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INVITED REVIEW

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Purinergic transmission in the central nervous system

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Abstract The adenosine 5′-triphosphate (ATP), discovered in 1929 by Karl Lohman, Cyrus Hartwell Fiske, and Yellagaprada SubbaRow, acts as an important extracellular signaling molecule. In the CNS, ATP can be released from synaptic terminals, either on its own or together with other neurotransmitters. After the release from the presynaptic terminals, ATP binds to a plethora of ionotropic and metabotropic receptors, which mediate its action as an excitatory neurotransmitter. Furthermore, ATP also acts as an important mediator in neuronal–glial communications because glial cells are endowed with numerous ATP receptors, which trigger Ca^{2+} signaling events and membrane currents in both macro and microglia. In addition, ATP can be released from astroglial cells, thereby acting as a mediator of glial–glial and glial–neuronal signaling.

Keywords Purinoreceptors · Synaptic transmission · ATP · Neuronal–glial interactions

The beginning

The molecule of adenosine 5′-triphosphate, ATP, was discovered simultaneously in Heidelberg and Harvard in 1929 by Karl Lohman and by Cyrus Hartwell Fiske and Yellagaprada SubbaRow. By stroke of luck or through the inspired leadership of Otto Meyrhof who was the director of Kaiser Wilhelm Institute for Physiology in Heidelberg, Lohman succeeded to publish his results in March 1929 [42], whereas Fiske and SubbaRow promulgated their report several months later, in October 1929 [23]. In this case, however, the fate was just and although the initial discovery is credited to Lohman, the name of ATP belongs to Fiske and SubbaRow, as Lohman called his molecule "adenylpyrophosphate." Very soon the importance of ATP as a universal source of chemical energy in biological systems was fully appreciated [41].

Incidentally, the idea that purines may serve not only important intracellular functions but also act as extracellular signaling molecules was also born in 1929 when Drury and Szent-Györgyi [14] found that purines trigger negative chronotropic effect on the heart, mediated dilatation of coronary vessels, and inhibited intestinal smooth muscle. Very soon, it also became apparent that it was ATP, which was responsible for many purine-mediated physiological reactions [13].

Thirty years after the discovery of ATP, Pamela Holton [30] made a seminal observation that ATP can be released from nerves upon stimulation. Using the firefly luminescence method for ATP detection (introduced by Strehler and Totter [57, 58]), Pamela Holton found that electrical stimulation of great auricular nerve of rabbit resulted in transient elevation of extracellular ATP (Fig. 1). Based on these experiments, she concluded that "when noradrenalin is liberated from sympathetic nerve endings ATP may also be liberated in to the tissue spaces" [30], thus establishing a foundation for the theory of purinergic neurotransmission.

In 1970, Geoffrey Burnstock et al. [9] presented the first direct evidence that ATP may act as a transmitter in "nonadrenergic, noncholinergic" nerves in the gut and in 1972, the same Geoffrey Burnstock [7] introduced the concept of "purinergic nerves" and "purinergic neurotransmission." It was once more Geoffrey Burnstock who, with his characteristic determination, developed and elaborated the concept of purinergic transmission in the peripheral nervous system and demonstrated that ATP fully conforms to the criteria of the definition of "neurotransmitter": (1) ATP is synthesized and stored in presynaptic terminals; (2) it is released upon nerve stimulation; (3) released ATP can be rapidly degraded by coenzymes; and (4) pharmacological agents, which inhibited effects of endogenous ATP,

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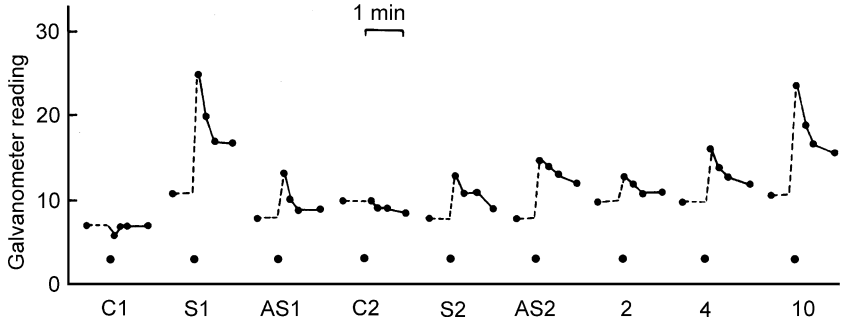

