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INVITED REVIEW

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Functions of neuronal P2Y receptors

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Abstract Within the last 15 years, at least eight different G protein-coupled nucleotide receptors, i.e., P2Y receptors, have been characterized by molecular means. While ionotropic P2X receptors are mainly involved in fast synaptic neurotransmission, P2Y receptors rather mediate slower neuromodulatory effects. This P2Y receptor-dependent neuromodulation relies on changes in synaptic transmission via either pre- or postsynaptic sites of action. At both sites, the regulation of voltage-gated or transmitter-gated ion channels via G protein-linked signaling cascades has been identified as the predominant underlying mechanisms. In addition, neuronal P2Y receptors have been found to be involved in neurotoxic and neurotrophic effects of extracellular adenosine 5-triphosphate. This review provides an overview of the most prominent actions mediated by neuronal P2Y receptors and describes the signaling cascades involved.

Keywords G proteins · P2Y receptor · Voltage-gated Ca^{2+} channel · Voltage-gated K^{+} channel · Synaptic transmission

Introduction

Adenine and uridine nucleotides are present in and released from all different types of cells including neurons and glia cells [9]. Extracellular nucleotides bind to a family of membrane-bound receptors that are named P2 receptors [30] and are converted to other nucleotides or degraded towards nucleosides by a family of ectoenzymes [105]. There are two principal subfamilies of P2 receptors which can be discerned from each other by structural and functional criteria: P2X-receptors are ligand-gated ion channels composed of three subunits, each having two transmembrane domains [145, 156], and P2Y receptors which belong to the superfamily of G protein-coupled receptors (GPCRs) with seven transmembrane domains [2, 12, 146]. Up to now, seven mammalian P2X receptor subunits (P2X1-7) [145, 184] and eight mammalian P2Y receptor subtypes ($P2Y_{1,2,4,6,11,12,13,14}$) [9, 43, 146, 156] have been characterized by molecular means. In addition, receptors for cysteinyl leukotrienes were reported to mediate actions of extracellular nucleotides, which indicates that some GPCRs may display multimodal ligand specificities [124, 125]. Furthermore, a considerable number of reports have described effects of nucleotides that were obviously mediated by receptors, but the receptors involved, such as the receptor for diadenosine-polyphosphates operating in the brain [128], have not been cloned. This review deals only with genuine P2Y receptors with known molecular correlates.

Originally, signaling via nucleotides was proposed to occur in the transmission between neurons of the autonomic nervous system and smooth muscle cells [29]. Nevertheless, in virtually, all peripheral tissues, even in those hardly innervated by the autonomic nervous system, extracellular nucleotides play important roles in a large number of physiological processes [156]. Accordingly, P2 receptors are widely distributed in a large variety of tissues also including the nervous system, and this applies to P2Y receptors even more than to P2X receptors.

Within the central and peripheral nervous system, both types of receptors display a widespread distribution and subserve a variety of functions in both, glial and neuronal cells. Astrocytes, for example, express some P2X and a larger number of P2Y receptors, activation of which first triggers increases in intracellular Ca^{2+} and then leads to long-term changes such as proliferation or cell death [55, 140, 191]. The functions of oligodendrocytes [6] and microglial cells [93] are also controlled by nucleotides acting at P2X and P2Y receptors. Likewise, neurons express both classes of P2 receptors: P2X receptors are mainly involved in fast synaptic transmission, whereas

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P2Y receptors rather mediate slow changes of synaptic transmission and neuronal excitability [31, 91]. In addition, P2 receptors may mediate long-term trophic or toxic effects of nucleotides, such as differentiation, neurite growth, survival, or cell death [42]. This review will only deal with neuronal P2 receptors and will disregard the receptors expressed in glial cells.

While ionotropic receptors are most commonly involved in fast neurotransmission, metabotropic receptors are rather involved in neuromodulation: typically, the activation of heptahelical transmembrane receptors elicits changes in neuronal excitability via heterotrimeric G proteins [95]. Accordingly, neuronal P2X receptors frequently mediate synaptic transmission in reponse to adenosine triphosphate (ATP) released from presynaptic nerve terminals by vesicle exocytosis [98]. P2Y receptors, however, may be activated not only by ATP, but also by other naturally occurring nucleotides or nucleotide-sugars, such as adenosine diphosphate (ADP), uridine triphosphate (UTP), uridine diphosphate (UDP), and UDP-glucose [1, 94, 166]. Hence, these latter receptors are not only the direct target of ATP; the nucleotide stored in vesicles at the highest concentrations [201], but also of other nucleotides and nucleotide degradation products. Therefore, the activation and functions of neuronal P2Y receptors depend not only on the release of ATP, but also on the presence of ATP degrading enzymes [135]. Whether activated by endogenously released nucleotides or exogenous agonists, neuronal P2Y receptors mediate neuromodulatory changes of neuronal excitability and/or synaptic transmission and control neurodegeneration and regeneration. Below, the most recent findings concerning these three types of effects of P2Y receptor activation in the nervous system are summarized.

Pharmacological characteristics and signaling mechanisms of P2Y receptors

A considerable number of heptahelical receptors sensitive to extracellular nucleotides have been cloned from various species. In accordance with the structural classification of P2 receptors, they were categorized as P2Y receptors and numbered in chronologic order. This led to the description of $P2Y_1$ through $P2Y_{15}$ receptors [92]. However, some of the receptors provided with P2Y receptor numbers were subsequently identified as species homologues of other P2Y receptors or as members of other families of G protein-coupled receptors [124, 125]. Hence, only eight different mammalian subtypes are currently viewed as members of the P2Y receptor family, namely, $P2Y_{1, 2, 4, 6, 11, 12, 13,}$ and $P2Y_{14}$. Below, the pharmacological characteristics of these P2Y receptors are shortly summarized. For more details, the reader is referred to excellent reviews that focus on this topic [3, 94, 156, 186].

