Purinergic Signalling (2007) 3:269–284
DOI 10.1007/s11302-007-9080-0

ORIGINAL ARTICLE

P2 receptor-mediated modulation of neurotransmitter release—an update

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Received: 13 July 2007 / Accepted: 28 August 2007 / Published online: 9 October 2007

Abstract Presynaptic nerve terminals are equipped with a number of presynaptic auto- and heteroreceptors, including ionotropic P2X and metabotropic P2Y receptors. P2 receptors serve as modulation sites of transmitter release by ATP and other nucleotides released by neuronal activity and pathological signals. A wide variety of P2X and P2Y receptors expressed at pre- and postsynaptic sites as well as in glial cells are involved directly or indirectly in the modulation of neurotransmitter release. Nucleotides are released from synaptic and nonsynaptic sites throughout the nervous system and might reach concentrations high enough to activate these receptors. By providing a fine-tuning mechanism these receptors also offer attractive sites for pharmacotherapy in nervous system diseases. Here we review the rapidly emerging data on the modulation of transmitter release by facilitatory and inhibitory P2 receptors and the receptor subtypes involved in these interactions.

Keywords Neuromodulation · Presynaptic · P2X receptor · P2Y receptors · Release · Transmitter

Abbreviations

ABC	ATP binding cassette
ACh	acetylcholine
AP	action potential
Ap_5A	P1,P5-di(adenosine-5′) pentaphosphate
BzATP	benzoylbenzoylATP
CNS	central nervous system
DA	dopamine
DRG	dorsal root ganglion
ENPP	ectonucleotide pyrophosphatase
EJP	excitatory junction potential
ENTPDase	ectonucleoside triphosphate diphosphohydrolase
EPP	end plate potential
EPSC	excitatory postsynaptic current
EPSP	excitatory postsynaptic potential
GABA	γ-aminobutyric acid
GPCR	G-protein coupled receptor
IL-1β	interleukin-1β
IPSC	inhibitory postsynaptic current
LC	locus coeruleus
LPS	lipopolysaccharide
mEPP	miniature EPP
mEPSC	miniature EPSC
NA	noradrenaline
NMJ	neuromuscular junction
NT	neurotransmitter
NTS	nucleus tractus solitarii
PNS	peripheral nervous system
sEPP	spontaneous EPP
sIPSC	spontaneous IPSC
UDP	uridine 5′-diphosphate
UTP	uridine 5′-triphosphate

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Introduction

Ionotropic P2X receptors and metabotropic P2Y receptors are the principal cell surface proteins, conveying the action of extracellular ATP, the ubiquitous signaling substance. P2X receptors are ligand-gated cation channels, composed of three individual subunits, whereas P2Y receptors belong to the superfamily of G protein-coupled receptors (GPCRs), with seven transmembrane domains. Various subtypes of

P2X and P2Y receptor families are expressed throughout the brain and involved in a wide array of functions from fast synaptic transmission to long-term plasticity and trophic changes important for development, neuron-glia interactions, and neuroimmunomodulation. In addition, ATP modulates synaptic transmission pre- and postsynaptically, both in a positive and negative direction via activation of P2X and P2Y receptors, respectively.

The presynaptic nerve terminal is an important regulatory site, whereby the efficacy of synaptic transmission could be locally and efficiently controlled. Accordingly, axon terminals in the central nervous system and in the periphery are equipped with a wide variety of auto- and heteroreceptors [1–4]. Whereas presynaptic metabotropic receptors convey negative feedback regulation of transmitter release, presynaptic ionotropic receptors could amplify synaptic transmission. Moreover the activation of ligand-gated cation channels with high Ca^{2+} permeability could directly elicit transmitter release triggered by the Ca^{2+} influx through the receptor-ion channel complex [2, 4]. Coactivation of different presynaptic receptors provides a fine-tuning mechanism whereby different neurotransmitters and modulators can mutually influence the activity of each other. Presynaptic and extrasynaptic receptors controlling transmitter release also offer attractive target sites for existing and future pharmacotherapy, as they may modify the normal and pathological synaptic information processing without all-or-none actions [3].

Since ATP and its related nucleotides are ubiquitous signaling molecules, it is not surprising that their receptors, i.e., ionotropic P2X and metabotropic P2Y receptors, participate both in the negative and positive feedback modulation of neurotransmitter release. Although the principal function proposed for ATP-sensitive P2 receptors was that they mediate the fast transmitter action of extracellular ATP in neuro-neuronal and neuro-effector synapses in the nervous system, it was already recognized in the early 1990s that they are also involved in the regulation of transmitter release [5, 6]. It was subsequently revealed that the release of the major neurotransmitters of the brain and the peripheral neurons [acetylcholine (ACh), noradrenaline (NA), dopamine (DA), serotonin, glutamate, γ-aminobutyric acid (GABA)] are modulated by P2X and/or P2Y receptors. In 2000, Cunha and Ribeiro reviewed the literature on the presynaptic modulator role of ATP and suggested that there is a mismatch between the abundance of P2 receptor expression, the robust release of ATP in almost all parts of the central nervous system (CNS) and peripheral nervous system (PNS), and the relative paucity of identified P2 receptor-mediated synapses, which implicates the major role of ATP as a neuromodulator, rather than a classic transmitter [7].

The focus of this mini-review is the facilitatory and inhibitory modulation of neurotransmitter release by different subtypes of P2X and P2Y receptors, irrespective of their localization, i.e., whether they are pre-, post-, or extrasynaptic.

Therefore, in addition to a brief summary of the determining factors of ATP availability in synapses, the structure, pharmacology, signal transduction, and distribution of P2X and P2Y receptors in the nervous system, available information on the release-modulating P2 receptors, and the receptor subtypes involved in these interactions will be detailed and updated.

