Review

Purinergic signalling in autonomic control

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Intercellular purinergic signalling, which utilizes ATP as a transmitter, is fundamental for the operation of the autonomic nervous system. ATP is released together with 'classical' transmitters from sympathetic and parasympathetic nerves supplying various peripheral targets, modulates neurotransmission in autonomic ganglia, has an important role in local enteric neural control and coordination of intestinal secretion and motility, and acts as a common mediator for several distinct sensory modalities. Recently, the role of ATP-mediated signalling in the central nervous control of autonomic function has been addressed. Emerging data demonstrate that in the brain ATP is involved in the operation of several key cardiorespiratory reflexes, contributes to central processing of viscerosensory information, mediates central CO_2 chemosensory transduction and triggers adaptive changes in breathing, and modulates the activities of the brainstem vagal preganglionic, presympathetic and respiratory neural networks.

Introduction

Historically, the concept of purinergic signalling was proposed by Burnstock in 1972 [1] after a purine nucleotide was shown to act as a neurotransmitter in non-adrenergic, non-cholinergic (NANC) nerves supplying the gut and urinary bladder. In fact, most of the early studies of purinergic signalling were focused on the autonomic nervous system and were largely concerned with rapid signalling in neurotransmission (for review, see Ref. [2]). Several years later ATP was proposed to act as a cotransmitter with 'classical' transmitters in sympathetic and parasympathetic nerves (for review, see Ref. [3]).

Now it is firmly established that ATP is used either as a sole transmitter or cotransmitter by many neurons in the peripheral and central nervous system (CNS) [4]. Receptors for purines and pyrimidines were cloned and characterized in the 1990s; four subtypes of G-protein-coupled P1 (adenosine) receptors, seven subtypes of ionotropic P2X receptor subunits (which form homomeric or heteromeric channels) and eight subtypes of G-protein-coupled metabotropic P2Y receptors for ATP have been identified [5,6].

Apart from a release of ATP by damaged or dying cells, physiological release of ATP from both neuronal and non-neuronal cells can be triggered by various stimuli [4,7]. Several mechanisms of ATP release have been described that include the involvement of vesicular exocytosis, connexin and/or pannexin hemichannels, maxi anion and $P2X_7$ channels [2,4]. In the extracellular space ATP is rapidly broken down by ectonucleotidases to ADP, AMP and adenosine [8]. Ectonucleotidase activity is important in shaping purinergic signalling by removing ATP and also by producing ATP metabolites, which are also active ligands for various purinergic receptors. Functionally, adenosine might be the most important product of ATP degradation by ectonucleotidases. In this review, however, we concentrate mostly on the functional role of ATP acting at P2 receptors. The effects of adenosine are not discussed in detail and can be found in recent reviews (for example, see Ref. [2]).

Abbracchio *et al.* [4] provided a general overview of purinergic signalling in the nervous system, discussing recent data on the release and extracellular fate of ATP and other nucleotides, structure and properties of purinergic receptors, ATP contribution to synaptic currents and neuronal–glial transmission in the CNS, and the role of ATP in development, regeneration and pathology of the nervous system. Here, we endeavour to summarize a substantial amount of data demonstrating an important role for ATP-mediated purinergic signalling in various aspects of autonomic control.

The autonomic nervous system

The autonomic nervous system can be viewed as the CNS neuronal circuits that receive sensory visceral information and generate control of the efferent output to various cardiovascular, thermoregulatory, respiratory, endocrine, reproductive and gastrointestinal targets. From the efferent point of view the autonomic nervous system has been historically divided into sympathetic and parasympathetic arms. Both systems consist of central neuronal circuits controlling cholinergic preganglionic CNS neurons, which, in turn, innervate autonomic ganglia, glands and peripheral semi-autonomous neural networks such as the enteric nervous system (ENS). The latter is now considered by some to be a third division of the autonomic nervous system [9]. ATP-mediated purinergic signalling seems to have an important role in the operation of the autonomic nervous system at multiple steps of the reflex pathways, from the transduction of sensory information to neuroeffector transmission.

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ATP signalling in autonomic neuroeffector transmission

There is considerable evidence that ATP has an important role as a signalling molecule of NANC nerves found in the respiratory, cardiovascular and urogenital systems, and in the gastrointestinal tract [2]. In the late 1960s many substances were examined as putative transmitters in the NANC nerves of the gastrointestinal tract and bladder, but the substance that best satisfied criteria for function as a neurotransmitter was ATP. Nerves utilizing ATP as their principal transmitter were subsequently named 'purinergic' [1].