At $P2Y_1$ receptors of most species, the typical rank order of agonist potency is 2-MeSADP>2-MeSATP>ADP>ATP with uridine nucleotides being inactive. At $P2Y_2$ receptors, ATP and UTP are equipotent agonists, and ADP, UDP, or 2-methylthio derivatives have weak or no activity [186]. $P2Y_4$ receptors are activated by UTP, and the rat and mouse receptors are also activated by ATP, whereas the human receptors are antagonized by ATP [97]. At $P2Y_6$ receptors, UDP is the most potent agonist and ADP, ATP or UTP are, if at all, only weak agonists [186]. Human $P2Y_{11}$ receptors display a rank order of agonist potency of ATP>2-MeSATP>ADP, and the observed agonistic activity of UTP depends on the signaling cascade that is activated by the receptor [192]. The nucleotide selectivity of canine $P2Y_{11}$ receptors is 2-MeSATP>ADP>ATP [154]. At $P2Y_{12}$ receptors, 2-MeSADP is much more potent an agonist than ADP, and the efficacy of ATP is species-dependent with high intrinsic activity at rat, but not at human, receptors [16, 172]. $P2Y_{13}$ receptors are activated by 2-MeSADP, ADP, and ATP, but the rank order of agonist potency is different for human, murine, and rat receptors [66, 121, 199]. The $P2Y_{14}$ receptor is sensitive towards various UDP sugars, but not towards adenine or uridine nucleotides [1, 36].

In light of the agonist profiles mentioned above, P2Y receptors can be categorized as receptors for purines ($P2Y_{1, 11, 12, 13}$), pyrimidines ($P2Y_{6, 14}$), or both families of nucleotides ($P2Y_{2, 4}$). Furthermore, these receptors can be classified as receptors preferring nucleoside tri- ($P2Y_{2, 4, 11}$) or diphosphates ($P2Y_{1, 6, 12, 13, 14}$). This latter subdivision is particularly important from a physiological point of view: extracellular nucleotides are released from virtually all cells and rapidly converted by ectoenzymes [105]. This interconversion between extracellular nucleotides is also a factor that needs to be kept in mind when P2Y receptors are characterized by agonistic nucleotides. For instance, the triphosphate-selectivity of $P2Y_2$ and $_4$ receptors can only be shown when the conversion of nucleoside diphosphates towards triphosphates is prevented [141]. In light of these experimental limitations with endogenous and exogenous agonistic nucleotides, the characterization of P2Y receptors should rather rely on the use of specific antagonists. A large number of compounds have been reported to block P2Y receptors, but only a few of them show sufficient selectivity and can be used to differentiate between various receptor subtypes.

The most widely used P2 receptor antagonists, suramin and reactive blue 2, block not only several P2Y receptor subtypes [186], but also P2X receptors and even unrelated proteins, such as NMDA receptors [150] and anion channels [67]. Other P2Y receptor antagonists, however, are more selective. For instance, adenosine-2′-phosphate-5′-phosphate (A2P5P) and adenosine-3′-phosphate-5′-phosphate (A3P5P) are partial agonists with low efficacy at $P2Y_1$ receptors [25]. Derivatives thereof, such as N^6-methyldeoxyadenosine 3′,5′-biphosphate (MRS 2179) or 2-chloro-N^6-methyldeoxyadenosine 3′,5′-biphosphate (MRS 2216) are selective and competitive antagonists at $P2Y_1$ receptors with nanomolar affinity [139]. The $P2Y_{12}$ receptor has been identified as the target of metabolites of the well-known antithrombotic drugs ticlopidine and clopidogrel [81]. ATP derivatives, such as cangrelor (AR-C69931MX), are also antagonists with high affinity at this receptor subtype and were developed for clinical use in

patients with acute coronary syndromes [181]. Unfortunately, this latter agent is not absolutely selective for $P2Y_{12}$, but also blocks $P2Y_{13}$ receptors. However, at $P2Y_{12}$, this agent is a competitive, and at $P2Y_{13}$, a noncompetitive antagonist [121]. For $P2Y_6$ receptors, selective antagonists with nanomolar affinities, such as 1,4-*di*-[(3-isothiocyanato phenyl)-thioureido]butane (MRS 2578), have also been developed [116].

After heterologous expression in nonneuronal cells, all P2Y receptor subtypes were found to mediate increases in inositol phosphates (IPs) or in intracellular Ca^{2+}; thus, indicating that they are coupled to phospholipase C (PLC) [137, 156, 198]. With $P2Y_1$, $_6$ and $_{11}$ receptors, the receptor-mediated increases in IPs did not involve pertussis toxin-sensitive G proteins, but with $P2Y_2$ and $P2Y_4$ receptors, these IP increases were reduced by this bacterial

Table 1 Distribution of P2Y receptors in the nervous system

Types of neurons	$P2Y_1$	$P2Y_2$	$P2Y_4$	$P2Y_6$	$P2Y_{11}$	$P2Y_{12}$	$P2Y_{13}$
Sympathetic	R[32,183] F[32]	R[32,144,183] F[15,144]	R[144] F[15,144]	R[32,144,183] F[15,32,143,144,183]		R[106] F[106]	R[106]
Parasympathetic	P[162,170]	R[111] P[162] F[48,111]	R[111] P[162]	P[162]		P[162]	
Sensory	R[132,161,163] P[63,71,161,163] F[63,71,161]	R[129,133,163] P[137,161] F[129,137,167,197,202]	R[163] P[15,161,163]	R[163]			
Enteric	F[83,117]	P[195]		P[196]		P[196]	
Central							
Amygdala	P[99]			R[131]	R[131]	R[81]	
Basal ganglia	R[131] P[130,170]	R[131]	R[131]	R[131]	R[131]		R[37,66]
Brain stem	P[63]						
Cerebellum	R[8,79] P[8,82,132] F[79,164,165]	R[8]	R[8,79,131] P[79]	R[8,79]	R[131]	R[79]	R[37]
Corpus callosum	R[32]					R[47, 81]	R[37]
Cortex	R[32,14,72] P[82,130] F[115,193]	F[193]	R[14]	R[14]		R[168]	R[66]
Globus pallidus	R[131] P[130]			R[131]	R[131]		
Hippocampus	R[148,160] P[78,82,99,130,131,132,160] F[24,164]	R[160] P[78,160]	R[160] P[160]	R[160] P[160]	R[191,160] P[160]	R[81,160,168] P[160]	R[37]
Hypothalamus	R[131] P[82,99]		R[131]		R[131]		
Medial habenula	P[132]	P[153]					
Midbrain	P[82,130]						
Substantia nigra					R[131]	R[81]	R[37]
Subthalamus	P[130]						
Thalamus			R[131]		R[131]	R[81]	R[37]
VTA	P[102] F[102]						

