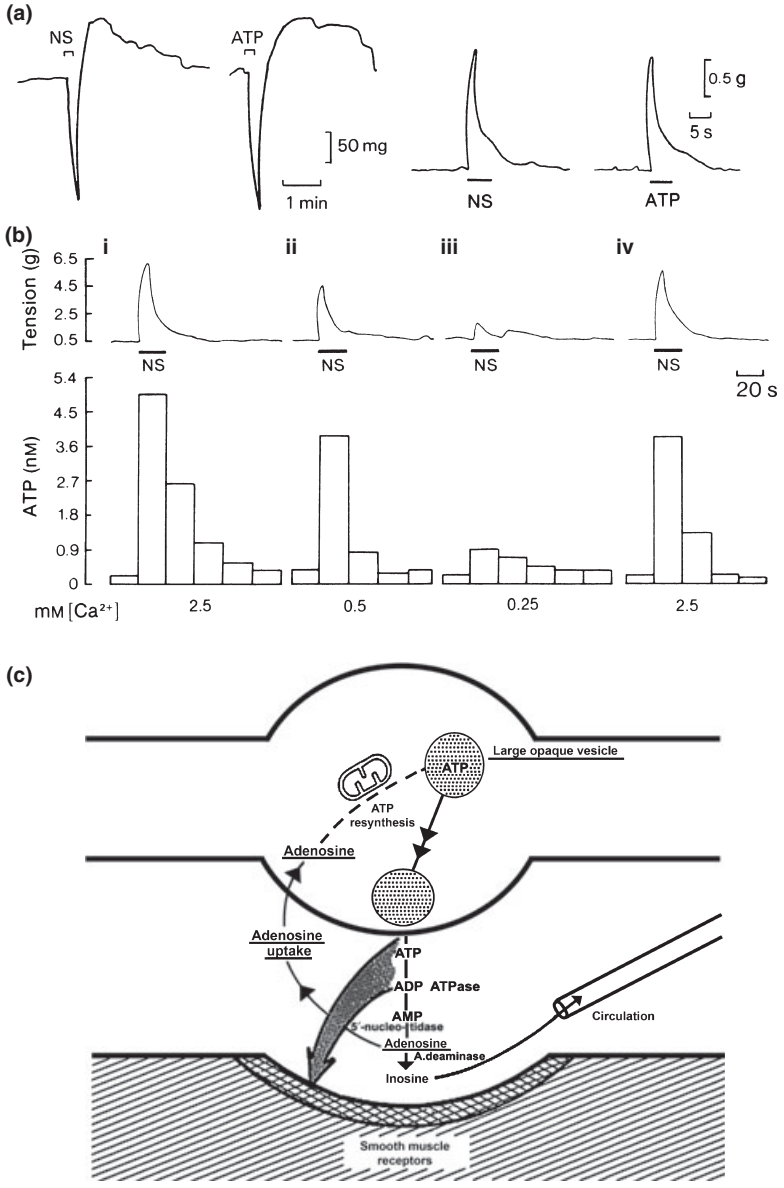

Figure 5 Evidence for ATP as a non-adrenergic, non-cholinergic (NANC) neurotransmitter. (a) Left-hand side: responses of the guinea-pig taenia coli to NANC nerve stimulation (NS: 1 Hz, 0.5 ms pulse duration, for 10 s at supramaximal voltage) mimicked by ATP (2×10^{-6} M). The responses consist of a relaxation followed by a 'rebound contraction'. Atropine (1.5×10^{-7} M), guanethidine (5×10^{-6} M) and sodium nitrite (7.2×10^{-4} M) were present. Figure reproduced with permission from Burnstock & Wong (1978). Right-hand side: a comparison of the NANC contractile responses of the guinea-pig bladder strip to intramural nerve stimulation (NS: 5 Hz, 0.2 ms pulse duration and supramaximal voltage) mimicked by exogenous ATP (8.5 μM). Atropine (1.4 μM) and guanethidine (3.4 μM) were present throughout. Figure reproduced with permission from Burnstock *et al.* (1978). (b) Effect of changing the calcium ion (Ca^{2+}) concentration on the release of ATP (measured with the firefly luciferin/luciferase technique) from the guinea-pig isolated bladder strip during stimulation of NANC nerves. Upper trace: mechanical recording of changes in tension (g) during intramural nerve stimulation (NS: 20 Hz, 0.2 ms pulse duration, supramaximal voltage for 20 s). Lower trace: concentration of ATP in consecutive 20 s fractions of the superfusate. The Ca^{2+} concentration in the superfusate varied as follows: (i) 2.5 mM (normal Krebs); (ii) 0.5 mM; (iii) 0.25 mM; (iv) 2.5 mM. The successive contractions were separated by 60 min intervals as indicated by the breaks in the mechanical trace. Atropine (1.4 μM) and guanethidine (3.4 μM) were present throughout. Figure reproduced with permission from Burnstock *et al.* (1978). (c) The purinergic neuromuscular transmission hypothesis depicting the synthesis, storage, release and inactivation of ATP. ATP, stored in vesicles in nerve varicosities, is released by exocytosis to act on postjunctional P2 purinoceptors on smooth muscle. ATP is broken down extracellularly by ATPases and 5′-nucleotidase to adenosine, which is taken up by varicosities to be resynthesized and restored in vesicles. If adenosine is broken down further by adenosine deaminase to inosine, it is removed by the circulation. Figure reproduced with permission from Burnstock (1972).

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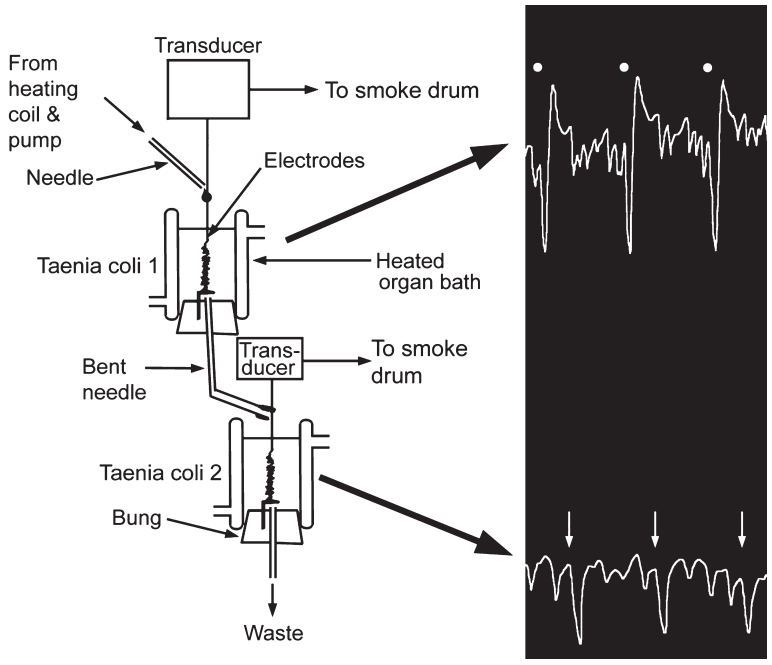