Fig. 1 Discovery of ATP release from nerve terminals. Galvanometer readings before and at 10, 20, 30, and 60 s after adding 0.5 ml test solution to the firefly enzyme. C1 and C2 perfusates collected during control period, S1 and S2 during stimulation, and AS1 and AS2 immediately after stimulation. The last three deflexions were caused by adding 2, 4, and 10 pmol ATP to the control perfusate (C2). Figure is reproduced with permission from Holton [30]

also suppresses the effects of nerve stimulation. Finally, Burnstock also challenged a Dale's principle, which postulated that each nerve cell produces and releases only one transmitter, by demonstrating that ATP may be coreleased with other neurotransmitters, such as noradrenalin or acetylcholine.

ATP mediates synaptic transmission in the CNS

Probably the first hints that ATP may act as a neurotransmitter in neuronal–neuronal synapses were obtained by Thomas White [68] who found the release of ATP from brain synaptosomes treated by veratridine or high extracellular K^+; later, he also demonstrated depolarization-induced ATP release from synaptosomes isolated from

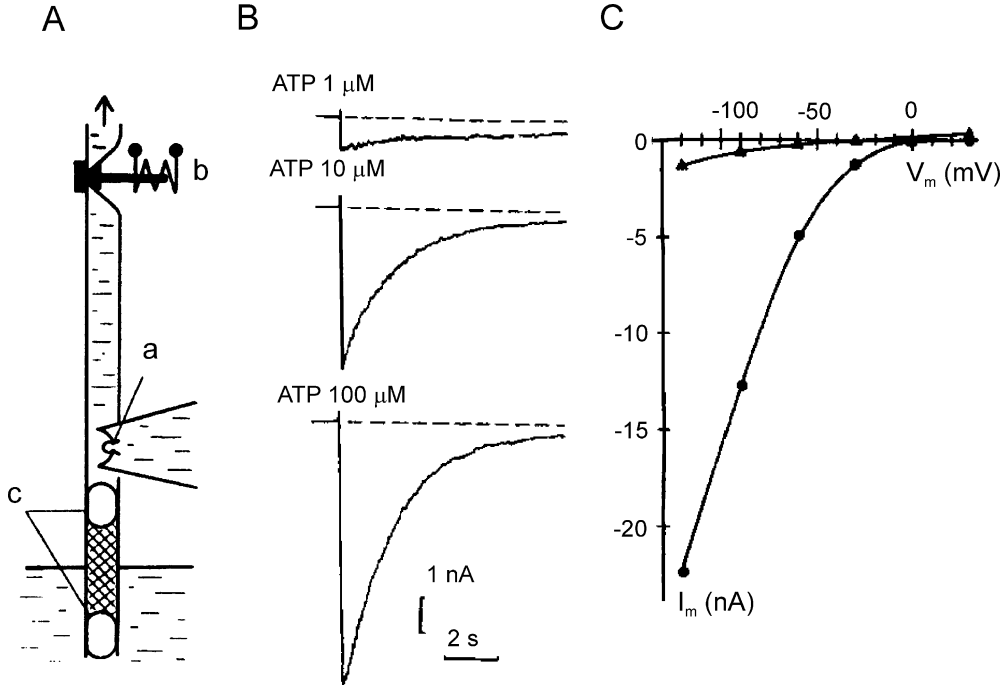

Fig. 2 First recordings of ATP-induced membrane currents in acutely isolated sensory neurones. **a** The "square pulse" application technique used for rapid application of ATP to internally dialyzed sensory neurones. The tip of the micropipette with the cell (*a*) is inserted into a plastic tube. The lower end of this tube can be exposed to different external solutions or to air. The suction applied to the upper end of the tube (indicated by *arrow*) is controlled by an electromagnetic valve (*b*). A preprogrammed sequence of current pulses applied to the valve allows a column of testing solution to form in the tube separated from the normal solution by air bubbles. Another sequence of pulses exposes the cell to the testing solution for the desired period of time by rapid displacement of the column along the tube. The electrical recording is unharmed because there is a thin layer of saline between the air bubbles and the walls of the tube. An invagination in the tip of the micropipette prevents the cell from damage. **b** ATP-activated inward current (*ordinate*) elicited by application of different concentrations of ATP as indicated on the graph. **c** The voltage-dependence of the peaks of ATP-activated current. ATP (5 μM) was applied in normal saline (*circles*) and in an external solution in which Na was substituted with TEA (*triangles*). Holding potential was −90 mV throughout. Figure is reproduced with permission from Krishtal et al. [39]

cortex and striatum and also found that in central nervous tissue, ATP was not coreleased with acetylcholine [70, 69].