The expression of P2Y receptors was evidenced by the determination of RNA (R), protein (P), and/or functional responses (F)

toxin to various degrees [156]. When $P2Y_{12,13}$, and $P2Y_{14}$ receptors were activated, increases in IPs were only detected when the receptors were coexpressed together with either $G\alpha_{16}$ or chimaeric G protein α subunits, and the actions mediated by these receptors were pertussis toxin-sensitive and thus mediated by inhibitory G proteins [36, 37, 198]. $P2Y_{11}$ receptors mediate increases in cyclic AMP in addition to the rises in IPs [38], and the coupling of this receptor subtype to different effector systems displays different agonist sensitivities [192]. $P2Y_{12}$ and $P2Y_{13}$ receptors mediate a pertussis toxin-sensitive inhibition of adenylyl cyclase [37, 81], and in pertussis toxin-treated cells, $P2Y_{13}$ mediates a stimulation of adenylyl cyclase [37].

Distribution of P2Y receptors in the nervous system

Most of the known subtypes of P2Y receptors are expressed in the central nervous system. Quantitative reverse transcriptase polymerase chain reaction (RT-PCR) revealed that $P2Y_1$ and $P2Y_{11}$ mRNA was present in the human brain in large quantities when compared with other tissues, but only low to moderate levels of $P2Y_2$, $P2Y_4$, and $P2Y_6$ were detectable [131]. In immunohistochemical stainings of human brain slices, a striking neuronal localization of $P2Y_1$ receptors was confirmed [130]. In contrast, in-situ hybridizations of human [81] and rat [168] brain sections revealed a mainly glial localization of the $P2Y_{12}$ receptor. An RT-PCR analysis detected $P2Y_{13}$ mRNA in various regions of the human brain, such as cerebellum, hippocampus, substantia nigra, and thalamus [37].

In the peripheral nervous system, mRNA for all P2Y receptor subtypes except $P2Y_{11}$ and $P2Y_{14}$ has been found in sympathetic neurons [106, 144, 183]. Sensory neurons, in contrast, were shown to express $P2Y_{1, 2, 4}$, and $P2Y_6$ [163]. In the intramural parasympathetic ganglia of the cat urinary bladder, the presence of $P2Y_{1, 2, 4, 6}$, and $P2Y_{12}$ was revealed by immunohistochemistry [162]. In the enteric nervous system of guinea pigs, evidence for the expression of $P2Y_1$ [83], $P2Y_2$ [195], $P2Y_6$, and $P2Y_{12}$ [196] receptors has been obtained. However, there is no evidence for a neuronal localization of $P2Y_{14}$, and the respective mRNA was only found in rat cortical astrocytes [65], where UDP-glucose also elicited a rise in intracellular Ca^{2+}. Further details about the distribution of P2Y receptors in the central and peripheral nervous system are given in Table 1.

Functions of P2Y receptors in neurons

Many neuronal functions are similar or even identical to those of other cells, but there is one fundamental difference: the principal tasks of neurons are to receive, modify, and transmit messages. Whether this flow of information occurs intracellularly within one neuron or extracellularly between different neurons, it always depends on electrical activity provided by ligand- and voltage-gated ion channels. Accordingly, changes in the responsiveness of a neuron are most frequently brought about by alterations in the opening and closure of ion channels, and such effects are in most instances mediated by heptahelical transmembrane receptors linked to G proteins [95]. Therefore, this review first deals with the modulation of neuronal ion channels via P2Y receptors. Apart from changes in the intrinsic electrical properties of a neuron, the major consequences of modified channel gating are alterations in synaptic transmission. Hence, a second focus of P2Y receptor functions described in this study is the pre- and postsynaptic modulation of synaptic transmission via P2Y receptors. Finally, P2Y receptors have been found to mediate trophic as well as degenerative effects of nucleotides on neurons.

Regulation of ion channels via P2Y receptors

P2Y receptors have been found to control a large variety of neuronal ion channels including voltage-activated Ca^{2+} and K^+ channels as well as transmitter-gated ion channels.

Ca^{2+} channels

Voltage-activated Ca^{2+} channels are classified by the genes encoding the pore forming α_1 subunits. One can discern between three subfamilies termed Ca_V1 to Ca_V3. Members of each of these families contribute to voltage-gated Ca^{2+} currents in neurons. Ca_V1-containing channels mediate L-type currents, whereas those containing $Ca_V2.1$ to $Ca_V2.3$ mediate P/Q-, N-, and R-type currents. Channels with Ca_V3 subunits mediate T-type Ca^{2+} currents [33]. Channels providing N- and P/Q-type currents are typically involved in excitation secretion coupling in nerve terminals. The other channels, in contrast, are primarily found at somatodendritic regions [33]. Modulation via G protein-coupled receptors has been described for a huge number of neurotransmitters and for all types of voltage-gated Ca^{2+} currents [51, 52, 80, 86]. L-type currents are either enhanced or inhibited, and these effects are mostly mediated by diffusible second messengers and protein kinases [51, 52]. In contrast, N and P/Q-type currents are most frequently inhibited via GPCRs, and this inhibition is generally independent of diffusible second messengers and protein kinases [80, 86], even though there are some exceptions to this rule [19, 48]. The pathway excluding diffusible second messengers and protein kinases is membrane-delimited and leads to a voltage-dependent inhibition of the currents, as the inhibition is attenuated by large depolarizations. This type of inhibition is most commonly abolished by pertussis toxin [80], and is based on a direct interaction between G protein $\beta\gamma$ subunits and Ca^{2+} channel proteins [52, 86]. Pathways involving the synthesis of diffusible second messengers most commonly

lead to a voltage-independent reduction of Ca^{2+} currents and have been shown to involve α subunits of the $G_{q/11}$ protein family [76, 96] and a phospholipase Cβ-dependent depletion of membrane phosphatidylinositol 4,5-bisphosphate (PIP_2) [69, 107].