ATP is released together with noradrenaline (NA) from sympathetic nerves supplying various peripheral targets [3] (Figure 1). These include smooth muscles of different blood vessels, vas deferens, taenia coli, seminal vesicles, epididymis, prostate and others. However, the relative contributions of the adrenergic and purinergic components are variable [3]. For example, the purinergic component is relatively minor in rabbit ear and rat tail arteries. However, ATP seems to be the prime transmitter in sympathetic nerves supplying arterioles in the mesentery and the submucosal plexus of the intestine, whereas NA released from these nerves acts as a modulator of ATP release [10]. Presynaptic actions of ATP at postganglionic sympathetic axons have been described: at the sympathetic neuromuscular junction activation of presynaptic ionotropic P2X receptors stimulates sympatho-effector transmission, whereas activation of P2Y receptors predominantly inhibits sympathetic transmitter release [11]. Inhibitory (A_1-receptor-mediated) and facilitatory (A_{2A}-receptors-mediated) presynaptic actions of adenosine at postganglionic sympathetic axons have also been described [12].

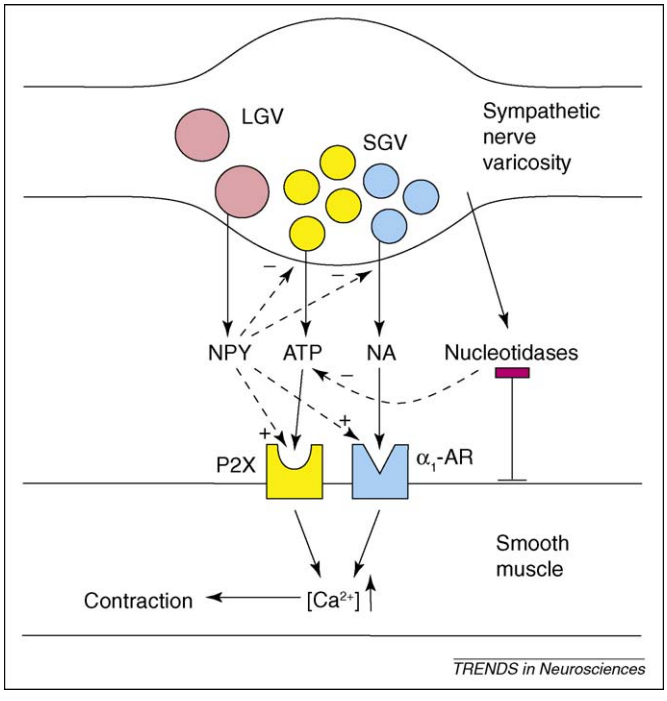

Figure 1. ATP as a cotransmitter in the autonomic nervous system: schematic of sympathetic cotransmission. ATP and noradrenaline (NA) released from small granular vesicles (SGV) act on P2X and α_1-adrenoceptors (α_1-AR), respectively, on smooth muscle, leading to an increase in $[Ca^{2+}]_i$ and contraction. Neuropeptide Y (NPY) stored in large granular vesicles (LGV) acts after release both as a prejunctional inhibitory modulator of ATP and NA release and as a postjunctional modulatory potentiator of ATP and NA actions. Soluble nucleotidases are released from nerve varicosities and are also present as ectonucleotidases. Presynaptic actions of ATP and NA are not illustrated. Modified from Ref. [2] with permission from the American Physiological Society.

Parasympathetic nerves supplying the urinary bladder utilize ATP and acetylcholine (ACh) as cotransmitters, in variable proportions in different species [13,14]. As with sympathetic nerves, ATP again acts through P2X ionotropic receptors, whereas the slow component of the response is mediated by ACh muscarinic metabotropic receptors. There is also evidence to suggest that there is parasympathetic, purinergic cotransmission to resistance vessels in the heart and the airways [15,16].

A subpopulation of inhibitory motoneurons in the myenteric plexus of the ENS release NANC neurotransmitters at neuromuscular junctions. ATP, nitric oxide (NO) and vasoactive intestinal polypeptide (VIP) are three key transmitters released from enteric inhibitory motoneurons, although their proportions vary considerably in different regions of the gut and in different species [17]. ATP, which evokes fast inhibitory junction potentials, is more prominent in non-sphincteric regions of the intestine [17].

Many non-excitable cells that express purinoceptors are activated by ATP released locally in an autocrine or paracrine manner. However, there are several examples in which these non-neural, non-muscle cells can also be activated by ATP released as a cotransmitter from autonomic nerves [18–21]. The autonomic neuroeffector junction is not a fixed structure. Rather, neurotransmission occurs when multiple varicosities actively migrate along extensively ramifying autonomic nerve fibres in close contact with effector cells and release cotransmitters within striking distance of the receptors expressed for the transmitters on the effector cells [22]. The evidence for a purinergic signalling control component is found in many exocrine glands such as salivary glands, gastric glands, pancreas, lacrimal glands, sweat glands and others [2]. Similarly, regulation of hormone release by many endocrine glands (e.g. pituitary, testis, endocrine pancreas and adrenal gland) has been shown to have a purinergic component [23].