Determining factors of ATP availability in synapses

The participation of ATP and related nucleotides in the regulation of neurotransmitter release presumes their accumulation in the extracellular space upon ongoing neuronal activity. Extracellular purine availability in the nervous system is basically determined by the balance of release and removal by enzymatic degradation and uptake.

Sources and stimuli that trigger ATP release

Since ATP is ubiquitous, all metabolically active cells of the nervous system provide a potential pool for its release. Therefore, besides the nerve terminals themselves, the cellular source of released purines participating in the modulation of neurotransmitter release could be any cell type located in contact with nerve terminals, i.e., astrocytes, microglia, and endothelia. A wide variety of stimuli are known to release ATP to the extracellular space, which could lead to purine levels sufficiently high to activate nucleotide receptors expressed on the surface of pre- and postsynaptic membranes [8, 9]. Although the stimulation-dependent release of ATP upon conventional [10, 11] and high-frequency (e.g., [12]) neuronal activity is well documented, these stimuli probably result in a spatially restricted, localized increase in extracellular purine levels, which serve the fast synaptic transmission and its modulation within the synaptic cleft. Furthermore, ATP-metabolizing ectoenzymes, present on the nerve terminal membrane, and glial cells [13], such as ectoNTPDases, and the CD39/ecto-5′nucleotidase [14], may strongly limit nucleotide availability under these conditions. On the other hand, pathological events are known also to stimulate purine release. These signals include mechanical [15–17], chemical [18], and hypotonic stimuli [19], hypoxia/hypoglycemia/ischemia and consequent energy deprivation [20–25], inflammatory signals, such as bacterial lipopolysaccharide (LPS) [26, 27], interleukin-1β (IL-1β) [28], and cellular injury. The pathological ATP release might result in a purine-rich extracellular milieu leading to a more widespread activation of receptors reaching also the extrasynaptic receptors on the neighboring nerve terminals or distant cells such as astrocytes. Therefore, P2 receptors could play a role

in the modulation of not only neuronal but also astrocytic transmitter release. Finally, nucleotides and nucleosides may promote further release of purines, by a homo- or hetero-exchange mechanism, if they reach a relatively high concentration in the extracellular space [29].

Mechanisms of ATP release

Since ATP is a highly polarized molecule, which cannot pass freely the cell membrane being released to the synaptic cleft, it could enter the extracellular space by the following mechanisms: (1) vesicular exocytosis, (2) carrier-mediated release, (3) release through channels and membrane pores, and (4) cytolytic release. (1) Vesicular exocytosis is a prototype mechanism for neurotransmitters and neuromodulators to enter the extracellular space, which is expected to be a $[Ca^{2+}]_o$-dependent process. Indeed, ATP is taken up and stored in synaptic vesicles of nerve terminals [8] and astrocytes [15] and $[Ca^{2+}]_o$-dependent ATP release in response to neuronal stimulation appears in many areas of the central and peripheral nervous system (for further references see [8, 9, 24, 30, 31]). Moreover, recent findings indicate that vesicular ATP could be released not only from nerve terminals but also from neuronal somata [32] and astrocytes [15]. (2) Although specific transporters capable of transmembrane movement of ATP are yet to be molecularly identified in the nervous system, ABC (ATP binding cassette) proteins have been implicated as ATP transporters [19, 33, 34] in non-neuronal cells. These transporters are also expressed in glial cells [35] and mediate ATP release upon hypo-osmotic challenge [36, 37]. (3) Channels and pores, such as connexin hemichannels [38], are also potential candidates to drive the transmembrane movement of ATP. They have been identified to mediate ATP release from astrocytes and other non-neuronal cells in response to mechanical stress [39, 40] and other stimuli [31, 41]. (4) Although only scarcely supported by direct experimental proof [42], the general assumption is that any kind of cellular injury could result in high local ATP concentrations in the extracellular space. In this case the millimolar cytoplasmic ATP is expected to leak out of the cell through the membrane damage.

Metabolism of ATP in the extracellular space

Several enzyme families are responsible for the extracellular degradation of ATP in the nervous system. The first step of the inactivation of ATP is mediated by the family of ectonucleoside triphosphate diphosphohydrolases (ENTPDases, EC 3.6.1.5, also known as ectoATPase or apyrase), which are able to hydrolyze ATP and adenosine diphosphate (ADP) to AMP [14]. Among these enzymes ENTPDase 1, 2, 3, and 8 are present in the brain [43, 44], having low micromolar K_m for ATP and ADP giving rise to rapid and highly effective hydrolysis of ATP in almost all neuronal tissues. In addition to the ENTPDase family, ATP and other nucleotides could also be dephosphorylated by ectonucleotide pyrophosphatases (ENPPs) and by alkaline phosphatases, both having broader substrate specificity, but also widespread tissue distribution [14]. The final step of extracellular inactivation is the hydrolysis of AMP by the ecto-5′-nucleotidase (EC 3.1.3.5) enzyme, which is the rate-limiting step giving rise to the formation of adenosine that acts on P1 receptors, which include A_1, A_{2A}, A_{2B}, and A_3 receptor subtypes. Thus, endogenous ATP is converted to adenosine to activate A_1 adenosine receptors within a second in the hippocampus [45, 46], whereas the hydrolysis of ATP seems slower in other brain regions, such as the cerebral cortex [47]. Ectoenzymes therefore have an important role in the substrate delivery to different subtypes of P2X and P2Y receptors. In spite of its short half-life, effective concentrations of nucleotides can be reached in the synapse for the activation of ionotropic P2X receptors and metabotropic P2Y receptors.