The first evidence for a regulation of voltage-activated Ca^{2+} channels via P2Y receptors was obtained in bovine adrenal chromaffin cells. There, ATP and ADP caused a pertussis toxin-sensitive reduction of current amplitudes [49]. Later on, this effect was reported to be voltage-dependent and sensitive towards reactive blue 2, and to involve an inhibition of N-and P/Q-type calcium channels [41, 70, 152]. Likewise, in rat adrenal chromaffin cells ATP also inhibited voltage-gated Ca^{2+} currents in a pertussis toxin-sensitive manner and this effect was again antagonized by reactive blue 2 [110]. An ATP-induced inhibition of Ca^{2+} currents was also observed in frog sympathetic neurons [54]. In NG108-15 mouse neuroblastoma × rat glioma cells, not only adenine nucleotides, but also UTP and UDP inhibited N-type as well as L-type Ca^{2+} channels [56], and the uridine nucleotides were more potent than the adenine nucleotides. The N-type, but not the L-type, channel inhibition was pertussis toxin-sensitive, but it remained unknown whether these two effects were mediated by two different receptor subtypes or by a single receptor coupled to more than one G protein [56].

In several other cases, the nucleotide receptors mediating an inhibition of neuronal Ca^{2+} channels were characterized in more detail (Fig. 1). In PC12 cells, for instance, adenosine nucleotides were reported to inhibit voltage-activated Ca^{2+} channels via $P2Y_{12}$ receptors [103, 104] in a

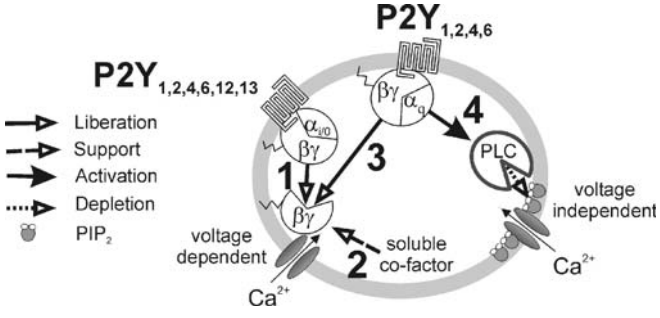

Fig. 1 Mechanisms underlying the regulation of voltage-activated Ca2+ channels via P2Y receptors. P2Y nucleotide receptors may use at least four different pathways to modulate the functions of neuronal Ca^{2+} channels: (1) Activation of P2Y receptors coupled to pertussis toxin-sensitive $G_{i/o}$ proteins sets βγ subunits free which directly interact with pore-forming Ca^{2+} channel proteins. This interaction is voltage-dependent (i.e., attenuated by large depolarizations), but generally independent of additional enzymes or second messengers. (2) However, in some cases [e.g. 60], this mechanism may also require a soluble cofactor in addition to the membrane-associated G proteins. (3) Some P2Y receptors may also mediate such a voltage-dependent inhibition of Ca^{2+} currents via pertussis toxin-insensitive G proteins [62]. (4) Activation of P2Y receptors linked to pertussis toxin-insensitive $G_{q/11}$ proteins initiates a signal cascade that involves diffusible second messengers and mediates a voltage-independent inhibition of Ca^{2+} currents [60]. For other $G_{q/11}$-coupled receptors (e.g., M1 muscarinic or B2 bradykinin), this pathway was found to involve an activation of phospholipase C and a depletion of membrane phosphatidylinositol 4,5-bisphosphate [69, 107]

voltage-dependent and pertussis toxin-sensitive manner [182]. The same receptor was also reported to mediate a voltage-dependent and pertussis toxin-sensitive inhibition of Ca^{2+} currents in rat superior cervical ganglion neurons [106]. In hamster submandibular neurons, the same effect was found when $P2Y_2$ receptors were activated [4]. In rat dorsal root ganglion neurons, $P2Y_1$ receptors were found to mediate a voltage-dependent inhibition of N-type calcium channels [71]. In HEK 293 cells expressing rabbit $Ca_V2.2$ α_1 subunits together with β_1 and $\alpha_{2\delta}$ subunits, ADP and ATP were found to mediate a voltage-dependent and pertussis toxin-sensitive inhibition of Ca^{2+} currents, and the receptor involved was suggested to be $P2Y_{13}$ [194].

However, nucleotides were not only reported to exert inhibitory effects on neuronal Ca^{2+} channels. ATP, for instance, has also been found to increase Ca^{2+} currents in hippocampal neurons [45], a result also reported for rat cardiac cells [169]. Unfortunately, the receptor subtypes and signaling mechanisms involved in these effects have not been elucidated in detail.