ATP signalling and neurotransmission in autonomic ganglia

Several studies have demonstrated the presence of P2 receptors in sympathetic ganglia. Both ionotropic P2X receptors [24] and inhibitory metabotropic P2Y receptors [25] are found on presynaptic sympathetic nerve terminals and postsynaptically. Studies of the release and metabolism of endogenous ATP in rat superior cervical ganglia suggests that ATP and ACh are released simultaneously in response to stimulation of preganglionic nerve terminals [26]. A likely functional role for ATP in sympathetic ganglia was demonstrated in coeliac ganglion neurons where excitatory synaptic potentials and currents are mimicked by ATP and blocked by suramin and α,β-methyleneATP desensitisation [27].

The expression profile of P2 receptors and the effects of ATP in parasympathetic ganglia usually are very similar to those observed in sympathetic neurons [2]. There are differences in the expression of various P2X and P2Y receptors and the effects evoked by ATP and its analogues

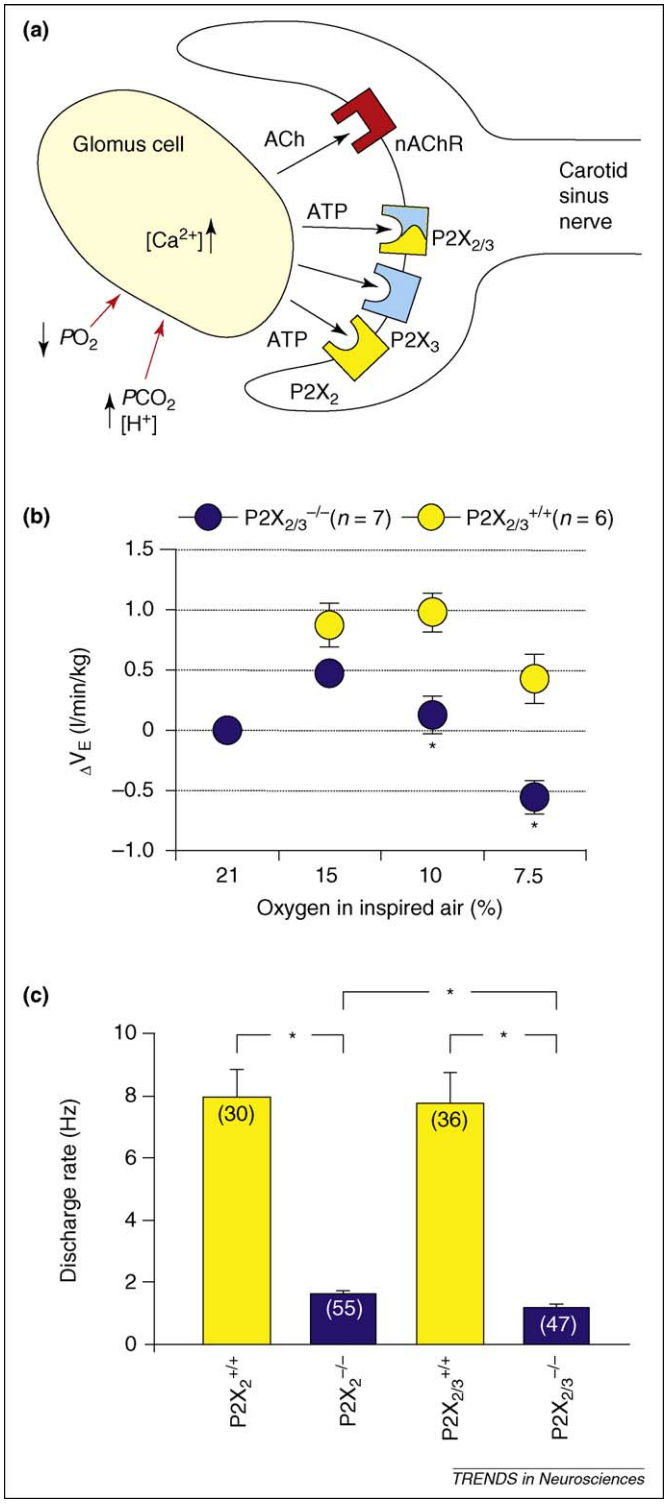

Figure 2. ATP as a mediator of sensory transduction, illustrated by the example of ATP-mediated transmission of afferent information in the carotid body. **(a)** Schematic of ATP-mediated fast chemosensory transduction in the carotid body. A decrease in PO_2 or an increase in PCO_2/[H^+] activates glomus cells, which release ATP and acetylcholine (ACh) to stimulate afferent terminals of the carotid sinus nerve. Other putative chemosensory transduction mechanisms and autocrine–paracrine modulations (including dopamine, GABA and other transmitters) are not shown for presentation purposes. **(b)** Breathing during hypoxia in mice with selective deletion of genes encoding $P2X_2$ and $P2X_3$ receptor subunits ($P2X_{2/3}^{-/-}$). V_E, minute ventilation (respiratory rate × tidal volume). Data are presented as means ± SE. Numbers in parentheses indicate sample sizes. * Denotes a significant difference, $P < 0.05$. Modified from Ref. [39] with permission from the Society for Neuroscience. **(c)** Hypoxia-induced changes in the carotid sinus nerve chemoafferent discharge in mice with selective deletion of genes encoding $P2X_2$ and $P2X_3$ receptor subunits. The plot represents average hypoxia-induced peak firing rates of single chemoafferent fibres of the carotid sinus nerve recorded in the superfused *in vitro* carotid body/carotid sinus nerve preparations taken from the $P2X_2^{-/-}$, $P2X_{2/3}^{-/-}$ and respective wild-type mice. Data taken from Ref. [39]. nAChR, nicotinic ACh receptors.

on parasympathetic ganglion cells in different species. The functional role of ATP-mediated signalling in parasympathetic ganglia is less clear, probably owing to the fact that these ganglia are smaller, have a more diffuse location, and, therefore, are much harder to study.

ATP signalling and sensory transduction