Structure, pharmacology, and signal transduction of P2X receptors

Ionotropic P2X receptors are nonselective cation channels consisting of at least three subunits. P2X receptor subunits are 379-595 amino acid long polypeptide chains, having two transmembrane domains (TM1 and TM2) and a large extracellular loop [48, 49]. Until now seven members of this receptor family have been identified molecularly, which are numbered from $P2X_1$ to $P2X_7$, and have individual kinetics and pharmacological phenotype [50]. These receptor proteins coassemble into various homo- or heterooligomeric assemblies to form functional receptors. Among possible combinations so far 16 variations have been proved to be functional [51]. These are all of the homooligomeric receptors, except $P2X_6$, which does not function in homooligomeric form, and the rest are heterooligomers, formed from $P2X_1$-$P2X_6$ subunits. However, recently it has been reported that by *N*-glycosylation even the homomeric $P2X_6$ receptor could be rendered functional [52]. On the other hand, the $P2X_7$ receptor functions only in homooligomeric form and does not coassemble with other known P2X receptor subunits. P2X receptors are permeable to both monovalent (Na^+, K^+) and divalent (Ca^{2+}) cations and the activation of the receptor generates an inward current leading to the local depolarization of the cell membrane; in addition, the Ca^{2+} influx through the receptor-ion channel complex could directly

trigger transmitter release. Moreover, upon prolonged or repetitive agonist application certain P2X receptors, especially the $P2X_7$ receptor, display pore dilation which makes the channel permeable to high molecular weight cations up to 800 Da.

Basically P2X receptors are sensitive to ATP and to its various synthetic analogues but not to AMP and adenosine and the ligand binding profiles of homomeric P2X receptors are well established (for further information, see [50, 53]). On the other hand, less is known about the pharmacology of heteromeric receptors; among them, the pharmacological profile of $P2X_{2/3}$, $P2X_{2/6}$, $P2X_{1/2}$, $P2X_{1/4}$, $P2X_{1/5}$, and $P2X_{4/6}$ are described [54–59]. However, the expression pattern and the ligand binding profile of individual assemblies of P2X receptors are highly overlapping, often creating difficulties in the identification of the P2X receptor subunit composition of receptors expressed in native tissues. Moreover P2X receptor assemblies also share common ligand binding properties with certain members of the P2Y receptor family. Therefore, transgenic mice genetically deficient in individual P2X receptor subtypes are being increasingly used for P2X receptor identification.

The distribution of P2X receptors in neuronal structures

In situ hybridization studies with specific riboprobes, and immunocytochemical studies using antibodies raised against individual P2X receptor subunits, revealed that all seven P2X receptors are widely expressed in the nervous system. However, the expression of different receptor subunits show species-, region-, and cell type-specific distinct distribution [60]. Among the P2X receptors, $P2X_2$, $P2X_4$, and $P2X_6$ seem to be most abundantly expressed in the brain, whereas other subunits show more restricted localization [60–63]. The typical localization of the $P2X_2$ receptor is on nerve terminals of the brain and the periphery [61, 64, 65], although it also appears postsynaptically [62]. $P2X_1$ receptors had initially been suggested to be exclusively expressed on smooth muscle membrane consistent with its role in mediating fast synaptic transmission at the autonomic neuroeffector junction [60]. However, recent studies with more sensitive probes revealed that its expression is more widespread, i.e., it is also present on central and peripheral neurons [63, 66]. The same holds true for $P2X_3$ receptors, which are primarily associated with sensory pathways, but functional studies indicate that they are also expressed in other brain regions and autonomic pathways [67–69]. The $P2X_4$ receptor shows substantial expression in several brain areas such as the cerebral cortex, hippocampus, thalamus, and brainstem [70] and is associated with postsynaptic specialization of synaptic contacts [62]. $P2X_5$ subunits have the most restricted localization in the brain, although it shows strong representation in certain areas, e.g., the nucleus tractus solitarii (NTS) [71]. Finally, $P2X_7$ receptors are also expressed in the brain, especially in reactive microglia and astroglia [72] and immunoelectron microscopic studies revealed a widespread presynaptic expression of $P2X_7$ receptor immunoreactivity in a number of different brain areas, including the brainstem, hippocampus, cortex, spinal cord, and the skeletal neuromuscular junction [73–75]. However, two studies, using the same antibodies, demonstrated that $P2X_7$ receptor immunoreactivity is still observable in the brain of $P2X_7$ receptor knockout animals and thereby raised doubts on the validity of previous immunocytochemical observations [76, 77]. Therefore, available $P2X_7$ receptor antibodies either recognize a site, which is not the $P2X_7$ receptor, or, as a recent study indicates [78], a brain analogue of the $P2X_7$ receptor, which shares its antibody binding domain with the cloned $P2X_7$ receptor and partially retains its functionality in $P2X_7$ receptor knockout animals.

Structure, pharmacology, and signal transduction of P2Y receptors

P2Y receptors all belong to G protein-coupled receptors, having seven hydrophobic transmembrane domains, and possess their ATP binding site on the external side of TM3 and TM7 domains [79–82]. The P2Y receptor family has eight individual members, numbered $P2Y_1$, $P2Y_2$, $P2Y_4$, $P2Y_6$, $P2Y_{11}$, $P2Y_{12}$, $P2Y_{13}$, and $P2Y_{14}$. P2Y receptors are basically activated by adenine and uridine nucleotides, such as ATP, ADP, uridine diphosphate (UDP), and uridine triphosphate (UTP), but not by nucleosides and they are classified according to their sensitivity to purines and/or pyrimidines: $P2Y_{1,\ 12}$ and $P2Y_{13}$ are adenine nucleotide-preferring receptors; $P2Y_6$ is preferred by uridine nucleotides; $P2Y_{2,\ 4}$ and $P2Y_{11}$ are receptors with mixed selectivity; whereas $P2Y_{14}$ is activated by UDP-glucose, UDP-galactose, UDP-*N*-acetylglucosamine, and UDP-glucuronic acid [83]. Although a minority of P2Y receptor subtypes are incompletely characterized and the pharmacological profiles of individual P2Y receptors are partially overlapping, ligands are available which display some selectivity to certain subtypes of the P2Y receptor family [for further information see 84, 85]. Nevertheless, identification of individual P2Y receptors requires careful pharmacological analysis and the use of receptor knockout animals, if available, and exclusion of the involvement of adenosine receptors in the effect of nucleotides used as P2Y agonists, because they may be metabolized to adenosine (see, e.g., [45,

47]). In addition, the potential heteromerization of P2Y receptor subtypes with each other and with A_1 adenosine receptors [86] should also be taken into account when individual P2Y receptors are identified.