Effects of nucleotides on voltage-activated Ca^{2+} channels in neurons have not only been observed with endogenous P2Y receptors, but also after the heterologous expression of recombinant receptors. Based on their findings that UTP activated pertussis toxin-sensitive as well as pertussis toxin-resistant pathways in NG108-15 cells to control various ion channels [56, 59], Alexander Filippov, Eric Barnard, David Brown, and collaborators used rat superior cervical ganglion neurons as an expression system for molecularly defined P2Y receptor subtypes. All of the P2Y receptors that were investigated ($P2Y_{1,2,4,6,12}$) were found to mediate an inhibition of voltage-activated Ca^{2+} channels. As expected for a $G_{i/o}$ coupled receptor, the inhibition of voltage-gated Ca^{2+} currents via $P2Y_{12}$ receptors was voltage-dependent and pertussis toxin-sensitive, and thus appeared to involve only the membrane-delimited pathway [172]. In contrast, the inhibition of Ca^{2+} currents via $P2Y_{1,2,4}$ and $_6$ receptors included two components: a voltage-dependent and pertussis toxin-sensitive membrane-delimited pathway as well as a pertussis toxin-resistant mechanism. The inhibition via $P2Y_2$ receptors included a voltage-dependent and pertussis toxin-sensitive component, on one hand, and a voltage-independent and pertussis toxin-resistant component, on the other hand [61]. By contrast, when $P2Y_6$ [62] or $P2Y_1$ [27, 57] receptors were overexpressed, the pertussis toxin-resistant component appeared to be voltage-dependent because the inhibition of the currents was attenuated by large depolarizing prepulses. Furthermore, the inhibition via $P2Y_6$ receptors was more pronounced in perforated-patch as compared to whole-cell recordings. Moreover, the inhibition observed in the perforated-patch configuration was hardly altered by pertussis toxin, but in whole-cell recordings, it was reduced by more than one half after treatment with this toxin. Similar results were obtained with overexpressed $P2Y_4$ receptors [60]: almost no inhibition was observed in the conventional whole-cell mode, but in the perforated-patch recordings, the currents were

reduced by about 50% in a pertussis toxin-sensitive and voltage-dependent manner. These findings indicate that even the membrane-delimited, PTX-sensitive pathway may require a soluble cofactor, and that a modulation of voltage-gated Ca^{2+} currents should be investigated in both, the perforated-patch and the whole-cell configuration of the patch clamp technique. Recently, the inhibition of voltage-gated Ca^{2+} currents of superior cervical ganglion neurons via endogenous bradykinin receptors was also found to be different when these two experimental techniques were used [107].

K^+ channels

Aside from voltage-gated Ca^{2+} channels, a variety of neuronal K^+ channels have been found to be modulated by extracellular nucleotides. The superfamily of voltage-dependent K^+ channels comprises many more members than that of Ca^{2+} channels and the K^+ channels are, in addition, very heterogeneous [73]. Quite a number of different K^+ channels were reported to be modulated by various neurotransmitters, but the most intensively studied examples of K^+ channel regulation via GPCRs are inward rectifier (Kir) channels and KCNQ channels which are now classified as K_V7 family [73]. Many inhibitory neurotransmitters cause hyperpolarizations by activating inwardly rectifying K^+ currents via receptors linked to pertussis toxin-sensitive G proteins. These effects involve proteins of the Kir3 family and G protein $\beta\gamma$ subunits [174]. However, the regulation of G protein-coupled inwardly rectifying K^+ (GIRK) channels does not only depend on $\beta\gamma$ subunits, but also on other proteins and/or second messengers. G protein α subunits, for instance, act as donors for $\beta\gamma$, on one hand, and directly block GIRK channels [149], on the other hand. Moreover, the kinetics of GIRK channel gating are determined by all three parameters, receptor type, G protein α, and G protein $\beta\gamma$ subunits [13]. In addition to G protein subunits, regulators of G protein signaling (RGS) determine the kinetics of GIRK activation [53]. GIRK channels are activated by PIP_2 [84], and the levels of PIP_2 are also regulated via G protein-coupled receptors and PLCβ [157]. Hence, activation of receptors coupled to G_q proteins may also contribute to the regulation of GIRK channels [118]. Finally, activation of Gs coupled receptors may lead to an increase in currents through GIRK channels [136].

Several different neurotransmitters depolarize neurons by reducing M-type K^+ currents (I_M) which are mediated by KCNQ channels [158] These ion channels are opened in the subthreshold voltage range for action potentials and are completely activated when neurons are further depolarized. Hence, activated KCNQ channels keep neurons polarized, and their closure causes depolarization and leads to increased neuronal excitability [26, 46,120]. The inhibition of I_M via GPCRs is most commonly mediated by α_q subunits of heterotrimeric GTP binding proteins [74] and a reduction in PIP_2 through an activation of phospholipase Cβ [75, 177]. In addition, this enzyme mediates the synthesis of inositol trisphosphate (IP_3), which then liberates Ca^{2+} from intracellular stores and cytosolic Ca^{2+} concentrations in the sub- to low-micromolar range block K_M channels [171] via calmodulin [68].

One of the first examples of a modulation of K^+ channels by nucleotides was the inhibition of I_M by UTP [5] and ATP [7] in bullfrog sympathetic neurons. Although the receptors involved in these effects remained unknown at that time, the inhibition of I_M by nucleotides was shown to be mediated by a G protein [112, 178]. In NG108-15 neuroblastoma × glioma hybrid cells, activation of the PLC-linked $P2Y_2$ receptor was reported to lead to an inhibition of I_M [59]. Thereafter, a uridine nucleotide preferring receptor, most likely $P2Y_6$, was found to mediate an inhibition of I_M in rat superior cervical ganglion neurons [17]. The signaling cascade underlying this effect involved an activation of PLC, generation of IP_3, and release of Ca^{2+} from intracellular stores [22]. In rat thoracolumbar sympathetic neurons [44], UTP and UDP also reduced I_M, but only in cultures isolated from 9-12 days old rats and not in cultures obtained from newborn animals. In bullfrog sympathetic neurons, the nucleotide-induced inhibition of I_M was suggested to be mediated by $P2Y_4$ receptors (Fig. 2) [127].

