Adenosine triphosphate as a neurotransmitter and neuromodulator

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The first hint that adenosine triphosphate (ATP) might be a neurotransmitter came in 1954 from Holton and Holton, who presented evidence for release of ATP from collateral branches of sensory fibers during antidromic impulses, in sufficient amounts to produce vasodilation in the rabbit ear artery.

In the early 1960s, Burnstock and his colleagues in Melbourne recorded inhibitory junction potentials (IJPs) in intestinal smooth muscle in response to stimulation of nonadrenergic, noncholinergic (NANC) nerves. Evidence was presented in 1970 to suggest that the purine nucleotide ATP or a related molecule was the transmitter released by these nerves, and the term *purinergic* was coined (Burnstock, 1972). The evidence included synthesis and storage of ATP in nerve terminals; release of ATP during nerve stimulation; mimicry of the responses to nerve stimulation by ATP; ectoenzymatic breakdown of ATP; and drugs that produced parallel block or potentiation of the responses to ATP and nerve stimulation. Later, ATP was claimed as the transmitter responsible for atropine-resistant excitation of the urinary bladder and as a cotransmitter in sympathetic nerves supplying visceral organs and blood vessels. It is now clear that ATP is a cotransmitter in many neuron types in both peripheral and central nervous systems (see Burnstock 1976, 1999a, and Figure 1).

Implicit in the purinergic nerve hypothesis is the existence of purinoceptors on the postjunctional membranes. Drury and Szent-Györgyi first recognized the potent actions of purine nucleotides and nucleosides on visceral and vascular organs in 1929 and, since then, there has been an expansion of knowledge of purinergic receptors (Ralevic and Burnstock, 1998). Subclasses of purinoceptors were first proposed by Burnstock in 1978. P1-purinoceptors are more responsive to adenosine and adenosine monophosphate (AMP) than to ATP and adenosine diphosphate (ADP); they are selectively antagonized by low concentrations of methylxanthines, such as caffeine and theophylline, and occupation activates or inhibits an adenylate cyclase system. P2-purinoceptors are more responsive to ATP and ADP, are antagonized by suramin, pyridoxalphosphate-6-azophenyl-2'-4'-disulphuric acid (PPADS), and Reactive Blue 2 or are selectively desensitized by α,β-methylene ATP. Purinergic transmission is mediated by postjunctional P2-purinoceptors, whereas inhibition of release of ACh and NE from cholinergic and adrenergic nerve terminals is mediated largely by prejunctional P1-purinoceptors.

On the basis of receptor cloning and selective agonists and antagonists, four subclasses of P1-purinoceptors are recognized so far, namely A_1, A_{2a}, A_{2b}, and A_3. The first subclasses for P2-purinoceptors, proposed by Burnstock and Kennedy in 1985, were P_{2X} and P_{2Y}, mediating contraction and relaxation of vascular and visceral smooth muscles respectively and including vasodilation via P_{2Y} receptors on endothelial cells leading to release of nitric oxide (NO). Further subdivisions followed, including P_{2T}-purinoceptors (which are ADP-selective receptors on platelets), P_{2Z}-purinoceptors (opening non-selective pores in mast cells, macrophages and lymphocytes of the immune system), P_{2U}-purinoceptors (equiresponsive to UTP and ATP), and P_{2D}-purinoceptors (a subtype tentatively termed for receptors responsive to diadenosine polyphosphates). However, following the cloning of P2 purinoceptors in the early 1990's and studies of the transduction mechanisms involved, Abbracchio and Burnstock in 1994 proposed a broad framework for P2-purinoceptor subclassification that allowed more rational development as more subtypes and molecular structures were recognized. Essentially, P2 purinoceptors were divided into two main families, namely a P2X purinoceptor family (with so far 7 subclasses cloned and characterized) mediating fast responses via ligand-gated ion channels, and a P2Y purinoceptor family (with so far 8 subclasses identified in mammals) mediating slower responses via G-proteins. The subdivisions in each of these two major families are numbered largely on the basis of the order of discovery of cloned receptors. This basic framework of fast and slow receptors is in accordance with that developed for other neurotransmitters, including ACh (nicotinic and muscarinic receptors), gamma amino butyric acid (GABA) ($GABA_A$ and $GABA_B$), and glutamate (ionotropic and metabotropic receptors [see Table 1]).