Whereas P2X receptors convey rapid changes in the neuronal excitability on the millisecond timescale, P2Y receptors act on a longer, second timescale, appropriate for the fine-tuning of synaptic transmission. As for the signal transduction pathways activated by various subtypes of P2Y receptors, $P2Y_1$, $P2Y_2$, $P2Y_4$, $P2Y_6$, and $P2Y_{11}$ receptors are coupled via $G_{q/11}$ proteins to stimulate phospholipase C, followed by increases in inositol phosphates and mobilization of Ca^{2+} from intracellular stores; in addition, the $P2Y_{11}$ receptor mediates an increase in adenyl cyclase activity [84]. On the other hand, $P2Y_{12}$, $P2Y_{13}$, and $P2Y_{14}$ receptors are coupled via $G_{i/o}$ proteins to inhibit adenyl cyclase activity followed by a decrease in intracellular cAMP levels [84]. The activation of G_i protein-coupled P2Y receptors leads to the voltage-dependent inhibition of N-type voltage-sensitive Ca^{2+} channels directly or indirectly and subsequent inhibition of neurotransmitter release [85]. The inhibition of voltage-sensitive Ca^{2+} currents has also been demonstrated for those P2Y receptors, which are coupled to the $G_{q/11}$ proteins [85]; however, this inhibition is voltage independent [85]. In addition, the $G_{i/o}$-coupled P2Y receptors are known to activate voltage-sensitive GIRK K^+ channels via direct interaction of Kir3 channel protein [85], which hyperpolarizes the neuronal membrane.

The distribution of P2Y receptors in neuronal structures

mRNA encoding all known P2Y receptors, i.e., $P2Y_1$, $P2Y_2$, $P2Y_4$, $P2Y_6$, $P2Y_{12}$, $P2Y_{13}$, and $P2Y_{14}$ are present in the brain [81, 87–89]. Although our knowledge of their cell-specific localization at the protein level is still incomplete, it appears that a number of them, such as $P2Y_1$, $P2Y_2$, and $P2Y_6$ receptors, are expressed both on neurons and astrocytes [90–96], whereas others are not exclusively, but predominantly localized to astrocytes ($P2Y_{13}$: [97] $P2Y_{14}$: [98]), oligodendrocytes ($P2Y_{12}$: [99]], or microglia ($P2Y_{12}$: [100]). P2Y receptor mRNA and protein can be detected in a number of different structures, including sympathetic and parasympathetic and sensory nerve terminals, basal ganglia, brainstem, cerebellum, cortex, hypothalamus, and hippocampus (for further references, see [85]). However, immunocytochemical data should be handled with caution due to the lack of verification of the specificity of many of the available antibodies. For detailed information on the distribution of individual P2Y receptor mRNAs and proteins, we refer to recent reviews on this particular topic [85, 101].

Modulation of neurotransmitter release by facilitatory P2 receptors

ACh

PNS

P2X receptors Since P2X receptors have relatively high Ca^{2+} permeability [102, 103], this property makes them capable of initiating neurotransmitter release by Ca^{2+} influx through the receptor-ion channel complex or facilitating Ca^{2+}-dependent neurotransmitter release, provided that they are located nearby the release sites (Table 1). The first report suggesting that P2 receptors are involved in the facilitatory modulation of neurotransmitter release stems from 1991 when we found that opposite to the well-known inhibitory action of adenosine, α,β-methylene ATP, a metabolically stable analogue of ATP, enhanced electrically evoked acetylcholine release from the myenteric plexus of guinea pig and facilitated the related contractile response [6]. This effect was not blocked by the antagonists of adenosine receptors, and therefore was proposed to be mediated by ATP-sensitive P2 receptors [6]. In the same time Fu and Poo observed that ATP potentiates the spontaneous secretion of acetylcholine from developing neuromuscular synapses in *Xenopus* cell culture by promoting Ca^{2+} influx through the plasma membrane. However, this effect was not recognized to be the result of P2 receptor activation [104]. Later on, P2 receptor-mediated facilitation of acetylcholine release was confirmed by electrophysiological recordings in chicken ciliary ganglion [105] and mouse motor nerve terminals [106]. Presynaptic P2X receptors, involved in the facilitation of acetylcholine release, have also been identified in developing and adult neuromuscular synapses of *Xenopus* [107] and rat [108]. Homomeric $P2X_7$ receptors are inserted into the membrane of mouse motor nerve terminals and their activation elicits vesicular exocytosis [74, 109]. However, there is no report about the presence of other subunit compositions of P2X receptors at the neuromuscular junction and it is also unclear whether such facilitatory receptors also exist on the terminals of central cholinergic neurons.

Monoamines (NA, serotonin, DA)

PNS

P2X receptors The presynaptic facilitatory action of ATP on noradrenergic transmission was described for the first time by Miyahara and Suzuki in rabbit ear artery [110]. It was followed by the demonstration of the facilitatory effect of ATP and its metabolically stable analogue