Figure 6 Loewi-inspired experiments carried out in 1966. The upper guinea-pig taenia coli innervated preparation was stimulated at 5 Hz for 40 s every 6 min at 50 V and 2 ms duration, in the presence of atropine and guanethidine to elicit typical non-adrenergic, non-cholinergic responses, fast relaxation followed by rebound contraction. The perfusate passed over the lower taenia coli preparation to produce slow relaxations, but not followed by rebound contractions. In later experiments, we showed that while the response of the taenia coli in the upper chamber was mimicked by ATP, the response in the lower chamber was mimicked by adenosine, the ATP released from the upper preparation being hydrolysed rapidly by ectonucleotidases to adenosine before reaching the lower preparation (unpublished experiments carried out by Burnstock & Smythe 1966).

Olsson & Pearson 1990, Hoyle 1992, Dubyak & el-Moatassim 1993, Zimmermann 1994, North 2002, Abbracchio *et al.* 2009), although there was also considerable opposition to this idea in the first decade after it was put forward (see Burnstock 1975b, Stone 1981, Gillespie 1982).

ATP as a co-transmitter

The concept that each nerve cell can synthesize, store and release only one neurotransmitter, generally known as Dale's principle (Dale 1935), was challenged by Burnstock (1976) and the existence of nerves that can synthesize, store and release more than one pharmacologically active substance is now widely accepted (see Burnstock 1983, 1990, 2004, 2009, Osborne 1983, Kupfermann 1991).

By the mid-1950s it was recognized that ATP was co-stored with catecholamines in adrenal medullary chromaffin cells (Hillarp *et al.* 1955, Blaschko *et al.* 1956) and soon after, the co-release of ATP with adrenaline from chromaffin cells was identified (Carlsson *et al.* 1957, Douglas & Poisner 1966). The molar ratio between noradrenaline (NA) and ATP in sympathetic nerve terminals was estimated to very between 7 : l and 12 : 1 (NA : ATP) (Schumann 1958, Eulerus *et al.* 1963, Stjärne & Lishajko 1966, Geffen & Livett 1971, Lagercrantz & Stajarne 1974). Su *et al.* (1971) demonstrated that stimulation of periarterial sympathetic nerves led to release of tritium from guinea-pig taenia coli pre-incubated in [^{3}H]adenosine (which is taken up and converted largely to [^{3}H]ATP) and that the release of both tritium and NA was blocked by guanethidine. Soon after, Nakanishi & Takeda (1973) showed evidence that ATP might be co-released with NA in synapses from the hypogastriac nerve to the seminal vesicle of the guinea-pig and Langer & Pinto (1976) suggested that the substantial residual NANC responses of the cat nictitating membrane, following depletion of NA by reserpine, might be due to the release of ATP remaining in sympathetic nerves. However, in other preparations, purine release by nerve stimulation was only a minor part due to co-release with NA (Fredholm *et al.* 1982). It was found that in some tissues adenosine was released in response to the actions of the released transmitter and that adenosine could act as a retrograde transmitter limiting excessive transmitter release by means of presynaptic inhibition (Hedqvist & Fredholm 1976, Fredholm & Hedqvist 1979, 1980).

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ATP acts as a co-transmitter with ACh in cholinergic nerves in various tissues, including the electric organ of elasmobranch fish (Dowdall *et al.* 1974, Zimmermann 1978), the phrenic nerve endings in rat diaphragm (Silinsky & Hubbard 1973, Silinsky 1975) and in the excitatory nerves of the guinea-pig urinary bladder (Kasakov & Burnstock 1982, MacKenzie *et al.* 1982, Westfall *et al.* 1983, see also Burnstock 1986a, Hoyle 1996 for reviews).

The most extensive evidence for sympathetic co-transmission, however, came from studies of the vas deferens, initially by Westfall and colleagues (Westfall *et al.* 1978, Fedan *et al.* 1981). Later studies from several laboratories, following on from the initial work of Su (1975), established sympathetic co-transmission in a variety of different blood vessels (see Burnstock 1988).

ATP as an excitatory transmitter in the CNS

Although the release of purines from gross brain structures was identified in the mid-1970s (Sulakhe & Phillis 1975), the first indication that ATP may act as a neurotransmitter in central synapses was recognized by Thomas White, who observed the release of ATP from synaptosomes prepared from the whole brain, the cortex and the striatum; the ATP release was triggered by exposure to high extracellular K^+ or to veratridine (White 1978, 1984, White *et al.* 1980). The next important step was electrophysiological recording of ATP-induced depolarization and ATP-induced currents in both sensory and central neurones (Jahr & Jessell 1983, Krishtal *et al.* 1983). Almost 10 years later, ATP-mediated synaptic transmission was identified in cultured coeliac ganglion cells (Evans *et al.* 1992, Silinsky *et al.* 1992) and in neurones in acute slices from medial habenula (Edwards *et al.* 1992, 1997). Subsequently, fast ATP/P2X-mediated synaptic transmission was found in various regions of the CNS, including spinal cord (Bardoni *et al.* 1997), hippocampus (Pankratov *et al.* 1998, Mori *et al.* 2001), locus coeruleus (Nieber *et al.* 1997) and cortex (Pankratov *et al.* 2002, 2003, see also North & Verkhratsky 2006). The quantal release of ATP was characterized in PC12 cells (Fabbro *et al.* 2004), in peripheral (Silinsky *et al.* 1999) and in central synapses (Pankratov *et al.* 2006, 2007). In addition, purinergic transmission is involved in a wide variety of trophic and developmental processes in the nervous system (see Abbracchio *et al.* 2009, Burnstock & Verkhratsky 2010 for reviews).

Purines as signalling molecules are particularly important for transmission in the neuronal–glial circuitry that forms the brain parenchyma and provides the substrate for CNS function (Verkhratsky 2006, 2009, Verkhratsky & Toescu 2006). It appears that all types of glial cells, be they of neural (astrocytes and oligodendrocytes) or myeloid (microglia) origin, express an extensive complement of purinoceptors. ATP triggers massive Ca^{2+} release from the endoplasmic reticulum (mediated via P2Y/inositol trisphosphate pathway) in both astrocytes and oligodendrocytes (Kirischuk *et al.* 1995a,b, Hamilton *et al.* 2008) and controls the same pathway in microglial cells (Moller *et al.* 2000, Farber & Kettenmann 2006). In addition, some types of astrocytes express fast P2X receptors (Lalo *et al.* 2008), whereas oligodendrocytes and microglial cells possess $P2X_7$ receptors (Ferrari *et al.* 1996, Haas *et al.* 1996, Matute *et al.* 2007, see also Verkhratsky *et al.* 2009 for a comprehensive review). Furthermore, ATP acts as a main gliotransmitter, which provides for both glial–glial and glial–neuronal signalling.