1. Sympathetic nerves

A substantial body of evidence shows that norepinephrine (NE) and ATP act as cotransmitters, being released from sympathetic nerves in variable proportions depending on the tissue and species. The ATP receptor involved in most sympathetically innervated tissues has been defined as a P2X-purinoceptor that mediates fast transmission via a ligand-gated cation channel. Many of the early and more detailed studies of purinergic cotransmission were made on the vas deferens. Evidence for purinergic cotransmission includes block of the prazosin-resistant (i.e. nonadrenergic) component of the responses to sympathetic nerve stimulation by the ATP antagonists suramin and PPADS, or by the selective desensitization with α,β-methylene ATP. Further, release of ATP during nerve stimulation (is abolished by 6-hydroxydopamine which destroys sympathetic nerves) but is unaffected by selective depletion of NE by reserpine. Finally, ATP antagonists selectively block excitatory junction potentials (EJPs) in response to sympathetic nerve stimulation and EJPs are mimicked by ATP but not by NE.

Studies of sympathetic cotransmission involving ATP and NE have now also been carried out on a number of different isolated blood vessels and in whole animals. In rabbit coronary vessels, in contrast to most other blood vessels—where NE and ATP cause synergistic constriction via α_1 adrenoceptors and P2X purinoceptors, respectively—the predominant effect of ATP is vasodilation via P2Y

purinoceptors. Because in this vessel the predominant effect of NE is vasodilation via ß-adrenoceptors, this is consistent with the synergism that appears to be characteristic of cotransmission.

Early studies established adenosine (arising from ectoenzymatic breakdown of released ATP) as the principal modulator of transmitter release from sympathetic nerves via prejunctional P1 purinoceptors on nerve terminals in various tissues. In the rat vas deferens and also in the iris, it has been suggested that prejunctional ATP receptors, probably of the P2Y-purinoceptor subtype, may also be involved. Recent experiments suggest that receptors for naturally occurring diadenosine polyphosphates on nerve terminals in the brain can also modulate the release of transmitters.

2. Parasympathetic nerves

Acetylcholine (ACh) and ATP appear to be cotransmitters in parasympathetic neurons in the bladder. It has been shown recently that there is plasticity in expression of cotransmitters in parasympathetic nerves supplying the human urinary bladder, in that the ratio of purinergic to cholinergic components of excitatory transmission is much increased in pathologic conditions such as obstructed bladder and interstitial cystitis. There is also indirect evidence for ATP being colocalized with ACh and the peptides neuropeptide Y (NPY) or somatostatin in subpopulations of intrinsic neurons in the heart and airways that project to small blood vessels in these organs.

3. Sensory nerves

Subpopulations of sensory nerves have been claimed to release ATP as well as substance P and calcitonin gene-related peptide at peripheral nerve terminals. By analogy with other systems, it seems likely that ATP coexists in different proportions with these two peptides, perhaps cooperating in axon reflex activity. Since the role of these nerves during axon reflexes to many organs is motor rather than sensory, they have been termed *sensory-motor nerves* to distinguish them from the other sub-population of afferent fibers that have a pure sensory role and whose terminals contain few vesicles and a predominance of mitochondria. Primary afferent nerve fibers express $P2X_3$ homomultimer and $P2X_{2/3}$ heteromultimer receptors and appear to be involved both in physiological reflex activities such as micturition and in nociception (Burnstock, 2000).

4. Enteric nerves

Evidence that ATP was the NANC inhibitory transmitter in nerves supplying the guinea-pig taenia coli was first presented in 1970. In the late 1970s evidence was presented for vasoactive intestinal polypeptide (VIP) as a slow NANC inhibitory transmitter in the gut. The current consensus of opinion is that ATP, VIP, and NO are probably cotransmitters mediating NANC responses with different time courses and that their proportions in NANC inhibitory nerves vary considerably in different regions of the gut and between species. P2X and P2Y receptor subtypes are present on neurons in both myenteric and submucosal nerve plexuses and in intestinal blood vessels as well as mucosal epithelial cells (Burnstock, 2001).

5. Somatic motor nerves

There are many reports of the coexistence and release of ATP with ACh at somatic motor nerve endings. ATP acts as a neuromodulator of both the release (following its degradation to adenosine) and action of ACh. There is little information available to date to support a cotransmitter role for ATP at these junctions of mature adults, but patch-clamp studies have shown that micromolar concentrations of ATP, as well as ACh, activate ion channels on the membrane of cultured myoblasts and myotubes.

6. Sensory and autonomic ganglia

The earliest report of the effect of ATP on autonomic ganglia was by Feldberg and Hebb in 1948, whereas the first demonstration of purinergic fast synaptic transmission in ganglia was demonstrated independently by Anne Marie Suprenant and her colleagues and by Silinsky and Gerzanich in the celiac ganglion in the early 1990s. There is now abundant evidence for purinergic signaling in sensory, myenteric, parasympathetic and enteric ganglia (see Dunn et al., 2001).