Table 1 Facilitatory modulation of neurotransmitter release in the PNS and CNS

Preparation	Measured effect	Proposed receptor	Reference
Acetylcholine			
Guinea pig ileum	NT quantification	P2	[6]
Chicken ciliary ganglion	Presynaptic current	P2X	[105]
Xenopus NMJ	sEPP/mEPP	P2	[104, 107]
Mouse NMJ	EPP/mEPP	P2	[106]
Mouse NMJ	Vesicular destaining, EPSC	$P2X_7$-like	[74, 109]
Rat NMJ	NT quantification	P2X	[108]
Noradrenaline			
Rabbit ear artery	EJP	P2	[110]
PC12 cells	NT quantification	P2	[111]
Guinea pig ileum	NT quantification	P2	[6]
Rat vas deferens	NT quantification	$P2X_1$, $P2X_3$, $P2X_{2/3}$	[113]
Guinea pig atrium	NT quantification	$P2X_3$, $P2X_{2/3}$	[114, 115, 118]
Human and porcine heart	NT quantification	P2X	[119]
Sympathetic neurons	NT quantification	$P2X_2$	[116]
LC neurons	AP discharge	P2X	[120]
Rat hippocampus	NT quantification	$P2X_1$, $P2X_3$	[68]
Serotonin			
Rat hippocampus	NT quantification	P2	[121]
Dopamine			
Rat striatum	NT quantification	P2Y	[122, 123]
Rat nucleus accumbens	NT quantification	P2	[124–128]
Glutamate			
Rat brainstem	mEPSC/NT quantification	$P2X_1$	[131, 157]
Rat NTS	EPSC	$P2X_3$, $P2X_{2/3}$	[129, 130, 132]
Rat hippocampus	NT quantification	$P2X_1$, $P2X_3$, $P2X_{2/3}$	[69]
Rat hippocampus	NT quantification	$P2X_7$	[75]
Mouse hippocampus	NT quantification	$P2X_7$	[137]
Rat hippocampus	EPSC	$P2X_2$	[133]
Rat hippocampus	EPSC	$P2X_7$	[134]
Rat hippocampal neurons	EPSC	P2	[135]
Rat cortical synaptosomes	NT quantification	$P2X_7$	[136]
Cultured astrocytes	NT quantification	$P2X_7$	[142]
Retinal Müller glial cells	NT uptake	$P2X_7$	[143]
Rat spinal cord	EPSC/mEPSC	$P2X_3$, $P2X_{1/5}$, $P2X_{4/6}$	[144–148]
Rat nucleus accumbens	NT quantification	P2	[149]
Rat medial habenula	EPSC	$P2Y_4$	[150]
Cultured astrocytes	NT quantification	$P2Y_1$	[151]
Cultured Schwann cells	NT quantification	P2	[152]
GABA			
Midbrain synaptosomes	NT quantification	$P2X_3$, dinucleotide R	[153]
Cultured dorsal horn neurons	IPSC	P2X	[154]
Cultured hippocampal cells	IPSC	P2	[156]
Cultured cortical cells	NT quantification	$P2X_7$	[155]
Rat brainstem	IPSC	$P2X_1$	[157]
Rat, mouse, and guinea pig hippocampus	NT quantification/IPSC	$P2X_7$ (indirect)	[75, 137, 158]
Cultured astrocytes	NT quantification	$P2X_7$	[159]
Rat hippocampus	IPSC	$P2Y_1$	[163, 206]

Table 1 (continued)

Preparation	Measured effect	Proposed receptor	Reference
Glycine			
Rat dorsal horn	IPSC	P2X	[161]
Rat trigeminal nucleus	sIPSC	P2X	[162]

AP action potential, *EJP* excitatory junction potential, *EPP* end plate potential, *EPSC* excitatory postsynaptic current, *IPSC* inhibitory postsynaptic current, *mEPP* miniature EPP, *mEPSC* miniature EPSC, *NMJ* neuromuscular junction, *NT* neurotransmitter, *sEPP* spontaneous EPP, *sIPSC* spontaneous IPSC

α,β-methylene ATP on [^{3}H]noradrenaline efflux in PC12 cells [111] and in the guinea pig ileum [6]. However, the knowledge on P2 receptors at that time did not allow the identification of P2 receptor subtypes involved in these effects. The issue has been reinvestigated and it was found that sympathetic nerve terminals are equipped with ionotropic P2X receptors, activation of which directly elicits or facilitates noradrenaline release elicited by nerve stimulation [1, 112–115] via a direct Ca^{2+} influx through the receptor-ion channel complex. The pharmacological phenotype of these receptors varies between species, between transmission sites of the sympathetic nervous system, and even between the somata and nerve terminals of an individual neuron. Thus, in cultured sympathetic neurons of the rat an α,β-methylene ATP-insensitive $P2X_2$-like receptor was identified [116], whereas in the guinea pig right atrium we found that α,β-methylene ATP stimulates noradrenaline outflow and the pharmacological profile of the underlying receptor was similar to that of $P2X_3$ or $P2X_2/P2X_3$ receptors, consistent with the expression of their mRNA in the sympathetic ganglia [115]. In another study the facilitatory P2X receptors involved in the modulation of noradrenaline outflow in the rat vas deferens were identified as $P2X_1$, $P2X_3$, or $P2X_2/P2X_3$ receptors [113]. In contrast, cultured mouse sympathetic nerve terminals do not seem to express facilitatory nucleotide-sensitive receptors [117]. Importantly, these receptors seem to be endogenously activated by ATP released in response to ongoing neuronal activity [115, 116] and by myocardial ischemia in the guinea pig [118], porcine, and human heart [119] and could contribute to ischemia-induced arrhythmia and ischemic heart dysfunction.

CNS

P2X receptors In the central nervous system, locus coeruleus (LC) neurons of the rat are equipped with ATP-sensitive P2X-like receptors, which facilitate the discharge of spontaneous action potentials [120]. Facilitatory P2X receptors have also been described in the noradrenergic axon terminals innervating the hippocampus, and the homomeric $P2X_1$ and $P2X_3$ receptors were identified as the most likely subunits responsible for this action [68].

P2Y receptors P2 receptors enhance the release of serotonin from the hippocampus [121] and that of dopamine from the striatum [122, 123], and the latter effects are thought to be mediated by P2Y receptors. However, the pre- or postsynaptic localization of receptors responsible for these effects were not clarified in these studies. The P2 receptor agonist 2-methyl-thio ATP releases dopamine from the nucleus accumbens through direct and indirect mechanisms [124–126] in vivo. Interestingly, P2 receptor activation-evoked dopamine release seems to play a role in the modulation of feeding behavior as P2 receptor antagonists inhibit feeding-induced dopamine release and concomitant behavioral changes after food deprivation [127, 128].