Adenosine in the nervous system

Kakiuchi *et al.* (1969) showed that nerve activity causes release of adenosine in sufficient amounts to activate even the low affinity adenosine A_{2B} receptors. The adenosine thus released was formed *de novo* and did not come from pre-existing stores. Furthermore, not even when release was examined from isolated nerve endings can the majority of the adenosine release be accounted for by release of ATP and subsequent extracellular degradation (Fredholm & Vernet 1979, Fredholm & Hedqvist 1980). Inhibition of transmitter release is an important effect of adenosine (see below) and this will cause protection against seizures (Dunwiddie *et al.* 1981, Dragunow *et al.* 1985, Fedele *et al.* 2006, Li *et al.* 2007). Similarly, there is a very important role of adenosine in limiting the extent of neuronal damage following e.g. ischaemia. This is in keeping with the proposed role as a 'retaliatory metabolite' (Newby 1984), the evidence for which is very strong (Rudolphi *et al.* 1992).

Much focus was initially on the A_1 receptors (see below), but it is becoming clear that the A_{2A} receptors that have a highly restricted distribution (Svenningsson *et al.* 1997c) are particularly important under physiological conditions, as they control the so-called indirect pathway from the basal ganglia and hence contribute to a variety of systems including sleep–wakefulness (Huang *et al.* 2005), locomotion (Svenningsson *et al.* 1997b, El Yacoubi *et al.* 2000) and mood (El Yacoubi *et al.* 2001).

Neuromodulation by purines

Neuromodulators can influence neurotransmission at two sites, either by acting on presynaptic receptors to reduce or enhance transmitter release, or by acting on postsynaptic receptors to alter the magnitude or time course of the transmitter on the postjunctional cell. The

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first studies of prejunctional modulation of transmitter release by purines concerned the isolated rat phrenic nerve-diaphragm preparation, where adenosine and adenine nucleotides reduced both the spontaneous and evoked release of ACh from motor nerve terminals (Ginsborg & Hirst 1972, Ribeiro & Walker 1975). These same purine compounds were later shown to cause prejunctional inhibition of NA release from peripheral sympathetic nerves in a wide variety of tissues, including rabbit kidney, canine adipose tissue, guinea-pig vas deferens (Hedqvist & Fredholm 1976, Clanachan *et al.* 1977), and rabbit central ear artery, saphenous vein, portal vein and pulmonary artery (Enero & Saidman 1977, Verhaeghe *et al.* 1977, Su 1978). Prejunctional modulation of ACh release from peripheral cholinergic nerves by purines was observed in the isolated guinea-pig ileum and the myenteric plexus longitudinal muscle preparation (Sawynok & Jhamandas 1976, Moritoki *et al.* 1978, Moody & Burnstock 1982). Adenosine and related compounds, iontophoretically applied to central synapses, decreased the rate of spontaneous firing of rat cerebral cortical neurones (Phillis *et al.* 1975, 1979). Similarly, the naturally occurring diadenosine polyphosphates were found to modulate transmitter release from central neurones through presynaptic receptors (Miras-Portugal *et al.* 1996).

Purine modulation of transmitter release was thought to be mediated largely via presynaptic P1 receptors both in adrenergic systems (Clanachan *et al.* 1977, Enero & Saidman 1977, Verhaeghe *et al.* 1977, Hom & Lokhandwala 1981) and cholinergic systems (Ginsborg & Hirst 1972, Sawynok & Jhamandas 1976, Vizi & Knoll 1976, Griffith *et al.* 1981). Clear evidence for this was presented by De Mey *et al.* (1979) who showed that the prejunctional actions of purine nucleotides were mediated by adenosine following the rapid breakdown of ATP, as slowly degradable analogues of ATP were ineffective. Results supporting this hypothesis have been presented for other preparations (Burnstock & Meghji 1981, Moody & Burnstock 1982, Bruns *et al.* 1983). It has also been suggested that ATP may act *per se* on Pl purinoceptors in guinea-pig atria (Collis & Pettinger 1982) or that both mechanisms operate during the time course of a response to ATP (Moody *et al.* 1984). Subsequently, evidence has been presented for a prejunctional modulatory action by ATP itself in the iris, rat vas deferens and tail artery via a 'P3' receptor (Shinozuka *et al.* 1990) or a P2Y purinoceptor (Fuder & Muth 1993, von Kugelgen *et al.* 1994). At the same time, in many of these studies a participation of breakdown products such as adenosine has not been rigorously excluded, and in at least some preparations presynaptic inhibitory effects of ATP were completely eliminated in mice lacking adenosine A_1 receptors (Masino *et al.* 2002).

Purine nucleotides and nucleosides can also act on postjunctional receptors to modulate cholinergic and adrenergic neurotransmission. Purines increase ACh receptor sensitivity in various preparations, including the rat diaphragm muscle (Ewald 1976), frog skeletal muscle (Akasu *et al.* 1981) and rabbit iris sphincter (Gustafsson & Wiklund 1986). These interactions are Ca^{2+} dependent and may involve interaction with the allosteric site of the receptor–ion channel complex. Purine nucleotides and nucleosides have been shown to interact with NA postjunctionally *in vitro* in guinea-pig seminal vesicles (Nakanishi & Takeda 1973), rabbit kidney (Hedqvist & Fredholm 1976), guinea-pig and mouse vas deferens (Holck & Marks 1978, Witt *et al.* 1991), rabbit mesenteric artery (Krishnamurty & Kadowitz 1983), and rat mesenteric bed (Ralevic & Burnstock 1990). All these neuromodulatory actions of purines have been extensively reviewed (Ribeiro 1979, Burnstock & Brown 1981, Stone 1981, Paton 1987, Hoyle 1992, Starke *et al.* 1996, Dunwiddie & Fredholm 1997, Cunha 2001, Sebastião & Ribeiro 2009).

Receptors for purines

Subdivision into P1 and P2 purinoceptors

The existence of specific receptors for purines, which dwell in postsynaptic/postjunctional membranes, was one of the keystones of the purinergic neurotransmission hypothesis. In 1978 Burnstock, after analysing a wealth of literature dedicated to the effects of purine nucleotides and nucleosides in a wide variety of tissues, proposed the first classification of purinergic receptors (Burnstock 1978). Based on several criteria, subclassification into Pl and P2 purinoceptors was proposed. The Pl purinoceptors are much more responsive to adenosine and AMP than to ADP and ATP and are selectively and competitively antagonized by methylxanthines, such as theophylline and caffeine. Occupation of Pl purinoceptors leads to changes in adenylate cyclase activity, resulting in alterations in intracellular levels of cAMP. P2 purinoceptors are more responsive to ATP and ADP than to AMP and adenosine. They are not antagonized by methylxanthines and occupation leads to an increase in the production of prostaglandins.