There is a vast literature on the distribution of the receptors and the effects of ATP on sensory neurons. The function and expression profile for native P2X receptors are characterized for sensory neurons from dorsal root, trigeminal, nodose and petrosal ganglia [2,28]. All P2X receptor subtypes (except $P2X_7$) and some P2Y receptors are expressed by sensory neurons, although the $P2X_3$ and $P2X_2$ receptor subunits have the highest level of expression [29,30]. These subunits form homomeric $P2X_3$ and $P2X_2$ and heteromeric $P2X_{2/3}$ receptors; when present on sensory fibres and terminals, these receptors sense changes in local concentrations of ATP released in response to an appropriate physiological stimulus or in pathological conditions. ATP is proposed to be a common mediator of several distinct sensory modalities, such as nociception [31–33], mechanosensitivity [31,34], thermal sensitivity [35,36], taste sensitivity [37,38], and oxygen and carbon dioxide chemosensitivities [39–41].

ATP-mediated chemosensory transduction in the carotid body is a prominent example of its role in transmitting afferent information (Figure 2). In adult mammals the specialized neurosecretory glomus cells of the carotid body are the primary functional peripheral O_2, CO_2 and pH chemosensors. When stimulated, glomus cells release ATP along with ACh to activate P2X and nicotinic ACh receptors, respectively, on afferent fibres of the carotid sinus nerve, which relays chemosensory information to the CNS [39,42]. Indeed, the work from our laboratory demonstrated that mice deficient in $P2X_2$ and $P2X_3$ receptor subunits display a markedly attenuated ventilatory responses to a decrease in the level of inspired O_2 (Figure 2b). $P2X_2$ receptor subunit deficiency resulted in a dramatic reduction in the responses of the carotid body to hypoxia (Figure 2c). These data suggest that in the carotid body the purinergic component substantially outweighs that of ACh: $P2X_2$ receptor knockout mice do not compensate for its loss and display dramatically reduced physiological responses to systemic hypoxia [39].

ATP signalling in the ENS

The ENS functions like an independent 'brain in the gut', which has the neural elements and integrated circuitry necessary for independent processing of sensory information and programming of organized behaviour of the intestinal effector systems [9,43]. Strong evidence implicates ATP as a neurotransmitter released by musculomotor and secretomotor neurons and interneurons in the ENS [17]. Although the concept of purinergic signalling arose from experiments designed to find the identity

of the NANC inhibitory neurotransmitter in the gut [44], it has taken many years for the importance of the various roles of ATP as a physiological messenger in the gut to be recognized (see, for example, Refs [45–47]). P2X and P2Y receptor subtypes have been identified on myenteric, submucosal, motor, sensory and interneurons involved in synaptic neurotransmission, neuromodulation and reflex activities including ascending excitatory and descending inhibitory pathways (Figure 3). ATP is now known to be co-released with NO and VIP and it is also co-released with NA at inhibitory sympathetic synapses on secretomotor neurons in the submucosal plexus and at inhibitory presynaptic receptors on nicotinic nerve terminals in the ENS microcircuitry [43]. ATP released by mucosal and epithelial cells during distension stimulates $P2X_3$ and $P2X_{2/3}$ receptors on subepithelial endings of intrinsic and extrinsic sensory nerves and modulates peristalsis and initiates nociception, respectively [48]. Nucleotide receptors have also been identified on enteric glial cells and interstitial cells of Cajal (Figure 3).