The excitatory action of ATP on neurones was found in 1983. First, robust inward currents induced by rapid application of ATP were recorded from internally dialyzed isolated sensory (nodose, vestibular, trigeminal, and dorsal root ganglia) neurones [39]. These currents were concentration-dependent (with K_D for ATP ~5 μM) and were carried mostly by sodium ions as the substitution of the latter by $Tris^+$, tetraethylammonium $(TEA)^+$, or $choline^+$ markedly suppressed the ATP-induced responses (Fig. 2).

Several months later, the ATP-induced excitatory responses were also found in cultured dorsal horn neurones, impaled with microelectrodes [32]. Applications of ATP in concentrations between 1 and 10 μM triggered rapid depolarizations (Fig. 3) in about 30% of the neurones and these responses were abolished by lowering the extracellular Na^+ concentration from 137 to 7.5 mM.

The year 1983 also witnessed another important discovery when Hans-Albert Kolb and Michael Wakelam identified ATP-activated single channel cation currents in membranes of myoblasts and myotubes [38]. They found several populations of channels with unitary conductances of 20, 48 (in myotubes), and 43 pS (in myoblasts), thus obtaining the first indication for heterogeneity of ATP receptors.

It took another decade before ATP-mediated synaptic transmission was experimentally identified. First, ATP-dependent synaptic currents were detected from cultured celiac ganglion cells [19, 55] and almost simultaneously, ATP-mediated excitatory postsynaptic currents and spontaneous "miniature" postsynaptic currents were detected from neurones in medial habenula from acutely isolated brain slices (Fig. 4a, [17, 18]). In all cases, the ATP-mediated synaptic currents were dissected using pharmacological approaches; in particular, the purinergic nature of the synaptic responses was confirmed based on their sensitivity to broad antagonist suramin [15] or by desensitization induced after incubation with α,β-methylene-ATP. Further investigations revealed ATP-mediated synaptic transmission in the spinal cord [3], hippocampus [44, 47], and cortex (Fig. 4b, [48, 49]).

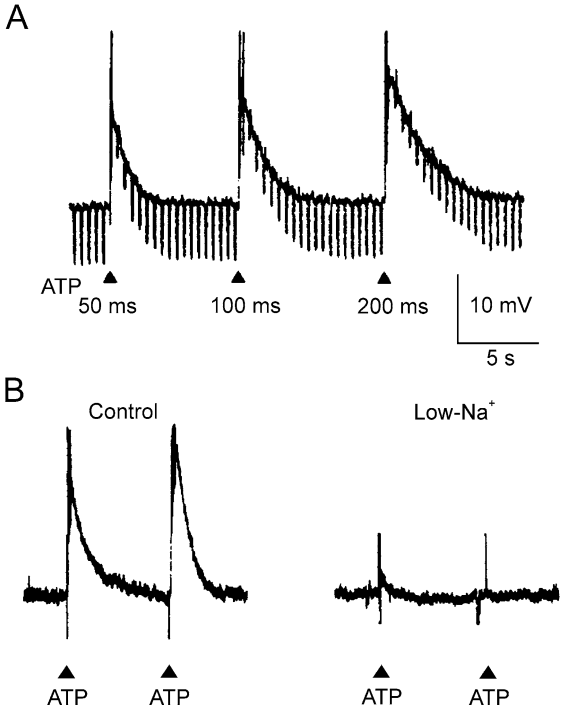

Fig. 3 First recordings of ATP-induced excitatory responses in cultured dorsal horn neurones. **a** Chart records of intracellularly recorded responses of dorsal horn neurones to ATP. Disodium ATP (10 μM) was ejected at the moments indicated on the graph by pressure (1.5 psi) from a micropipette positioned ~15 μm from the soma of the recorded neurone in pulses of 50, 100, and 200 ms in duration. The fast downward deflections were produced by injecting constant current hyperpolarizing pulses of 100 ms at 80 pA through the recording electrode and by providing a measure of input resistance. Resting potential=−62 mV. **b** Ionic-dependence of ATP-evoked depolarization of dorsal horn neurone. Voltage responses of the neurone to iontophoresis of Tris glutamate and Mg-ATP in control medium ($[Na^+]_o$=137 mM) and after switching to medium containing 7.5 mM Na^+. Figure is reproduced with permission from Jahr and Jessell [32]