Excitatory amino acids (glutamate, aspartate)

CNS

P2X receptors In addition to ACh and monoamines, the release of excitatory amino acid transmitters is also modulated by presynaptic P2X receptors in the CNS, as demonstrated partly by neurochemical and partly by electrophysiological methods.

Activation of P2X receptors elicits glutamate release in the brainstem [129–132], hippocampus [69, 75, 133–135], and cortical synaptosomes [136]. As for the underlying receptor subunits involved in these effects, $P2X_1$ [69], $P2X_2$ [133], $P2X_3$, and $P2X_{2/3}$ receptors [69, 130] as well as $P2X_7$ [75, 132, 134, 136, 137] were identified. The involvement of $P2X_2$ receptors [133] and $P2X_7$ receptors [137] has been confirmed by the use of transgenic mice deficient in $P2X_2$ and $P2X_7$ receptors, respectively. Moreover the activation of $P2X_7$ receptors not only elicits glutamate release but also permits the activation of other ligand-gated ion channels on the nerve terminals, such as α7 nicotinic receptors, as demonstrated recently in rat cortical synaptosomes [136]. The activation of a $P2X_7$-like receptor promotes Ca^{2+} influx in cortical

synaptosomes [138] and in isolated midbrain synaptic terminals [139] and activates p38MAP kinase enzyme in the hippocampus [140]. This latter effect seems to participate in the effect of ATP to elicit glutamate release as it was sensitive to the inhibition by the specific p38MAP kinase inhibitor, SB203580 [140]. Nevertheless, the exact mechanism whereby the $P2X_7$ receptor and subsequent activation of p38MAP kinase enzyme leads to increased glutamate release awaits further investigation. In addition, it has been reported that the $P2X_7$ receptor agonist BzATP depresses synaptic transmission at the mossy fiber-CA3 synapse [141] in a p38MAPK-dependent way. However, more recently the participation of $P2X_7$ receptors in this latter effect has been disproved [76, 77]. In addition to nerve terminals, $P2X_7$ receptor activation also elicits glutamate release from cultured astrocytes [142] and inhibits the uptake of glutamate in Müller glial cells of the retina [143].

The activation of P2X receptors facilitates excitatory transmission in the spinal cord, releasing glutamate from primary afferent fibers terminating in lamina II [144–148] and lamina V [144]; these actions are mediated by $P2X_3$, $P2X_{1/5}$, and $P2X_{4/6}$ receptors, respectively. Finally, the ability of the P2 receptor ligand 2-methyl-thio ATP to release glutamate has also been demonstrated in vivo in the dopamine-depleted nucleus accumbens [149], although the underlying receptor subtype was not identified in this study.

P2Y receptors Interestingly, the activation of P2Y receptors is also implicated to elicit and potentiate glutamate release in the central nervous system. In the medial habenula nucleus UDP and UTP increase presynaptic release probability and elicit a non-Hebbian-type long-term potentiation of excitatory transmission, an effect probably mediated by $P2Y_4$ receptors [150]. In addition, the activation of $P2Y_1$ receptors elicits vesicular glutamate release from astrocytes [151] and from cultured Schwann cells [152].

Inhibitory amino acids (GABA, glycine)

CNS

P2X receptors ATP or P1,P5-di(adenosine-5′) pentaphosphate (Ap_5A) elicits an increase in the intrasynaptosomal calcium and induces subsequent GABA release in midbrain GABAergic synaptosomes via activation of $P2X_3$ and a dinucleotide receptor [153]. The regulation of GABA release by P2X receptors has also been reported in the spinal cord [154], cultured cortical [155] and hippocampal [156] cells, and the brainstem, where the excitatory and inhibitory synaptic transmission is facilitated via $P2X_3$ and $P2X_1$ receptors, respectively [157]. In addition to direct modulation of glutamate release, $P2X_7$ receptor activation also releases GABA from the hippocampus through the activation on non-NMDA-type glutamate receptors [75]. This effect is absent in mice genetically deficient in $P2X_7$ receptors [137] and mediated by the sodium-dependent reversal of the GABA transporter [75]. P2X receptor-mediated, TTX-sensitive GABA release has been implicated in the accelerated recovery of guinea pig hippocampal slices from a hypoxic/hypoglycemic insult [158]. The activation of $P2X_7$ receptors also releases GABA from cultured RBA astrocytes, however, with a different mechanism, by participation of the HCO_3^-/Cl^- exchanger [159]. On the other hand, no evidence was found for a direct facilitation of GABA release by P2 receptors in the hippocampal nerve terminal preparation [160]. Nevertheless, the release of another inhibitory transmitter, glycine, is augmented by P2X receptor activation in the dorsal horn [161] and in the brainstem trigeminal nucleus [162].

P2Y receptors In addition to P2X receptors, activation of $P2Y_1$ receptors leads to an increase of the inhibitory postsynaptic current (IPSC) frequency in an acute hippocampal slice in a manner dependent on action potential generation, indicating that this effect is related to the activation of receptors present on the somata/dendrites of hippocampal interneurons [163].

Modulation of neurotransmitter release by inhibitory P2 receptors

In addition to facilitatory modulation, P2 receptors are also involved in the inhibitory modulation of the release of various transmitters and the metabotropic P2Y receptors are thought to play a major role in these actions (Table 2).