In addition to the inhibition of KCNQ channels, the P2Y receptor-mediated modulation of several other neuronal potassium channels has been reported. In several papers, Ikeuchi and Nishizaki described outwardly rectifying potassium currents activated by nucleotides. These currents were found in neurons from various brain regions of the rat, such as striatal neurons [87], inferior colliculus neurons [88], superior colliculus neurons [142], cerebellar neurons [89], and hippocampal neurons [90]. Although the currents

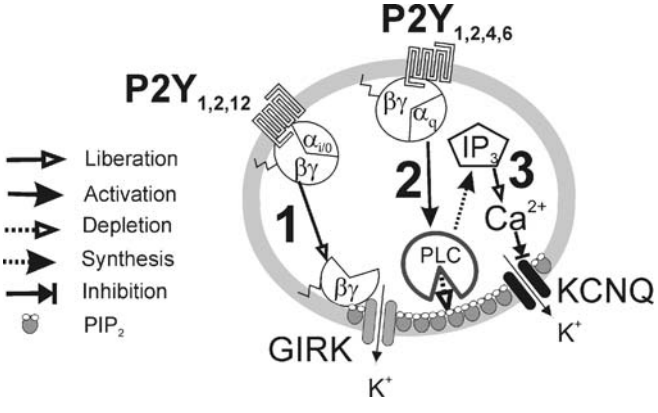

Fig. 2 Mechanisms underlying the regulation of GIRK and KCNQ channels via P2Y receptors. P2Y nucleotide receptors may use at least three different pathways to modulate the functions of GIRK and KCNQ channels: (1) Activation of P2Y receptors coupled to pertussis toxin-sensitive $G_{i/o}$ proteins sets $\beta\gamma$ subunits free which directly interact with Kir3 proteins to activate the channels [172]. (2) Activation of P2Y receptors linked to pertussis toxin-insensitive $G_{q/11}$ proteins leads to the activation of phospholipase C, which uses membrane phosphatidylinositol 4,5-bisphosphate (PIP_2) to synthesize inositol trisphosphate (IP3) and diacyl glycerol. Via the depletion of PIP_2, GIRK channels [84] as well as KCNQ channels [177] are closed. (3) The accumulating IP3 liberates Ca^{2+} from intracellular stores, and the increase in cytosolic Ca^{2+} inhibits KCNQ channels via calmodulin [68]

that were induced by the nucleotides appeared to be the same in all these neurons, the signal transduction mechanisms and the receptor subtypes involved were different. Responses induced by ATP in striatal neurons and by adenosine in superior colliculus and hippocampal neurons involved a diffusible second messenger and protein kinase C. In contrast, the actions of ADP in inferior colliculus neurons were membrane delimited and presumably based on a direct interaction of βγ subunits of a pertussis toxin-insensitive G protein with the channel protein. In rat hippocampal neurons, ATP was also found to inhibit a voltage-gated K^+ channel [138]; UTP was as potent as ATP, and ADP and α,β-methylene ATP also inhibited the outward current. In *Xenopus* spinal neurons, an inward rectifier current was found to be inhibited by adenine and uridine nucleotides [28]. There, a majority of the neurons responded to ADP, but not to ATP or UTP, and the authors speculated about the presence of two different P2Y receptor subtypes, one mediating the effects of the triphosphates and the other one mediating the effects of ADP.

The modulation of potassium channels by nucleotides has also been investigated after the heterologous expression of P2Y receptors, and the channels that were assessed most frequently were the KCNQ channels and the GIRKs (Fig. 2). Again, the receptors were expressed most frequently in rat superior cervical ganglion neurons; activation of the $G_{q/11}$-coupled receptors $P2Y_{1,2,4}$ and $P2Y_6$ led to an inhibition of I_M in a pertussis toxin-resistant manner [27, 60–62]. However, when the $P2Y_{12}$ receptor was expressed in these neurons, no inhibition of I_M by nucleotides could be observed [172]. When rat GIRK1 and GIRK2 (Kir3.1 and 3.2 subunits) were coexpressed with $P2Y_{12}$, 2MeSADP, and 2MeSATP, two appropriate agonists, evoked K^+ currents through GIRK channels. This result agrees with the general concept that $G_{i/o}$ coupled receptors mediate an activation of GIRK channels. Unexpectedly, the $G_{q/11}$-linked $P2Y_1$ receptor, when coexpressed with Kir3.1 and 3.2 subunits, also mediated a pertussis toxin-sensitive activation of GIRK. This further supports the idea that a single P2Y receptor may couple to multiple types of G proteins. However, with $P2Y_1$, the fast activation was followed by a slower but almost complete inactivation of the current in the continuing presence of the agonist [172]. Such a slow inhibition, but no activation, of recombinant GIRK channels in superior cervical ganglion neurons was also observed when $P2Y_4$ or $P2Y_6$ receptors were coexpressed with GIRK channels and subsequently activated. These latter effects were pertussis toxin-insensitive and involved α_q subunits of G proteins [58]. Similarly, when mouse $P2Y_2$ receptors were coexpressed together with GIRK channels in *Xenopus* oocytes, ATP and UTP activated K^+ currents in a pertussis toxin-sensitive manner [134]. Furthermore, $P2Y_2$ receptor activation did not only induce GIRK currents, but also led to a subsequent inhibition via a Ca^{2+}- and PLC-dependent mechanism [119].

Transmitter-gated ion channels

Although a large number of transmitter-gated ion channels are known, only a few of them were found to be regulated via P2Y receptors. One prominent example is the glutamatergic *N*-methyl-D-aspartate (NMDA) receptor, which is also controlled by other GPCRs. The activation of muscarinic acetylcholine receptors, for instance, has been shown to enhance NMDA receptor currents via protein kinase C and nonreceptor tyrosine kinase [113]. In contrast, D_2-like dopamine receptors reduce currents through NMDA receptors via transactivation of receptor tyrosine kinases [100]. In addition, D_1 dopamine receptors were found to directly interact with NMDA receptors [109]. Adenine and uridine nucleotides were reported to enhance currents elicited by NMDA in layer V pyramidal neurons of the rat prefrontal cortex. This effect was most likely mediated by $P2Y_2$ receptors [193]. In contrast, activation of $P2Y_1$ receptors inhibited currents through the NMDA receptors [115] in the very same cells. In addition, ATP was found to inhibit NMDA receptors independently of P2Y receptors; this effect involved a direct binding of the nucleotide to the glutamate-binding site of the NR2B subunit of NMDA receptors [147].