Fast excitatory postsynaptic potentials (EPSPs) are the primary mechanism of transmission between vagal efferents and ENS neurons in the stomach. Most fast EPSPs in the ENS are mediated by ACh at nicotinic receptors. However, some of the non-cholinergic fast EPSPs are purely serotonergic or purely purinergic or reflect a summation of purinergic and serotonergic inputs [43]. Although $P2X_2$, $P2X_3$ and $P2X_7$ receptor subunits are present in the ENS, the purinergic component of fast EPSPs is lost in $P2X_2$ knockout mice, suggesting that the $P2X_2$ receptor is the dominant receptor involved in fast purinergic transmission in the ENS [43].

Purinergic modulation of AH-type neurons (their name comes from prolonged and substantial afterhyperpolarizing potentials that follow action potentials) is largely adenosine mediated; when accumulating spontaneously or applied experimentally, adenosine suppresses slow EPSPs in AH neurons. In S neurons (S stands for synaptic, given that these neurons exhibit large amplitude synaptic potentials when their inputs are stimulated), which can be musculomotor, secretomotor or interneurons, adenosine evokes slow EPSP-like excitatory responses mediated via A_{2A} receptors [49]. Adenosine is also responsible for most presynaptic inhibitory actions in the ENS [43]. Interestingly, adenosine is not responsible for presynaptic inhibition at synaptic terminals where ATP is acting as a neurotransmitter; slow EPSPs in submucosal secretomotor neurons, which are mediated by ATP acting at $P2Y_1$ receptors, are not suppressed by activation of adenosine receptors [49].

The $P2Y_1$ purinergic receptor is expressed in the circular muscle coat of the human colon and the guinea pig ileum. ATP released from ENS inhibitory musculomotor neurons acts via the $P2Y_1$ receptor to suppress contractile activity of the circular muscle of both [50–52]. ATP is also co-released with ACh from neurons in the myenteric plexus that project and synapse with secretomotor neurons in the submucosal plexus. ACh evokes fast nicotinic EPSPs while co-released ATP acts at $P2Y_1$ receptors on the same neurons to evoke slow EPSPs [53].

Secretomotor neurons in the submucosal plexus, which receive inhibitory noradrenergic synaptic input from sympathetic postganglionic neurons, are found to express $P2Y_1$ receptors. The action of ATP is opposite to NA: activation of the $P2Y_1$ receptors on secretomotor neurons by stimulus-evoked sympathetic release of ATP is excitatory [53]. These secretomotor neurons also receive excitatory purinergic input from the myenteric plexus and other neurons elsewhere in the submucosal plexus, suggesting the ATP might be involved in the minute-to-minute control of mucosal secretion at the ENS microcircuit level [53–55]. In the small intestine and colon, ATP was found to stimulate water, Cl^- and HCO_3^- secretion – the effects also mediated by $P2Y_1$ receptors [56,57].

ATP signalling in the central nervous control of autonomic function

ATP-mediated purinergic signalling has been implicated in the central control of autonomic function in the hypothalamus and the brain stem. At the hypothalamic level ATP is involved in the regulation of neurohormone (vasopressin and oxytocin) release (for review, see Ref. [2]) and in the mechanisms of body temperature control [58,59]. The functional role of ATP in the brainstem has been under particular scrutiny in recent years. Indeed, there is evidence that ATP contributes to neurotransmission and integration of sensory information at the brainstem site where cardiorespiratory afferents terminate, mediates central CO_2 chemosensory transduction triggering adaptive changes in breathing and also modulates the activities of vagal preganglionic and presympathetic neuronal networks of the medulla oblongata. Later, we review and discuss these recent data in greater detail.

At the level of dorsal medullary nucleus of the solitary tract (NTS) ATP-mediated signalling is involved in the operation of several key cardiovascular and respiratory reflexes. The NTS is a central relay station for viscerosensory information to respiratory, cardiovascular and digestive neuronal networks [60,61]. The NTS receives inputs from the peripheral receptors located within the gastrointestinal, gustatory, cardiovascular and respiratory systems. NTS has multiple central connections with other brainstem regions including the ventrolateral medulla and hypothalamus and reflexly influences autonomic motor outputs, which control gastrointestinal motility, arterial blood pressure, heart rate, airway resistance and respiratory activity [60].