Perhaps the first indication, contained in a single study, of subtypes of receptors preferring ATP vs. adenosine was presented by Gillespie (1934), who described ATP as being more potent than its dephosphorylated relatives in causing relaxation of the guinea-pig ileum, and adenosine as being more potent than its phosphorylated derivatives in causing coronary vasodilatation or inducing hypotension in cats and rabbits. Mihich *et al.* (1954) noted that, although the effects of ATP were similar to those of adenosine in the isolated

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rabbit intestine, the action of ATP was qualitatively distinct, in that preparations rendered tachyphylactic to adenosine or its 2-substituted derivatives retained their responsiveness to ATP. Adenosine and ATP produced opposite responses in the renal vascular bed; adenosine and AMP caused an increase and ATP a decrease in vascular resistance. Furthermore, theophylline, although antagonizing the responses to adenosine and AMP, was unable to reduce the vasodilatation produced by ATP (Haddy & Scott 1968), suggestive of two distinct receptor populations for these compounds in this tissue. Adenosine and ATP appeared to have different actions in guinea-pig bladder (Burnstock *et al.* 1972), rat portal vein (Sjöberg & Wahlström 1975) and chicken rectum (Bartlet 1974). In the guinea-pig taenia coli, the log concentration–response curves for the inhibitory effects of ATP and ADP were found to be substantially more potent and non-parallel to those for AMP and adenosine (Burnstock *et al.* 1970, Satchell & Maguire 1975). 2,2′-Pyridylisatogen tosylate was able to block the inhibitory responses of the guinea-pig taenia coli to ATP and ADP, but not to adenosine (Spedding & Weetman 1976).

The subclassification of Pl and P2 purinoceptors was supported by numerous pharmacological, biochemical and molecular biological studies performed during the last three decades (Fredholm *et al.* 1994, 2001, Ralevic & Burnstock 1998, Khakh *et al.* 2001, North 2002, Abbracchio *et al.* 2006, Surprenant & North 2009).

Subtypes of adenosine purinoceptors (P1)

The existence of adenosine receptors was postulated by Degubareff & Sleator (1965) based on studies showing caffeine antagonism of adenosine actions in atrial muscle, and in the early 1970s by several scientists including Rall and Daly based on their studies showing the ability of adenosine analogues to raise cAMP levels in brain slices from several organs (*vide supra*). The competitive antagonism between adenosine and methylxanthines was shown (Fig. 7) and this suggested that the two structurally similar compounds acted at the same site/receptor to exert their effects. This tentative conclusion was further supported by work examining a series of adenosine analogues and demonstrating the type of dose–response relationships typical of receptors (Cobbin *et al.* 1974).

Evidence for subclasses of adenosine receptors emerged at the same time as the realization that adenosine and ATP had different activities. A distinction was made between the adenosine receptor-mediated stimulation and inhibition of adenylate cyclase. First, Londos & Wolff (1977) demonstrated that adenosine and its analogues stimulated adenylate cyclase by a mechanism involving an external membrane receptor which required an essentially unmodified ribose moiety (hence called the R site). They also demonstrated a high dose effect directly on adenylate cyclase that required an unchanged purine moiety (and this was called the P-site). Concurrently, van Calker *et al.* (1978, 1979) put forward evidence that both stimulation and inhibition of adenylate cyclase could be mediated by adenosine at the external R site. Londos *et al.* (1978, 1980) at the same time also demonstrated two different extracellular adenosine receptors, and consistent with his R- vs. P-site distinction called the receptor whose activation *inhibited* adenylate cyclase an R_i receptor, whereas receptors whose stimulation

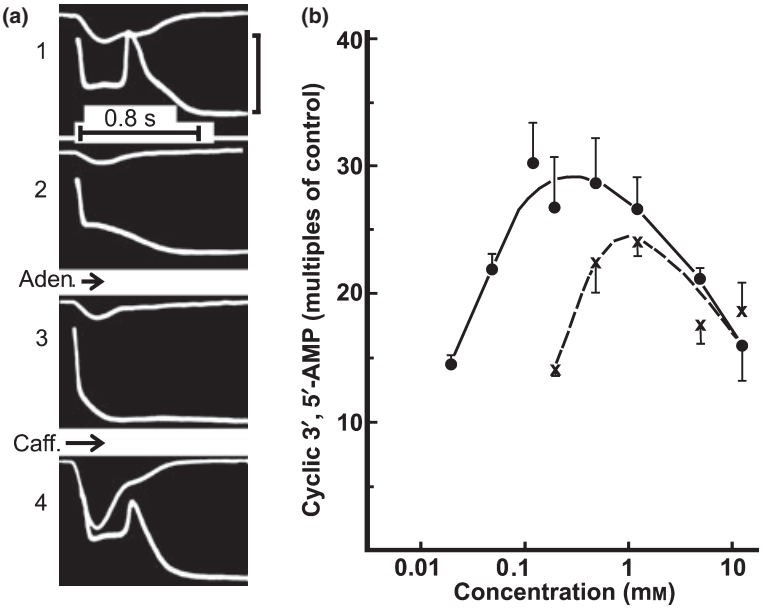

Figure 7 Early demonstration that adenosine and methylxanthines (caffeine in panel a, theophylline in panel b). (a) Isolated arterial strips with contractions shown in the upper part and action potentials in the lower part. Adenosine, added between panels 2 and 3 causes relaxation and hyperpolarization, which is antagonized by caffeine (added between panels 3 and 4) (from Degubareff & Sleator 1965 with permission). (b) Ability of adenosine to stimulate cAMP accumulation in brain slices, and the ability of theophylline to competitively antagonize this (from Sattin & Rall 1970 with permission).

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resulted in the *activation* of adenylate cyclase were termed R_a receptors. It was soon realized that the two terminologies referred to the same entities and Londos subsequently agreed that the terms A_1 and A_2 would be preferable in the pharmacological literature as activation of the adenosine receptors is not always linked to adenylate cyclize, because it has priority and because it agrees with procedures for naming receptors, and these terms are now firmly established (see Fredholm *et al.* 1994). The two adenosine receptors were shown to have different agonist profiles (Daly 1982). In general, at the A_1 purinoceptor, N^6-substituted adenosine analogues were shown to be more potent than 5′-substituted analogues. Numerous specific pharmacological agents acting at P1 receptors have been synthesized since (for recent reviews, see Linden 1994, Olah & Stiles 1995, Fredholm *et al.* 2001, Baraldi *et al.* 2006, 2008, Gao & Jacobson 2007, Elzein & Zablocki 2008, Borea *et al.* 2009, Cristalli *et al.* 2009, Kalla *et al.* 2009, Kiesman *et al.* 2009).