ATP receptors

All purinoreceptors are divided into two fundamentally distinct classes, the P1 receptors activated by adenosine and P2 receptors sensitive to ATP and its analogs (the subdivision proposed by Burnstock in 1978 [8]). The P2 receptors, in turn, are further split into two groups, the ionotropic P2X and metabotropic P2Y receptors [1, 46]. The P2X receptors are ligand-gated cationic channels, which, upon ATP-binding, undergo rapid conformational change that allows the passage of Na^+, K^+, and Ca^{2+} through the channel pore. There are seven P2X receptors subunits ($P2X_1$–$P2X_7$) encoded by distinct genes. These subunits may form homo- or heteromeric receptors with each functional receptor containing at least three monomers (see Fig. 5 and [35, 53, 60, 61, 65] and this issue for comprehensive reviews). The $P2X_7$ receptor is unique in a sense that after its activation, it is followed by the appearance of a big pore, which allows the passage of molecules with molecular weight up to 900 Da. All P2X subunits are expressed in the brain and several subunits can be present within an individual neurone. Functional P2X receptors are also Ca^{2+}-permeable and Ca^{2+} permeability relative to monovalent cations can range between 2 and 12 [16, 48, 53]. In this high Ca^{2+} permeability, the P2X receptors resemble the NMDA ones, albeit with one fundamental difference: P2X receptors can be activated at resting membrane potentials, whereas opening the NMDA ones requires membrane depolarization, which removes the Mg^{2+} block. As a consequence, the P2X receptors may provide an important Ca^{2+} influx pathway in resting neurones.

The P2Y receptors are classical 7-transmembrane-domain metabotropic receptors coupled to G proteins. These receptors are represented by at least ten subtypes out of $P2Y_1$, $P2Y_6$, $P2Y_{11}$, $P2Y_{12}$, $P2Y_{13}$, and $P2Y_{14}$ detected