Various P2 receptor subtypes are identified in the NTS (see, for example, Ref. [62,63]) and profound cardiovascular and respiratory effects of ATP applied into the NTS are described in *in vivo* studies using anaesthetized and conscious experimental animals [64–67].

Blockade of P2 receptors in the NTS impairs baroreflex control of heart rate [68] and depresses reflex bradycardia evoked by activation of the peripheral chemoreceptors [69]. Simultaneous blockade of P2 and excitatory amino acid (EAA) receptors in the NTS significantly attenuates increases in arterial blood pressure and thoracic sympathetic activity in response to chemoreceptor stimulation [70], suggesting that ATP signalling is involved in mediating the sympathoexcitatory component of the arterial chemor-

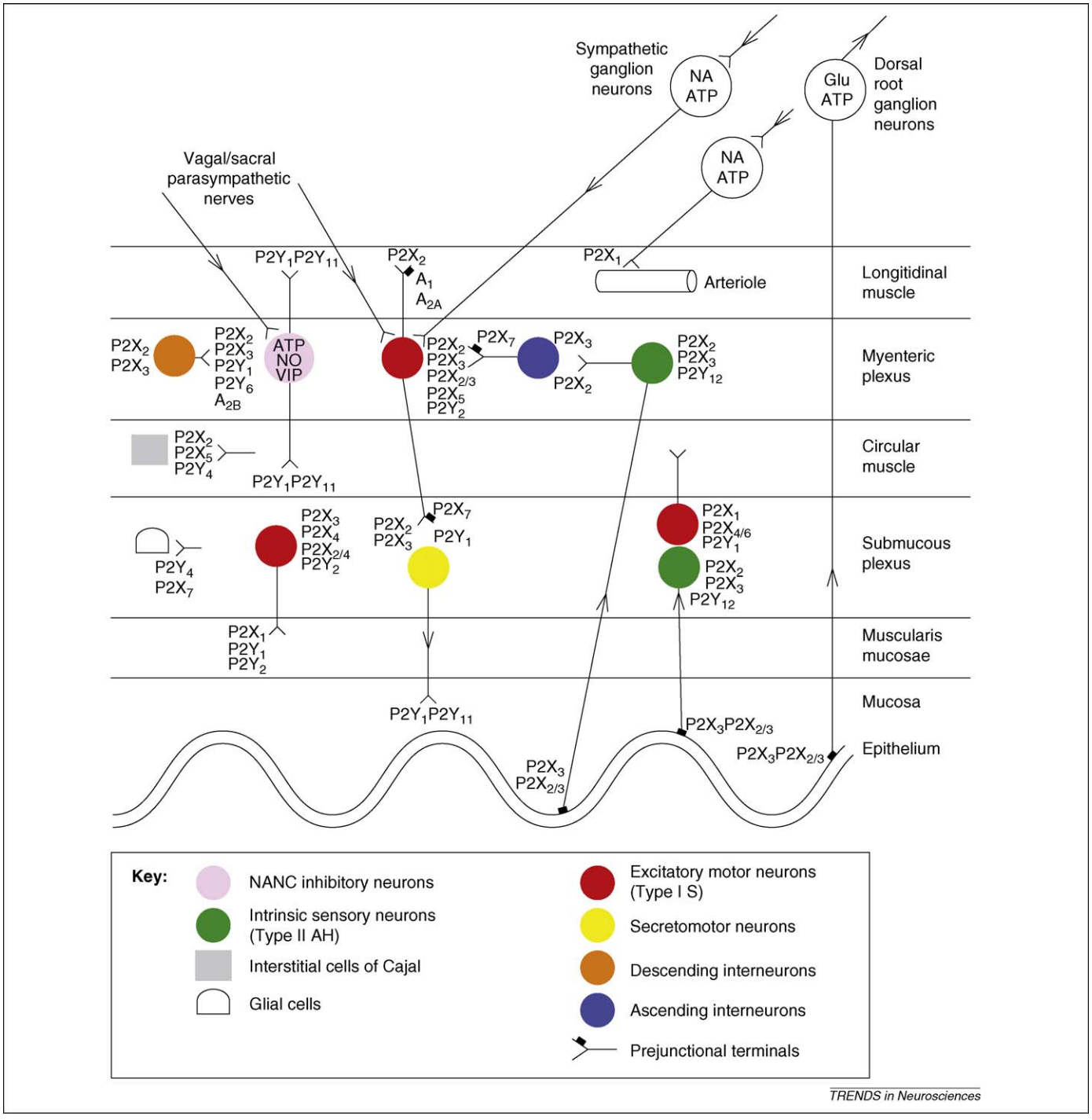

Figure 3. ATP signalling in the gut. Schematic showing the localization of receptors of purines and pyrimidines on neurons and non-neuronal effector cells in the gut, although some of the interacting pathways are not yet known. Extrinsic vagal and sacral parasympathetic nerves connect with non-adrenergic, non-cholinergic (NANC) inhibitory neurons in the myenteric plexus expressing $P2X_2$, $P2X_3$, $P2Y_1$, $P2Y_6$ and A_{2B} receptors, in addition to cholinergic motor neurons; these neurons are also activated by descending interneurons. Extrinsic sympathetic nerves modulate motility via excitatory motor neurons and constrict blood vessels in the gut via $P2X_1$ receptors. Extrinsic sensory nerves arising from cell bodies in the dorsal root ganglia and with subepithelial terminals mediate nociception. Intrinsic sensory neurons in both myenteric and submucosal plexuses express $P2X_2$ and $P2X_3$ receptors, and a subpopulation also express $P2Y_{12}$ receptors; they connect with motor pathways involved in peristalsis. Excitatory motor neurons express $P2X_2$, $P2X_3$, $P2X_{2/3}$ heteromultimer, $P2X_5$ and $P2Y_2$ receptors and connect with both interneurons and secretomotor neurons. Interneurons express $P2X_2$ and $P2X_3$ receptors. Enteric glial cells express $P2Y_4$ and $P2X_7$ receptors, whereas interstitial cells of Cajal express $P2X_2$, $P2X_5$ and $P2Y_4$ receptors. $P2X_7$ and P1 receptors seem to act as prejunctional modulators of both motor and interneurons. Abbreviations: Glu. Glutamate; NA, noradrenaline. Modified from Ref. [89] with permission from BMJ Publishing Group.