7. Central nervous system (CNS)

Although there was early evidence for the role of adenosine as a powerful prejunctional modulator of the release of excitatory transmitters in the CNS, recent evidence for P2X receptor involvement in synaptic transmission in the medial habenula, locus caeruleus, and hippocampus has been presented (see Nörenberg and Illes, 2000; Burnstock 2003). Many papers also describe the distribution of P2X and P2Y receptor mRNA and proteins in different regions of the brain and spinal cord and of ATP release from brain slices and synaptosomes. In addition to neurones, P2 receptors and ATP release have also been observed for glial cells, suggesting that both short- and long-term (trophic) neuronal-glial cell interactions are taking place in the CNS.

8. See also

Neurotransmitters
Serotonin
Gamma-aminobutyric acid
Noradrenaline
Sodium pump.

9. Further reading

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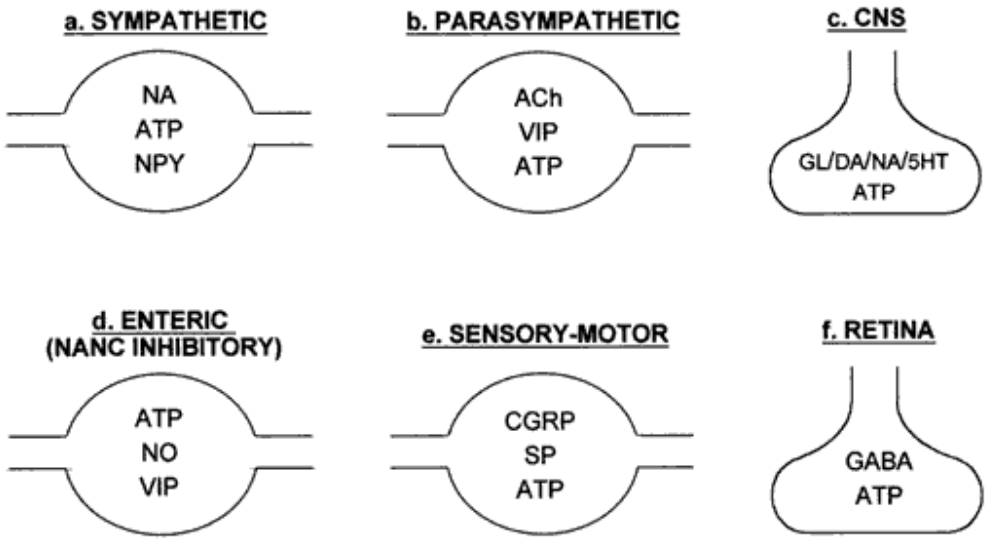

Figure 1. Schematic diagram of the principal cotransmitters with ATP in the nervous system. Nerve terminal varicosities of a, sympathetic; b, parasympathetic; d, enteric (NANC inhibitory); and e, sensory-motor neurons. There is more recent evidence that ATP is also a cotransmitter with glutamate (GL), dopamine (DA), norepinephrine (NE) and 5-hydroxytryptamine (5-HT) in different (c) neurones of the central nervous system and with gamma-amino butyric acid (GABA) in (f) nerve terminals of the retina

Table 1. Comparison of fast ionotropic and slow metabotropic receptors for acetylcholine (ACh), γ-aminobutyric acid (GABA), glutamate, and 5-hydroxytryptamine (5-HT) with those for purines and pyrimidines (modified from Abbracchio and Burnstock, 1998).

Messenger	Receptors	
	Fast ionotropic	Slow metabotropic
ACh	Nicotinic Muscle type Neuronal type	Muscarinic M_1 - M_5
GABA	GABA A	GABA B
Glutamate	AMPA* Kainate NMDA†	$mGlu_1$ - $mGlu_7$
5-HT	$5\text{-}HT_3$	$5\text{-}HT_{1A\text{-}F}$ $5\text{-}HT_{2A\text{-}C}$ $5\text{-}HT_4$ $5\text{-}HT_{5A\text{-}B}$ $5\text{-}HT_6$ $5\text{-}HT_7$
ATP	P2X1-7	$P2Y_1$, $P2Y_2$, $P2Y_4$, $P2Y_6$, $P2Y_{11}$, $P2Y_{12}$, $P2Y_{13}$, $P2Y_{14}$

*AMPA, 2-(aminomethyl)phenylacetic acid
†NMDA, *N*-methyl-D-aspartate