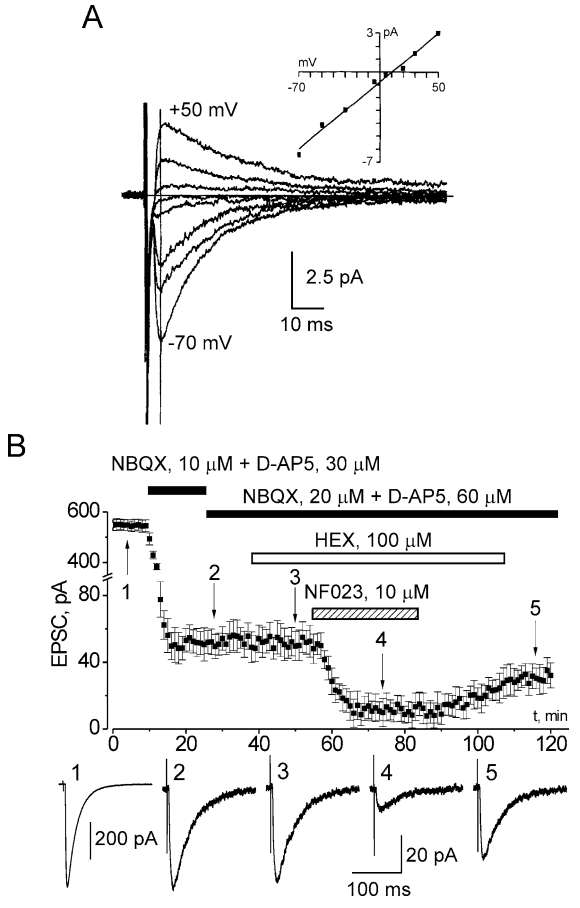

Fig. 4 ATP-mediated synaptic transmission in CNS neurones. **a** Voltage-dependence of ATP-mediated synaptic currents. ATP-mediated postsynaptic currents shown were recorded from a medial habenula neurone from a 24-day-old male rat in Krebs solution containing 5 mM Ca^{2+}. Stimulus pulses (13 V, 200 μs) were delivered at 2 Hz and 53–215 currents recorded before the holding potential was stepped to the next voltage. The traces are averages of all responses (including failures). The peaks of the currents shown are plotted in the *inset* and fitted to a *straight line* using a linear regression. Peak current was measured from the single exponential fit of each current at the time indicated by the *vertical line*. The membrane potentials shown in this plot are −70, −50, −30, −5, +5, +20, +30, and +50 mV. Note that the voltage dependence of peak current amplitude is well fitted by a *straight line* with clear outward currents at positive holding potentials. Figure is reproduced with permission from Edwards et al. [18]. **b** Dissection of ATP-mediated component of excitatory postsynaptic currents (EPSCs) in the pyramidal neurone of layer II of somatosensory cortex. *Top*, changes in the amplitude of EPSC after bath application of glutamatergic antagonists NBQX and D-AP-5, cholinergic antagonist HEX, and P_{2X} receptor antagonist NF023 as indicated on the graph. Each *point* represents mean±SD for six sequential trials, holding a potential of −80 mV, stimulation frequency 0.1 Hz. *Bottom*, the examples of EPSC (average of six traces) recorded at moments (1–5) indicated on *upper graph*. Figure is reproduced with permission from Pankratov et al. [48]

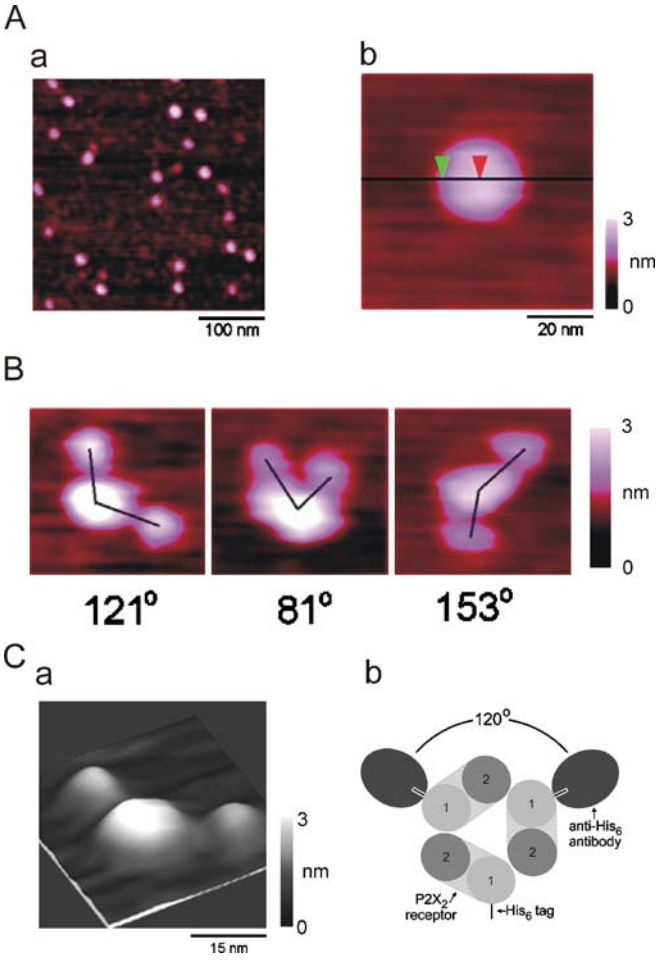

Fig. 5 Trimeric structure of $P2X_2$ receptors. **a** Imaging of $P2X_2$ receptors. (*a*) A low magnification and (*b*) a high magnification image of $P2X_2$ receptors bound to mica. **b** Atomic force microscope imaging of complexes between $P2X_2$ receptors and anti-His_6 antibodies showing images of receptors that are liganded by two antibodies. The *angles* between the two bound antibodies in are shown *beneath the images*. **c** Trimeric model of $P2X_2$ receptor assembly. (*a*) A three-dimensional atomic force microscopy image of a receptor liganded by two anti-His_6 antibodies. The *angle* between the bound antibodies is 121°. (*b*) The arrangement of antibodies bound to two His_6 tags, assuming trimetric receptor architecture. Figure is modified from Barrera [4]

in the CNS [31]. Activation of neuronal P2Y receptors regulate both outwardly and inwardly rectifying K^+ channels, potentiate high-voltage activated Ca^{2+} channels, and trigger $InsP_3$-mediated release of Ca^{2+} from endoplasmic reticulum Ca^{2+} stores (see [31] for review).