eflex (Figure 4). Rhythmic release of ATP and glutamate phase-locked to lung inflation and independent of the central respiratory drive was recorded in the NTS, suggesting that both transmitters are released from the central terminals of the lung stretch-receptor afferents [71]. P2 and EAA receptor antagonists significantly reduce baseline lung-inflation-induced firing of the NTS second-order relay neurons, which receive monosynaptic inputs from these receptors [71]. These data demonstrate that at the NTS level ATP contributes to neurotransmission of the

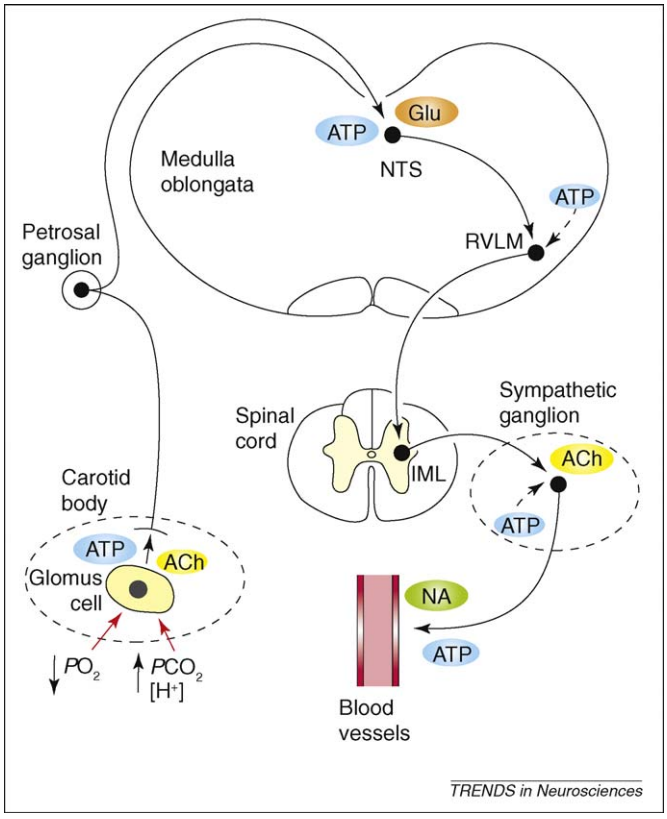

Figure 4. ATP signalling in autonomic reflex pathways, illustrated by the example of sympathoexcitatory arterial chemoreflex. In the carotid body, a decrease in PO_2 or an increase in $PCO_2/[H^+]$ activates glomus cells, which release ATP along with acetylcholine (ACh) to stimulate afferent terminals of the carotid sinus nerve. Together, ATP and glutamate (Glu) mediate transmission of the sympathoexciatory pathway of the arterial chemoreflex at the level of dorsal medullary nucleus of the solitary tract (NTS). ATP modulates the activity of presympathetic neuronal circuitry of the rostral ventrolateral region of the medulla (RVLM), which receives NTS input and provides the excitatory drive to sympathetic preganglionic neurons in the intermediolateral column (IML) of the spinal cord. Neurotransmission in sympathetic ganglia is also modulated by ATP. Sympathetic postganglionic fibres innervate blood vessels and increase vascular resistance and arterial blood pressure via release of noradrenaline (NA). The relative contribution of the ATP purinergic component at different vascular targets could be variable.

pulmonary stretch receptor (Breuer-Hering) reflex pathway – a key respiratory mechano-reflex influencing the duration of inspiration.