Another transmitter-gated ion channel that was found to be modulated by nucleotides is the vanilloid receptor 1 (VR1). In rat dorsal root ganglion neurons, capsaicin-evoked currents through VR1 were enhanced by nucleotides [179]. This potentiation was abolished by a protein kinase C inhibitor, and mimicked by phorbol esters. These results indicated that a P2Y receptor linked to protein kinase C via $G_{q/11}$ proteins was involved, and the $P2Y_1$ receptor was considered to be the most likely candidate. However, the ATP-induced potentiation was also observed in dorsal root ganglion neurons of $P2Y_1$ receptor-deficient mice [133], and rat dorsal root ganglion neurons were found to coexpress VR1 and $P2Y_2$ mRNA, but not $P2Y_1$ mRNA. Moreover, UTP was reported to be as potent an agonist as ATP, and suramin (which blocks $P2Y_2$ but not $P2Y_4$) abolished the potentiation of VR1 by UTP. Therefore, it was concluded that $P2Y_2$ receptors mediated the facilitatory effects of nucleotides on VR_1 in mouse and rat dorsal root ganglion neurons [133].

A third family of transmitter-gated ion channels regulated via P2Y receptors are the ATP-gated P2X receptors. Again in rat dorsal root ganglion neurons, the activation of $P2Y_1$ receptors was reported to modulate $P2X_3$ receptors via pertussis toxin-insensitive G proteins, but in this case, currents were reduced [72] instead of enhanced. In contrast, when $P2Y_1$ or $P2Y_2$ receptors were coexpressed with the $P2X_1$ receptor in *Xenopus* oocytes, their activation caused a significant potentiation of the P2X receptor-mediated current [185].

Regulation of synaptic transmission

Synaptic transmission requires the release of transmitters from presynaptic nerve terminals and the ensuing activa-

tion of postsynaptic receptors by the released transmitters. Accordingly, synaptic transmission can be modulated either by changes in the presynaptic release or by changes in either the excitability of the postsynaptic membrane or in the signaling capabilities of the postsynaptic receptors. In both cases, the regulation of synaptic transmission via P2Y receptors relies most commonly on the modulation of ion channels as described above. Voltage-activated Ca^{2+} channels, in particular N- and P/Q-type channels, are located at presynaptic nerve terminals and link invading action potentials to transmembrane Ca^{2+} influx and concomitant vesicle exocytosis. As a consequence, the modulation of these ion channels via GPCRs leads to changes in transmitter release [175]. The waveforms of presynaptic action potentials are shaped by voltage-activated and Ca^{2+}-dependent K^+ channels, and the modulation of these channels via GPCRs can also lead to changes in vesicle exocytosis [50, 123]. In contrast, inwardly rectifying K^+ channels such as GIRKs are hardly present at presynaptic nerve terminals and are generally not involved in the control of transmitter release [114, 123]. With respect to KCNQ channels, contrasting results have been obtained. In peripheral neurons, no evidence could be obtained that these ion channels are involved in action potential-evoked noradrenaline release [101, 108]. However, in central synaptosomes, modulators of these ion channels were found to affect the release of various transmitters [122]. Taken together, the regulation of Ca^{2+} channels and Ca^{2+}-dependent K^+ channels via P2Y receptors will preferentially lead to changes in synaptic transmission via a presynaptic modulation of transmitter release, whereas the control of GIRKs and KCNQ channels will rather cause changes in the postsynaptic excitability. And the modulation of transmitter-gated ion channels will mostly cause alterations in the signaling of postsynaptic receptors, unless these ion channels are also located at presynaptic sites. In fact, P2Y receptors were found to mediate nucleotide-dependent changes in synaptic transmission via both, pre- and postsynaptic effects.

In various regions of the central nervous system, nucleotides were found to either inhibit or enhance the release of acetylcholine, dopamine, noradrenaline, serotonin, glutamate, GABA, or glycine via presynaptic receptors. However, in many cases, the receptor subtypes involved in these presynaptic effects of nucleotides were not unequivocally identified. The release-enhancing effects of nucleotides appeared to be mostly mediated by receptors of the P2X family [40]. The inhibitory effects, in contrast, rather involved P2Y receptors as suggested for the release of noradrenaline [190], serotonin [187], and dopamine [180]. In hippocampal neurons, presynaptic P2Y receptors were reported to mediate an inhibition of glutamate, but not of GABA, release [126]. This effect involved pertussis toxin-sensitive G proteins and an inhibition of voltage-activated Ca^{2+} currents, but the precise P2Y receptor subtype(s) involved were not identified [200]. In the medial habenula, a presynaptic $P2Y_4$-like receptor was shown to enhance glutamate release, whereas a presumed $P2Y_2$-like receptor mediated an inhibition [153].