Direct characterization of the adenosine receptor by ligand binding techniques was performed in 1978, when Malbon *et al.* used [^{3}H]adenosine to bind to the adenosine receptor in fat cells (Malbon *et al.* 1978). However, just as with attempts to use labelled adenine nucleotides directly the rapid metabolism and the presence of other sites (e.g. transporters and enzymes) prevented good specific binding to be detected and even when great care was taken both bona fide receptors and the P-site contributed to binding (Schwabe *et al.* 1979). In 1980, three different groups independently demonstrated receptors of the A_1 subtype using metabolically stable adenosine analogues including R-N^6-phenylisopropyladenosine (Schwabe & Trost 1980); N^6-cyclohexyladenosine (CHA) and 1,3-diethyl-8-phenylxanthine (DPX) (Fig. 8) (Bruns *et al.* 1980) and 2-chloroadenosine (Williams & Risley 1980). It took much longer to obtain good binding data for A_2 receptors, because the initial attempts failed. The first entirely satisfactory demonstration used labelled *N*-ethyl-carboxamido adenosine (NECA) and unlabelled CHA to displace the binding of this non-selective ligand from A_1 receptors (Bruns *et al.* 1986). The study of A_2 receptors really benefited from the development of a highly specific agonist, CGS 21680, useful in binding studies (Jarvis *et al.* 1989) and by the later development of really selective antagonists (Poucher *et al.* 1995, Zocchi *et al.* 1996).

However, by this time it was clear that there were two types of A_2 receptors. Whereas the classical cAMP elevating A_2 receptor in cortical brain slices required rather high levels of adenosine analogues for activation and could not be demonstrated in cell-free extracts, two groups showed that in the dopamine-rich regions of the brain adenylate cyclase in membrane preparations could be stimulated by low concentrations of adenosine analogues (Fredholm 1977, Premont *et al.* 1977). Subsequent work would clearly demonstrate that the A_{2A} subform of the receptor is indeed highly enriched in the basal ganglia (Jarvis & Williams 1989, Parkinson & Fredholm 1990, Svenningsson *et al.* 1997c). Formal proof for the two (high and low affinity subtypes, A_{2A} and A_{2B}, respectively) receptors were obtained in Daly's laboratory on the basis of structure–activity relationships and binding studies (Bruns *et al.* 1980, 1983, Daly *et al.* 1983). The subclassification into A_1, A_{2A} and A_{2B} was further corroborated by molecular cloning (Libert *et al.* 1989, 1991, Maenhaut *et al.* 1990, Stehle *et al.* 1992). The latter cloning studies have revealed a receptor from the rat testis and brain that, when compared with the other G protein-coupled Pl receptors, was found to correspond to a novel functional adenosine receptor and termed an A_3 receptor (Meyerhof *et al.* 1991, Zhou *et al.* 1992). Another potential candidate for the role of A_3 receptor, identified by Ribeiro & Sebastiao (1986) was, most probably, an A_1 receptor coupled to intracellular Ca^{2+} signalling. The physiological role of the A_3 receptor is still largely unknown, although it is widely distributed in many peripheral tissues and in the brain (Zhou *et al.* 1992, Dixon *et al.* 1996) and in the immune system, where it appears to be involved in the modulation of release of allergic mediators from mast cells and other cells involved in the immediate hypersensitivity reaction

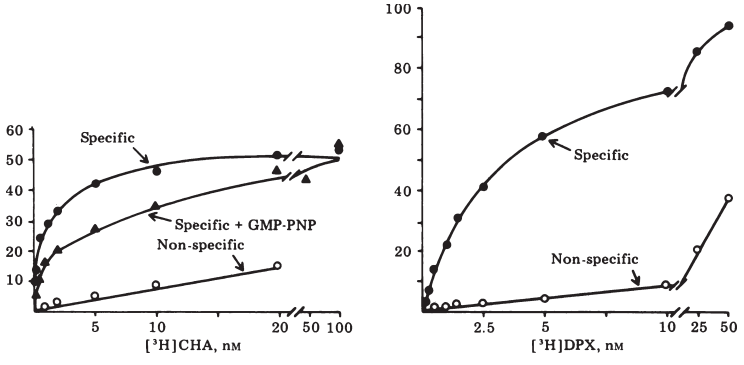

Figure 8 Discovery of adenosine (A_1) receptors using agonist (CHA) and antagonist (DPX – now called DPCPX) binding. Note that the agonist binding demonstrates a typical GTP-shift demonstrating that it is a G protein-coupled receptor. Data from Bruns *et al.* (1980) with permission.

(Ramkumar *et al.* 1993). N^6-BenzylNECA has been found to be a highly potent and moderately selective agonist at the A_3 receptor (van Galen *et al.* 1994) and BW-A522 has potent antagonist properties, at least at ovine and human A_3 receptors (Linden *et al.* 1993, Salvatore *et al.* 1993, Fozard & Hannon 1994). For further reading on adenosine receptors, we recommend to the curious reader a number of excellent reviews (Olah & Stiles 2000, Fredholm *et al.* 2005, 2007, Jacobson & Gao 2006, Dare *et al.* 2007, Klaasse *et al.* 2008, Jenner *et al.* 2009). These reviews also highlight several areas where drugs acting on adenosine receptors are being developed.

Subtypes of P2 purinoceptors

The functional heterogeneity of ATP responses that hinted at several receptor classes was recognized rather early. Phosphate-modified analogues of ATP and ADP showed considerably steeper log dose–response curves for their inhibition of the guinea-pig taenia coli than those for ADP and ATP (Maguire & Satchell 1979). Frew & Baer (1979), using these same analogues on the rabbit small intestine, concluded that the α,β-methylene (α,β-meATP) isosteres of ATP and ADP acted at a different receptor site from ATP. The P2 purinoceptor mediating inhibition of the guinea-pig taenia coli displayed stereoselectivity and a different relative potency order of agonists, compared with the P2 purinoceptor mediating contraction of the guinea-pig bladder and frog heart (Satchell & Maguire 1975, Cusack & Planker 1979, Burnstock *et al.* 1983). Shuba & Vladimirova (1980) suggested that there might be subclasses of the ATP receptor based on their observations that apamin, a potassium channel blocker, antagonized the inhibitory actions of ATP in guinea-pig caecum and stomach (Banks *et al.* 1979), but not the excitatory actions in the guinea-pig bladder and uterus. Su (1981) suggested that postjunctional P2 purinoceptors should be named 'P_{2a}-receptors' and prejunctional P2 purinoceptors named 'P_{2b}-receptors'. Fedan *et al.* (1982) proposed that two P2 purinoceptors may exist in the smooth muscle of the guinea-pig vas deferens, based on pharmacological studies using ATP analogues and arylazidoarninopropionyl ATP ($ANAPP_3$), an antagonist at the P2 purinoceptor. In contrast to the P2 purinoceptors on smooth muscle, where ADP and ATP are often equipotent, the receptors on platelets responsible for aggregation are highly specific for ADP, whereas ATP inhibits platelet aggregation (Cusack *et al.* 1979).