Cardiovascular and respiratory afferent information is processed and integrated by the NTS neuronal circuits and then transmitted to the respiratory, vagal preganglionic and presympathetic neuronal networks, which generate appropriate commands to the respiratory muscles, heart and different vascular beds. It seems that ATP influences the activity of all these brainstem networks.

The neuronal circuits responsible for the generation and shaping of the respiratory pattern and transmitting this pattern to motoneurons controlling respiratory muscles are located in the pons and the medulla oblongata [72]. The stimulatory effects of ATP on the activity of the medullary respiratory rhythm-generating network and individual brainstem respiratory neurons were demonstrated in several studies from our and other laboratories [73–77]. Studies of the release of endogenous ATP revealed that in response to an increase in inspired CO_2 (hypercapnia) or decrease in inspired O_2 (hypoxia) ATP is released from the ventral areas of the medulla oblongata located in a close proximity to the medullary respiratory rhythm and pattern generator [40,41,78]. Experiments in which P2 receptors in the ventral medullary region were blocked pharmacologically suggested that released ATP contributes to adaptive changes in breathing in response to CO_2 [40] and helps to maintain respiratory activity in the face of the hypoxia-induced centrally mediated decline in ventilation [78].

Presympathetic neuronal circuitry of the rostral ventrolateral region of the medulla (RVLM) provides the excitatory drive to sympathetic preganglionic neurons in the spinal cord and is believed to be the most important for generation of sympathetic vasomotor tone [79]. ATP, or stable ATP analogues, when applied increase firing of bulbospinal presympathetic RVLM neurons and evoke marked increases in arterial blood pressure, heart rate and renal sympathetic nerve activity [80–82]. However, P2 receptor blockade in the RVLM had no effect on resting cardiovascular variables [80] and only a fraction of RVLM presympathetic neurons were inhibited by P2 receptor blockade at rest [82]. Thus, the functional role of purinergic signalling in modulating the activity of central sympathetic control circuits might have functional importance in conditions associated with increases in local concentration of ATP, such as during systemic hypoxia [78,83] or hypercapnia [40].

Cardiac vagal preganglionic motoneurons are also under purinergic control. These neurons are found in two medullary locations: in the dorsal vagal motonucleus and within and near the nucleus ambiguus of the ventrolateral medulla oblongata [60]. Purinergic modulation of the latter population has been studied recently, demonstrating that ATP might presynaptically modulate both excitatory glutamatergic [84] and inhibitory GABAergic and glycinergic inputs [85] to these neurons. Functionally, during recovery from hypoxia, ATP (perhaps released by astrocytes [86]), mediates respiratory-related enhancement of glutamatergic excitatory input to cardiac vagal preganglionic motoneurons [87].

Conclusions

ATP is a ubiquitous cellular energy source and intercellular messenger molecule that mediates purinergic signalling fundamental for the operation of the autonomic nervous system. Although purinergic receptors are arguably the most abundant receptors in living organisms [4], the fact that the same transmitter is involved at multiple steps of the autonomic reflex pathways – from the transduction of sensory information to neuroeffector transmission (illustrated in Figure 4 by the example of sympathoexcitatory arterial chemoreflex) – seems very interesting from the physiological and evolutionary points of view.

The evidence suggesting an important role of ATP signalling in the central nervous control of autonomic function is rapidly accumulating. Activities of the CNS vagal preganglionic, presympathetic and respiratory neural networks are all modulated by ATP. The physiological role and importance of this modulation is revealed when the organism is challenged, for example during systemic hypoxia.

Although substantial progress has been made recently, we still do not know the exact mechanisms underlying physiological actions of ATP on CNS autonomic circuits. These can be either direct pre- or postsynaptic effects of ATP on central neurons and/or indirect via ATP actions on the functional states of glial networks and cerebral vasculature. A recent report [88] demonstrating in conscious animals that extracellular ATP levels in the brain increase during systemic inflammation suggests that purinergic signalling might also contribute to modifications of the central nervous autonomic control in pathological states.

Although it has taken a long time, it is now clear that the extracellular actions of purines have important roles in both peripheral and central mechanisms of autonomic control of the activities of the cardiovascular, respiratory, gastrointestinal and urogenital systems. The time has come for serious exploration of the therapeutic potential of modulating the purinergic signalling for a variety of autonomic disorders.

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