In the peripheral nervous system, the release of acetylcholine or noradrenaline was also reported to be controlled by presynaptic P2X and P2Y receptors [40]. Because ATP and noradrenaline have long been known to be cotransmitters in the sympathetic nervous system, presynaptic P2 receptors have been studied in greatest detail there. First evidence for presynaptic nucleotide receptors in sympathetic neurons has been obtained more than 20 years ago [176]. More recently, agonistic nucleotides were found to reduce, whereas P2 receptor antagonists were found to enhance noradrenaline release from the mouse vas deferens as indication of inhibitory presynaptic P2Y autoreceptors [188]. In numerous other sympathetically innervated tissues, nucleotides were also reported to inhibit transmitter release [18, 21]. The P2Y receptor subtypes involved in these effects remained elusive for quite some time, but evidence has been presented that $P2Y_{12}$ and/or $P2Y_{13}$ receptors mediated autoinhibition of transmitter release from sympathetic neurons [155]. Most recently, it was the $P2Y_{12}$ receptor subtype that was shown to mediate autoinhibition of transmitter release in sympathetic neurons and in the ontogenetically related PC12 cell line. Furthermore, the signaling cascade involved in this effect was found to include pertussis toxin-sensitive G proteins and a voltage-dependent inhibition of voltage-activated Ca^{2+} channels [106]. In sensory neurons, $P2Y_1$ receptor activation was found to reduce synaptic transmission in pain pathways [71] and it also involved an inhibition of voltage-activated Ca^{2+} channels [23].

Via effects at postsynaptic sites, nucleotides were also reported to either inhibit or enhance synaptic transmission. In the prefrontal and parietal cortex, for instance, activation of a $P2Y_1$-like receptor reduced glutamatergic transmission, but only the component involving NMDA receptors. Furthermore, the receptor mediated an inhibition of depolarizations caused by NMDA, but not of those induced by alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid [115]. In sensory neurons, in contrast, the very same receptor subtype was suggested to facilitate touch-induced impulse generation [137], but the underlying mechanisms remained unknown. In this context, the modulation of VR1 via P2Y receptors might be a relevant mechanism [179]. In autonomic neurons, $P2Y_1$ receptors were also reported to mediate excitatory postsynaptic effects. In the enteric nervous system, excitatory postsynaptic potentials were found to be blocked by a $P2Y_1$ receptor antagonist. The direct activation of these receptors caused a Na^+-dependent increase in membrane conductance, but the precise ionic mechanisms were not further investigated [83]. In postganglionic sympathetic neurons, P2Y receptors also mediated excitatory postsynaptic effects. UTP was found to depolarize sympathetic ganglia and to trigger transmitter release from dissociated sympathetic neurons via receptors different from those activated by ATP [20, 39, 189]. UDP was equipotent to UTP in triggering noradrenaline release [20, 144], and both nucleotides also caused an inhibition of I_M [17, 144]. The receptor mediating both effects was suggested to be $P2Y_6$, but the stimulation of noradrenaline

release did not only involve the inhibition of KCNQ channels, but also an activation of protein kinase C [183].

Regulation of neurodegeneration and regeneration

Extracellular ATP has been found to be toxic for a variety of mature differentiated neurons, including cerebellar, striatal, and hippocampal neurons. The nucleotide was reported to induce both, apoptotic and necrotic features of degeneration after only a few minutes of exposure and with a time lag of at most 2 h [8]. In accordance with this finding, P2 receptor antagonists were reported to exert protective effects against neuronal cell death elicited by various stimuli in cerebellar granule and hippocampal neurons as well as in PC12 cells [34, 35]. However, the P2 receptors involved were not further characterized, and the neurotoxic effects of ATP appear to be mediated by P2X rather than P2Y receptors [64].

In contrast to the toxic effects described above, extracellular nucleotides may also exert trophic actions in neural development and growth as well as regeneration and proliferation of the nervous system [64]. The underlying mechanisms have been studied most frequently in the pheochromocytoma cell line PC12. Although ATP itself did not affect differentiation of these cells [77], it stimulated the synthesis and release of neuronal (NGF) and fibroblast growth factor (FGF) and synergized with the trophic factors to enhance neurite outgrowth and differentiation [10, 42, 44, 85]. In addition, ATP and NGF promoted survival of PC12 cells after serum deprivation by upregulating the expression of the heat shock proteins HSP70 and HSP90, by preventing the cleavage and activation of caspase-2, and by inhibiting the release of cytochrome C from mitochondria into the cytoplasm [43]. UTP was also found to increase neurite growth and branching in PC12 cells, and this effect was antagonized by PPADS, thus, suggesting that it was at least in part mediated by P2Y receptors [151]. In support of this conclusion, $P2Y_2$ receptors were shown to colocalize and associate with the NGF receptor tyrosine receptor kinase A (TrkA) upon stimulation with ATPγS and NGF and to mediate an enhanced neurite formation in PC12 cells and dorsal root ganglion neurons. This effect involved an increased sensitivity towards NGF due to the phosphorylation of TrkA and early response kinases (ERKs) [11]. P2 receptor activation was also reported to promote fiber outgrowth in the developing hippocampus [78], but it remained elusive whether this effect was mediated by P2X or P2Y receptors. In addition, extracellular ATP may influence neurite outgrowth in hippocampal neurons by modulating the adhesion mediated by neuronal cell adhesion molecules [173].

Conclusion

Extracellular nucleotides are ubiquitous signaling molecules in neuronal as well as nonneural tissues. In the nervous system, ATP acts as a fast synaptic transmitter via ionotropic P2X receptors [159]. In addition, not only ATP, but various other types of nucleotides act on metabotropic P2Y receptors to mediate slow neuromodulatory effects as well as trophic or neurodegenerative actions. A large variety of consequences of neuronal P2Y receptor activation are summarized above and they reveal that nucleotides are as multifaceted neurotransmitters as, for instance, glutamate, GABA, acetylcholine, or serotonin. In light of all these actions mediated by neuronal P2Y receptors, one may expect that these receptors will prove to be valuable drug targets as previously exemplified by the $P2Y_{12}$ receptor of platelets [181]. In addition, the knowledge of functions of neuronal P2Y receptors may help to explain unexpected effects observed with well-established P2Y receptor ligands, such as the antithrombotic $P2Y_{12}$ antagonists ticlopidin or clopidogrel. With the forthcoming development of new P2Y receptor ligands [94], the ongoing elucidation of P2Y receptor functions in neuronal as well as nonneural tissues will further gain in importance.

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