ACh

PNS

It has been known for a long time that ATP is involved in the inhibitory presynaptic modulation of cholinergic transmission [164]. However, it has been the subject of a long-standing debate whether ATP itself is responsible for this effect or its degradation product adenosine [165–167], whereas an alternative was that ATP itself acts on adenosine receptors [168] or activates a putative P3 receptor bearing pharmacological features of both P1 and P2 receptors [169]. A more definitive proof for the involvement of P2 receptors in the inhibition of acetylcholine release was obtained later in the frog neuromuscular junction [170], rat submandibular ganglia [171], and rabbit retina [172]. Presynaptic P2Y

Table 2 Inhibitory modulation of neurotransmitter release in the PNS and CNS

Preparation	Measured effect	Proposed receptor	Reference
Acetylcholine			
Frog ganglion	EPSC	P2	[165]
Guinea pig ileum	NT quantification	P2	[164, 166, 167]
Ileal synaptosomes	NT quantification	P1	[168]
Guinea pig submucosal neurons	EJP	P3	[169]
Frog NMJ	EPP	P2	[170]
Rat submandibular ganglion	EPSC	P2	[171]
Rabbit retina	NT quantification	P2	[172]
Mouse NMJ	sEPP	P2Y	[173]
Noradrenaline			
Mouse vas deferens	NT quantification	P2Y-like	[5, 174, 181, 182]
Rat vas deferens	NT quantification	P3	[178]
Rat vas deferens	NT quantification	P2Y	[181]
Rat vas deferens	NT quantification	$P2Y_{12}$, $P2Y_{13}$	[113]
Guinea pig vas deferens	NT quantification	P2Y-like	[179]
Guinea pig saphenous artery	EJP	P2	[175]
Rat caudal artery	NT quantification	P3, P2Y	[176, 177, 180]
Rat atrium	NT quantification	P2Y-like	183
Rat iris	NT quantification	P2Y-like	[184]
Rat kidney	NT quantification	P2	[185]
Rat pancreas	NT quantification	P2	[186]
Chick sympathetic neurons	NT quantification	P2, $P2Y_{12}$	[187, 188, 189]
Bovine chromaffin cells	NT quantification	P2Y12	[190, 194]
Rat cortex	NT quantification	P2Y	[195]
Rat hippocampus	NT quantification	P2Y	[196]
Serotonin			
Rat cortex	NT quantification	P2	[197]
Dopamine			
Rat striatum	NT quantification	P2	[198]
Glutamate			
Rat cortex	EPSC	P2	[199]
Rat hippocampus	EPSC	P2Y	[200, but see 201]
Rat spinal cord	Polysynaptic EPSP	P2Y	[204]
Hippocampal slice culture	EPSC	P2Y	[205]

EJP excitatory junction potential, *EPP* end plate potential, *EPSC* excitatory postsynaptic current, *EPSP* excitatory postsynaptic potential, *NMJ* neuromuscular junction, *NT* neurotransmitter, *SEPP* spontaneous EPP

receptors responsible for the inhibition of spontaneous acetylcholine release were recently identified at the mouse neuromuscular junction [173]. In this study the underlying subcellular mechanism of the inhibition of acetylcholine release was also explored: the activation of P2Y receptors is coupled to $G_{i/o}$ proteins and modulates presynaptic Ca^{2+} channels related to tonic secretion of acetylcholine [173].

CNS

Inhibitory P2 receptors involved in the modulation of ACh release have been demonstrated in rat cerebral cortex [47]. By contrast, in the hippocampus, ATP primarily inhibits acetylcholine release through its breakdown to adenosine and subsequent action on A_1 adenosine receptors [47].

Monoamines (NA, serotonin, DA)

PNS

The presence of nucleotide-sensitive inhibitory P2 receptors on postganglionic sympathetic neurons was recognized relatively early [5, 174–179], although initially these receptors were qualified as P2Y-like [5] or as putative

P3 receptors, which are "hybrid" receptors between P1 and P2 receptors and sensitive to adenine nucleotides but also to theophylline derivatives [176–178]. These receptors have been described and characterized in sympathetic nerves innervating the rat caudal artery [176, 177, 180], guinea pig saphenous artery [175], vas deferens [5, 178, 179, 181, 182], atrium [183], iris [184], kidney [185], and pancreas [186] as well as in cultured sympathetic neurons [187, 188]. As for subtype-specific identification, Queiroz et al. [113] identified presynaptic inhibitory nucleotide receptors on the noradrenergic axon terminals of the rat vas deferens as $P2Y_{12}$ and/or $P2Y_{13}$ receptors, whereas on cultured sympathetic neurons [189] and bovine adrenal chromaffin cells [190] only $P2Y_{12}$ receptors have been identified. Interestingly, it appears that mouse sympathetic neurons [191] and noradrenergic nerves innervating the rat adrenal cortex [192] do not express an inhibitory P2 receptor. The mechanism of P2Y receptor-mediated inhibition of noradrenaline release has also been explored in several studies: the activation of P2Y receptors inhibits voltage-dependent Ca^{2+} influx and thereby limits the Ca^{2+}-dependent vesicular exocytosis and subsequent efflux of noradrenaline to the extracellular space [189, 193, 194].

CNS

Similar inhibitory P2Y receptors have also been reported in the CNS in the rat brain cortex [195] and hippocampus [196]; however P2Y receptor subtypes involved were not identified in these early studies.

In the CNS, ATP inhibits the release of serotonin [197] and dopamine [198] via activation of metabotropic P2 receptors.

Excitatory amino acids (glutamate, aspartate)

CNS

ATP and its metabolically stable analogue ATP-γ-S inhibits depolarization-evoked glutamate release from rat brain cortex slices [199] and inhibits glutamatergic EPSPs in hippocampal CA1 synapses [200]. Although the underlying receptor was sensitive to theophylline derivatives, the authors proposed that ATP acted through a putative pertussis toxin-sensitive P2Y receptor. However, this hypothesis was challenged by showing the rapid and highly effective hydrolysis of ATP in the hippocampal slices [45, 46] and by the demonstration of the complete absence of nucleotide-mediated modulation of excitatory synaptic transmission in the hippocampi of A_1 receptor$^{-/-}$ mice [201]. In a recent study Rodrigues et al. demonstrated that single hippocampal pyramidal neurons do express $P2Y_1$, $P2Y_2$, and $P2Y_4$ receptors, and the release of glutamate, measured by a neurochemical technique, is inhibited by these receptors [69]. The discrepancy between the observations obtained in electrophysiological and neurochemical studies might be explained by the fact that in the former, individual synapses, whereas in the latter, glutamate release from all synapses of the hippocampal slice were simultaneously investigated. Nevertheless, the exact conditions under which the activation of P2Y receptors by endogenous ligands gain significance remain to be identified.