ATP and neuronal–glial interactions

Purinergic transmission is particularly important for neuronal–glial integration in the CNS. It became exceedingly clear that the function of the nervous system is executed through continuous interaction of two cellular circuits, the neuronal and the glial [28, 45, 66]. Glial cells are an integral part of the synaptic contacts and they are endowed with numerous receptors allowing them to detect neuronal activity. In particular, glial cells are specifically sensitive to ATP as all types of glia, astrocytes, oligodendrocytes, Schwann cells, and microglia express ATP receptors (see, e.g., [11, 21, 27, 36, 37, 43, 54, 63]). In astrocytes and oligodendrocytes, the ATP-mediated signaling predomi-

nantly occurs through the P2Y receptors, which in turn trigger intracellular Ca^{2+} release and propagate Ca^{2+} waves, which serve as a substrate for glial excitability [24, 64]. The role for $P2X_{1–6}$ receptors in astrocytes remains obscure, although P2X-mediated currents were detected in astroglial cells in culture [67] and $P2X_{1–4}$ and $P2X_6$ receptor mRNAs and proteins were detected in astrocytes in situ [22, 40]. $P2X_7$ receptors are widespread in astrocytes and may be important upon pathological conditions [20]. Particularly important P2X and P2Y receptors are for microglia where they are abundantly expressed and may serve as sensors for neighboring cell damage, which may be associated with massive ATP release [29, 43, 51].

The second important role for ATP in neuronal–glial relations is associated with its capacity to act as a "glio" transmitter, as indeed, glial cells are capable to release several transmitters both in exocytotic and nonvesicular way ([5, 62, 66], see also Todd & Robitaille in this issue). ATP released by astrocytes can signal onto the neighboring astrocytes, thus assisting propagating Ca^{2+} waves in astroglial syncytium [11, 26]. Similarly, astrocyte-originated ATP can signal onto neurones. For example, in neuronal–glial cocultures prepared from hippocampus, ATP secreted by astrocytes was shown to inhibit glutamatergic synapses through activation of presynaptic P2Y receptors [71]. Alternatively, astroglial release of ATP may cause (through ATP degradation) an accumulation of adenosine, which in turn, may produce tonic suppression of synaptic transmission by acting on adenosine receptors [50].

ATP release

The fact that ATP molecule cannot cross the plasma membrane by diffusion was realized very early [10, 25]. This implies the necessity of specialized pathways for ATP release; furthermore, to provide for meaningful intercellular signaling, this pathway must be coupled with cellular excitation. Several release pathways can be operative in the CNS. First, ATP may be accumulated in synaptic vesicles together with other neurotransmitters and then both can be coreleased. This corelease of ATP is widespread in the peripheral nervous system [6]; in the CNS, ATP was reported to be coreleased with GABA [33, 34] and glutamate [44]. Alternatively, ATP may be released on its own from specific ATP-reach vesicles ([52], Pankratov et al., this issue), which may coexist with other neurotransmitter vesicles in the same presynaptic terminal or certain neurones can have pure ATP-releasing terminals. Which mechanism dominates in the CNS and what regional differences it may experience remains yet to be resolved. ATP may also be released by a nonvesicular mechanism, such as through gap junction hemichannels or via volume-sensitive chloride channels or indeed, via dilated P2X7 receptors [2, 12, 56, 59]. These latter mechanisms are likely to be associated predominantly with glial cells. Identifying the mechanisms and functional significance of ATP released from different elements of the CNS is of specific importance for further understanding of the role of purinergic transmission in the brain.

When coming up with this special issue, we tried to cover all fundamental aspects of purinergic transmission in the CNS, including the role of purinergic mechanisms in the regulation of CNS development (H. Zimmerman), molecular physiology, pharmacology of P2X (Roberts et al., Egan, Ford) and P2Y (Hussl & Boehm) receptors, intracellular signaling cascades involved in purinoreceptors action (Weisman & Erb), role of purinoreceptors in sensory transmission (Gu et al.), mechanisms of ATP release in central synapses (Pankratov et al.), signaling through dinucleoside polyphosphates (Delicado et al.), role of purinergic transmission in neuronal–glial interactions (Todd & Robitaille), and involvement of ATP in brain pathology (Färber & Kettenmann, Illes, Salter). We hope that this collection of essays, prepared by the leading experts in the field, will provide useful information on purinergic neurotransmission in the CNS.

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