However, it was not until 1985 that Burnstock & Kennedy (1985) proposed the first clear subdivision of P2 purinoceptors into P_{2X} purinoceptors (that mediate vasoconstriction and contraction of visceral smooth muscle, with α,β-meATP as a potent agonist) and P_{2Y} purinoceptors [that mediate vasodilatation as well as relaxation of the smooth muscle of the gut, with 2-methylthio ATP (2-MeSATP) as a particularly potent agonist]. Soon after, two further P2 purinoceptors were tentatively proposed (Gordon 1986): an ADP-selective P_{2T} purinoceptor that is present on platelets and thrombocytes, and a P_{2Z} purinoceptor, which appears to be activated by ATP^{4-} and is prominent in macrophages, lymphocytes and mast cells. Later, a P_{2U} purinoceptor was proposed, where ATP and uridine 5′-triphosphate (UTP) are equipotent (O'Connor *et al.* 1991) and a P_{2D} purinoceptor for diadenosine polyphosphates (Miras-Portugal *et al.* 1996), with some less-accepted subtypes: P_{2S} (Wiklund & Gustafsson 1988a,b), P_{2R} (von Kugelgen & Starke 1990) and the P_{2n} receptor that is synonymous with the P_{2U} receptors (Abbracchio *et al.* 1993). It was clearly shown that there were ATP-activated ion channel purinoceptors in excitable cells (Bean *et al.* 1990) and that P2Y purinoceptors involved G protein activation and were members of the G protein-coupled receptor (GPCR) family (Dubyak 1991). More recently, the possibility that some P2Y purinoceptors act via G_i proteins to inhibit adenylate cyclase has been raised (Harden *et al.* 1995) and the existence of pyrimidine nucleotide-selective G protein-linked receptors has been proposed (Lazarowski & Harden 1994, Chang *et al.* 1995, Communi *et al.* 1995b, Nguyen *et al.* 1995).

Various antagonists at P2 purinoceptors have been claimed over the years, including: quinidine (Burnstock *et al.* 1970, 1972); imidazolines (Madinaveitia & Raventos 1949, Satchell *et al.* 1973); 2-2′-pyridilisatogen (Spedding *et al.* 1975); $ANAPP_3$ (Hogaboom *et al.* 1980); apamin (Brown & Burnstock 1981); selective desensitization with α,β-meATP (Kasakov & Burnstock 1982); reactive blue 2 (Kerr & Krantis 1979, Manzini *et al.* 1986, Burnstock & Warland 1987); pyridoxalphosphate-6-azophenyl-2,4′-disulphonic acid (PPADS) (Lambrecht *et al.* 1992, Ziganshin *et al.* 1994); suramin (Dunn & Blakeley 1988, Hoyle *et al.* 1990); 4,4′-diisothiocyanostilbene-2,2′-disulphonate (Soltoff *et al.* 1993, Bultmann & Starke 1994a). More recently, 2-propylthio D-β,γ-difluoromethylene ATP (FPL 66092) has been claimed as a P_{2T}-selective antagonist (Humphries *et al.* 1994) and reactive red 2 as a P_{2Y}-selective antagonist (Bultmann & Starke 1995).

The term 'P3' has been suggested for an adenine nucleotide receptor claimed to be methylxanthine-sensitive (Shinozuka *et al.* 1988) in the rat tail artery, on the basis that adenosine and ATP, together with their analogues 2-chloroadenosine and β,γ-meATP, inhibit NA release from sympathetic nerves, an effect that was antagonized by 8-p-sulfophenyltheophylline; this subclass, however, has not been generally accepted.

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The first P2 purinoceptors to be cloned were G protein-coupled purinoceptors of the P2Y family: a $P2Y_1$ purinoceptor was isolated from chick brain (Webb *et al.* 1993) and a P_{2U} purinoceptor (later designated $P2Y_2$) from neuroblastoma cells (Lustig *et al.* 1993). A year later, two ligand-gated ion channel ATP receptors of the P2X family were also cloned – one from vas deferens (Valera *et al.* 1994) and another from rat pheochromocytoma PCl2 cells (Brake *et al.* 1994).

In the paper prepared by the IUPHAR subcommittee concerned with the nomenclature of P2 purinoceptors (Fredholm *et al.* 1994), it was emphasized that the contemporary purinoceptor subclassification, with so many letters of the alphabet being somewhat randomly added as new receptor subtypes were discovered, was unsatisfactory. The subcommittee supported, in principle, a new system of classification proposed by Abbracchio & Burnstock (1994). In this proposal, it was suggested that P2 purinoceptors should be divided into two major families: a P2X family consisting of ligand-gated cation channels and a P2Y family consisting of GPCRs. It was pointed out that this classification brought ATP into line with most other neurotransmitter receptors, such as ACh, γ-amino butyric acid, glutamate and 5-hydroxytryptamine, where ligand-gated and GPCR subclassifications have already been established (see also Burnstock 1996b). The current position with regard to subtypes has been summarized by Ralevic and Burnstock (1998) and Burnstock (2007b).

P2X purinoceptor family. Seven P2X purinoceptor subtypes are currently identified. The proteins deduced from the cDNA sequences have 379 ($P2X_6$) to 595 ($P2X_7$) amino acid residues and share 26–46% identity with each other (North 2002). They are characterized by two transmembrane (TM) domains with a large extracellular loop, where l0 cysteines are preserved; both N and C terminals are intracellular. Northern blots and *in situ* hybridization show a widespread distribution of the RNAs with $P2X_1$ expressed predominantly in smooth muscle, $P2X_4$ and $P2X_6$ most heavily expressed in the brain, $P2X_3$ found only in sensory neurones and $P2X_7$ dominant in cells of the immune system (Bo & Burnstock 1994, Collo *et al.* 1996, Surprenant *et al.* 1996), although the specific expression of P2X receptors in various cells varies and still requires precise characterization.