Functional data suggest that the release of glutamate in the spinal cord is modulated by inhibitory P2Y receptors. The activation of P2Y receptors causes blockade of the N-type calcium channels in dorsal root ganglion (DRG) cells [202], and this effect may decrease the release of glutamate from DRG terminals in the spinal cord and thereby partly counterbalance the algogenic effect of ATP [203, 204]. This assumption is supported by the findings that the $P2Y_{1/12/13}$ receptor agonist ADP-β-S inhibits polysynaptic, but not monosynaptic excitatory postsynaptic potentials in the hemisected spinal cord and exhibits antinociceptive potential in the tail flick test [204].

Recent studies revealed that modulators released from glial cells also regulate neurotransmitter release from nearby nerve terminals by the activation of P2 receptors. Hence mechanical stimulation of astrocytes in hippocampal cell culture leads to the generation of Ca^{2+} waves in astrocytes, which spread by the release of ATP and subsequent activation of P2 receptors and lead to the depression of excitatory synaptic transmission between neurons [205]. This glia-driven synaptic depression is partly mediated by ATP itself acting on P2Y receptors and partly by adenosine acting on A_1 adenosine receptors [205]. A similar mechanism has also been demonstrated in intact hippocampal slices, where ATP released from neurons and astrocytes acts on $P2Y_1$ receptors to excite interneurons, resulting in increased synaptic inhibition within intact hippocampal circuits [206]. On the other hand, to our knowledge there is no information regarding whether the release of GABA and other inhibitory amino acids is subject to modulation via inhibitory P2 receptors.

Potential therapeutic utilization of P2 receptors involved in the regulation of neurotransmitter release

P2X and P2Y receptors involved in the regulation of neurotransmitter release offer attractive, although not yet utilized sites for pharmacotherapy in nervous system diseases. For instance, facilitatory P2X receptors present on axon terminals could be activated not only during normal neuronal activity, but also during pathological situations, when cellular damage provides an ATP-rich extracellular milieu nearby the receptors. Thus, P2X

receptors present on the sympathetic nerve terminals supplying the heart seem to be endogenously activated by ATP by myocardial ischemia [118, 119] and could contribute to ischemia-induced arrhythmia and ischemic heart dysfunction. Therefore, inhibition of these facilitatory P2X receptors might have therapeutic relevance in ischemic heart disease. The pathological activation of CNS P2X receptors, regulating the release of glutamate during ischemic-like conditions, was also recently described [207]. Increased activation of P2X receptors could contribute to ischemia-evoked glutamate release and thereby to glutamatergic excitotoxicity and resultant neuronal death; therefore, inhibition of these receptors could be a promising approach to treat ischemia-related neurodegenerative diseases. An analogous mechanism could play a role in the spinal cord during the sensitization process leading to various forms of sensory neuropathy; therefore, attenuation of increased glutamate release from the central terminals of primary sensory neurons by the inhibition of P2X receptors is a potential pathway which could be utilized in neuropathic pain. Since inhibitory P2Y receptors are frequently coexpressed on nerve terminals that are equipped with P2X receptors, activation of P2Y receptors could have a similar effect as the inhibition of P2X receptors. Therefore P2Y receptor agonists might also have therapeutic value in the areas described above. However, one should bear in mind that different subtypes of P2X and P2Y receptors affect various other aspects of physiological and pathological neuronal functions, which could also modify their potential.

Conclusion

In conclusion, substantial advances have been obtained in the identification and characterization of neurotransmitter release modulating P2 receptors in recent years. It appears that almost all major neurotransmitters of the nervous system are subject to neuromodulation by nucleotide-sensitive P2 receptors. Although there are exceptions to this rule, in general the release of different transmitters is subject to a dual modulation similar to modulation of other transmitters of the CNS and PNS: facilitatory modulation is conveyed by ionotropic P2X receptors, whereas inhibitory modulation is mediated by G protein-coupled metabotropic P2Y receptors. Amongst P2X receptors, $P2X_1$, $P2X_2$, $P2X_3$, $P2X_{2/3}$, $P2X_{1/5}$, $P2X_{4/6}$, and $P2X_7$ receptors were identified to be responsible for facilitatory modulation in different areas of the CNS and PNS. In addition, P2Y receptors ($P2Y_1$, $P2Y_4$) could also mediate facilitation of transmitter release in certain areas. Inhibitory modulation of neurotransmitter release is mediated by $P2Y_{12}$ and $P2Y_{13}$ receptors; however, individual P2Y receptor subtypes involved in these interactions are far from fully explored yet. It appears that not only neuronal, but also glia-derived ATP play a role in the modulation of neurotransmitter release. The intensity of P2 receptor-mediated modulation, the balance between the facilitatory and inhibitory modulation and the participating individual receptor subtypes, however, varies between individual transmission sites, depending on the expression pattern of P2 receptors and the factors determining the nucleotide levels in the vicinity of release of modulatory P2 receptors. Therefore, further progress is necessary in order to obtain a precise mapping of P2 receptor-mediated modulation of neurotransmitter release. The in vivo relevance of most of the in vitro observations on presynaptic P2 receptors awaits further investigation. Finally, physiological and pathological situations where presynaptic P2 receptors become endogenously activated by released nucleotides need to be identified.

Acknowledgments This study was supported by a grant from the Hungarian Research and Development Fund (NKFP1A/002/2004).

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