P2X receptors are assembled in trimeric form (Nicke *et al.* 1998) that was recently directly confirmed when the crystalline structure of the $P2X_4$ receptor was visualized (Kawate *et al.* 2009); P2X channels share an overall organization similarity with acid-sensitive Na^+ channels (ASICs) and possibly with other members of the superfamily of epithelial sodium channels (Gonzales *et al.* 2009). The P2X receptors formed through homo- or heteromeric assembly of $P2X_1$ to $P2X_6$ subunits (hitherto homomeric assembly was shown for $P2X_{1\text{-}5}$ subunits, the $P2X_6$ subunits apparently cannot olygomerize; heteromeric compositions described so far are represented by $P2X_{1/2}$, $P2X_{1/4}$, $P2X_{1/5}$, $P2X_{2/3}$, $P2X_{2/6}$ and $P2X_{4/6}$ channels) are activated by low micromolar ATP concentrations, whereas homomeric $P2X_7$ receptors require millimolar ATP concentrations for full activation (for a comprehensive list of references, see Khakh 2001, North 2002, Stojilkovic *et al.* 2005, Khakh & North 2006, Roberts *et al.* 2006, Jarvis & Khakh 2009, Surprenant & North 2009).

P2Y purinoceptor family. Eight P2Y purinoceptor subtypes have currently been identified. The P2Y purinoceptor subtypes show slower responses to agonists than P2X purinoceptors and are coupled to several intracellular second messenger systems. Similar to other GPCRs, the P2Y receptor is composed from seven transmembrane domains with short extracellular N and intracellular C terminals (Barnard *et al.* 1994, 1996, Boarder *et al.* 1995, Harden *et al.* 1995). The receptors consist of 308–377 amino acids, with a mass of 4l–53 kDa after glycosylation; TM3 displays a high degree of conserved amino acid residues within the P2Y purinoceptor family (Boarder *et al.* 1995, Van Rhee *et al.* 1995). Northern blots and *in situ* hybridization show a wide distribution of P2Y purinoceptor subtypes in many tissues (Abbracchio *et al.* 2006). The possibility that $P2Y_4$, together with other subtypes should be considered as a subfamily of pyrimidinoceptors inside the P2Y purinoceptor family, has been raised (Communi *et al.* 1995b), but did not acquire wide appreciation. Recent reviews about P2Y receptor operation, structure and distribution are available (von Kugelgen & Wetter 2000, Abbracchio *et al.* 2006, Hussl & Boehm 2006, von Kugelgen 2006, Van Kolen & Slegers 2006, Fischer & Krugel 2007, Goncalves & Queiroz 2008).

Pharmacology of P2 receptors. Selective agonists and antagonists for the different P2X and P2Y purinoceptor subtypes are beginning to be identified (see Jacobson *et al.* 1995, Burnstock 2007b). Meanwhile, in general, 2-MeSATP is the most active of the P2Y purinoceptor agonists, whereas α,β-meATP is more active at most native P2X purinoceptors (but seldom at cloned P2X purinoceptors) although there are clear exceptions and the reported potency of some agonists is complicated by their breakdown by ectonucleotidases (Burnstock *et al.* 1994, Ziganshin *et al.* 1994, Kennedy & Leff 1995). Some receptor subtypes are selective to ADP, UTP, or UDP, others not, whereas some exhibit desensitization, others not (North 1996). P2 purinoceptor antagonists in current use, including suramin, PPADS, and reactive

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blue 2, do not appear to be selective for different recombinant receptor subtypes, but have been used selectively in isolated preparations (Hoyle 1992, Ziganshin *et al.* 1993, 1994, Windscheif *et al.* 1994, Abbracchio & Burnstock 1994, Ralevic & Burnstock 1998). There are some recent reports of the development of P2 receptor antagonists that are small molecules, orally bioavailable, stable *in vivo* and can cross the blood–brain barrier. For example, RO4 and RO5 $P2X_3$ receptor antagonists (Gever *et al.* 2006, 2010) and A-740003 and A-438079 $P2X_7$ receptor antagonists (Donnelly-Roberts & Jarvis 2007).

The quest for P2X receptor structure

A brief history of ion channel structure takes us back about 60 years. It was then thought likely that ions crossed membranes in association with a lipoid carrier (Hodgkin & Katz 1949) but soon thereafter the careful quantitative measurements of ionic currents by Hodgkin & Huxley (1953) led to the conclusion that ions passed through pores or channels. The first inferences about ion channel structure came from measurements of the number of ions per second (i.e. current) that flowed through a single open channel. Katz & Miledi (1972) estimated this by analysing fluctuations in the amplitude of the current passing through many channels, but soon afterwards Neher & Sakmann (1976) resolved single channel currents directly. A complementary approach was to estimate the size of the ionic pore by determining the cut-off for permeability of ions of known atomic dimensions (Dwyer *et al.* 1980).

An explosive advance in our knowledge of ion channel structure came when amino acid sequences were deduced from complementary DNA clones of channel proteins, the first being the α-subunit of the ACh nicotinic receptor (Noda *et al.* 1982). When combined with site-directed mutagenesis, heterologous expression and functional studies, this approach has allowed remarkable reconstructions of the complex assemblies of proteins that form channel complexes. It was into this era that P2X receptors were born, being convincingly shown to be ion channels in 1983 (Jahr & Jessell 1983, Krishtal *et al.* 1983) and having the protein sequences determined from cDNAs cloned in 1994 (Brake *et al.* 1994, Valera *et al.* 1994). The ensuing 15 years allowed steady progress in our understanding of P2X receptor structure and function – their assembly as trimers, the key role of the second transmembrane domain in ion permeation and the finding of the critical residues contributing to ATP binding (North 2002, Surprenant & North 2009).

The provision of atomic structure from X-ray crystallography revolutionized our understanding yet again. The first major advances occurred about 1998, with the structures of a human water channel (Walz *et al.* 1997), a bacterial potassium channel (Doyle *et al.* 1998) and a bacterial mechanosensitive channel (Chang *et al.* 1998). It was 10 years more before the first crystal structure of a 'P2X-like' channel was solved by the Gouaux laboratory: this was a chick ASIC (Jasti *et al.* 2007). ASICs (as well as epithelial sodium channels or ENaCs) share a fundamental similarity with P2X receptors, in the sense that they have two transmembrane domains separated by a large ectodomain that contains cysteine-rich regions. Although ASICs and ENaCs have clear amino acid sequence similarity, this does not extend to P2X receptor subunits. Moreover, whereas P2X receptors were known to form trimeric channels, it was widely believed that ASICs and ENaCs were tetramers until their crystal structure was solved (Jasti *et al.* 2007).

In 2009, the structure of a trimeric P2X receptor was solved at 3.5 Å by Kawate *et al.* (2009). This was a zebra-fish receptor, somewhat truncated to remove intracellular N and C-termini, but which nonetheless formed functional channels when expressed in human embryonic kidney cells. This structure at once allowed the fine detail interpretation of the mutagenesis over the previous 15 years. It revealed the symmetrical trimeric assembly of three interlocking subunits (yellow, red and blue in Fig. 9, top), which surround a central cavity. This cavity extends through the central axis of the ectodomain and continues into the transmembrane domain. Here the narrowest part of the channel (Fig. 9, bottom: visualized in the close state) is formed by the side chains of Thr^{339} from each of the three intersecting TM2 helices. This high resolution structure has already allowed much progress in our understanding of the way in which ATP binds to and activates the channel, and the inter-subunit molecular motions that take place during channel opening (Browne *et al.* 2010). It is to be expected that it will provide the template for the design of new agonists and antagonists that are selective for subtypes of P2X receptor. Such tools will be critical to the further understanding of the physiological roles of P2X receptors, and may find direct therapeutic use.

The expanding field of purinergic signalling in the last decade

Among the more dramatic events in recent years has been the elucidation, by crystallography, of the structures of P2X (Fig. 9) and adenosine receptors (Fig. 10). As expected, the adenosine A_{2A} receptor (Jaakola *et al.* 2008) had a structure that showed considerable similarity to the previously clarified bovine rhodopsin (Palczewski *et al.* 2000) and the mammalian β-adrenergic receptor (Rasmussen *et al.* 2007, Warne *et al.*

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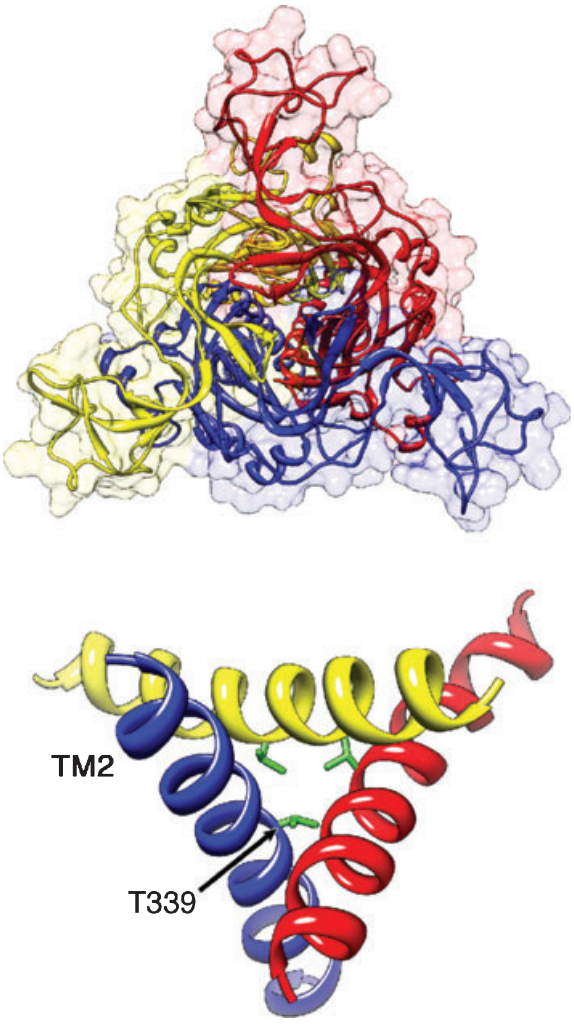

Figure 9 Crystal structure of P2X receptors. Atomic structure of rat $P2X_2$ receptor determined by molecular modelling on the coordinates of the zebra-fish $P2X_{4.1}$ receptor (Kawate *et al.* 2009). Top: holoprotein viewed from the outside, looking down the central axis. A, B and C chains are red, yellow and blue. The three TM2 helices can be seen centrally, deep in the structure. Bottom: backbone ribbon representation of the three TM2 helices, showing only the side chain of Thr^{339}. This side chain projects into the narrowest part of the closed channel, but it is also exposed to permeant ions when the channel is open (Cao *et al.* 2009).

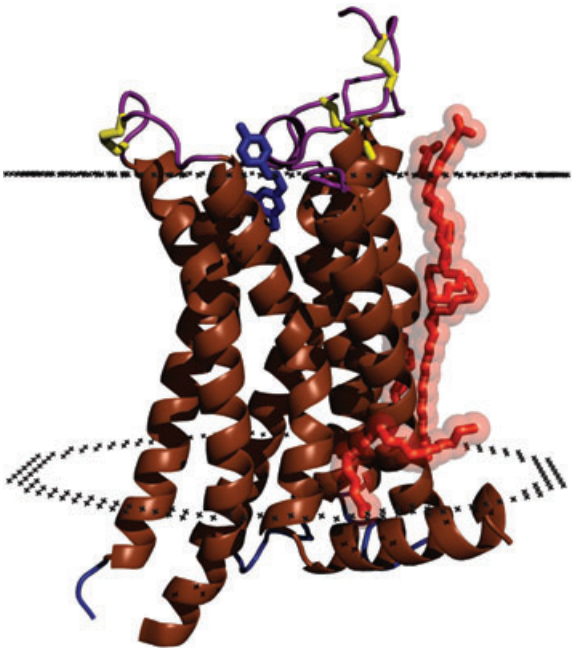

Figure 10 Crystal structure of an adenosine A_{2A} receptor stabilized by a T4 insert (not shown in this figure but illustrated in the original publication; Jaakola *et al.* 2008). The view is of the receptor perpendicular to the cell membrane with the extracellular face upwards. The helices are shown in brown, the bound antagonist ligand (ZM241385) in blue and associated five lipid molecules in red. The four disulphide bonds are shown in yellow. Figure kindly provided by V.P. Jaakola, Oulu Biocenter and Department of Biochemistry, University of Oulu, Finland.

2008). It is anticipated that these structures will be of assistance in the targeting of novel drugs (Katritch *et al.* 2010).

Furthermore, there has been a dramatic expansion of research into purinergic signalling in the last decade. This is partly a consequence of the recognition that purinergic signalling first appeared early in evolution (see Burnstock & Verkhratsky 2009) and is widespread in most non-neuronal as well as neuronal cell types (see Burnstock & Knight 2004) and partly as a consequence of the recognition that there is long-term (trophic) purinergic signalling in cell proliferation, differentiation, motility and death in development and regeneration, as well as short-term purinergic signalling in neurotransmission and secretion (Abbracchio & Burnstock 1998, Neary & Zimmermann 2009, Burnstock & Verkhratsky 2010). There are some exciting studies of purinergic signalling in the special senses area (Housley *et al.* 2009). There is increasing interest in the roles of purines and pyrimidines in pathophysiology and the therapeutic potential of the signalling system (Burnstock 2006b) for the treatment of diseases, including thrombosis and stroke (employing clopidogrel, an antagonist to the $P2Y_{12}$ receptor, that mediates platelet aggregation and made $8.6 billion in 2007), osteoporosis, kidney failure, bladder incontinence, cystic fibrosis, dry eye and cancer. There is also considerable interest in the involvement of P2X receptor antagonists for the treatment of acute and neuropathic pain (Inoue 2007) and diseases of the CNS (Burnstock 2008).

Conflict of interest

There is no conflict of interest.

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