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P2 Receptors for Extracellular Nucleotides in the Central Nervous System: Role of P2X7 and $P2Y_2$ Receptor Interactions in Neuroinflammation

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Abstract

Extracellular nucleotides induce cellular responses in the central nervous system (CNS) through the activation of ionotropic P2X and metabotropic P2Y nucleotide receptors. Activation of these receptors regulates a wide range of physiological and pathological processes. In this review, we present an overview of the current literature regarding P2X and P2Y receptors in the CNS with a focus on the contribution of P2X7 and $P2Y_2$ receptor-mediated responses to neuroinflammatory and neuroprotective mechanisms.

Keywords

$P2Y_2$ Receptor; P2X7 receptor; neuroprotection; neuroinflammation

Introduction

Extracellular nucleotides, such as adenosine 5-triphosphate (ATP) and uridine 5'-triphosphate (UTP), are released from cells under a variety of physiological and pathological conditions whereupon they activate P2 nucleotide receptors on the surface of neighboring cells (Burnstock *et al.*, 1997; Heilbronn *et al.*, 1997). P2 receptors are a diverse family of plasma membrane proteins that can be segregated into two subtypes: the P2X receptors that are ATP-selective cation channels and the P2Y receptors for ATP, UTP or their metabolites that are coupled to heterotrimeric G proteins (Abbracchio and Burnstock, 1994; von Kügelgen and Wetter, 2000). To date, genes for 7 P2X receptors and 8 P2Y receptors have been cloned and their protein products have been extensively characterized in a variety of cell and tissue types (Burnstock and Kennedy, 1985; Sak and Webb, 2002). In the central nervous system (CNS), multiple P2X and P2Y receptor subtypes are expressed in neurons, glial cells, oligodendrocytes, macrophages and endothelium where they regulate physiological responses, including neurotransmission, pain perception, phagocytosis, and maintenance of the blood-brain barrier (Weisman *et al.*, 2005; Gonzalez *et al.*, 2005; Peterson *et al.*, 2010). Pathophysiological responses are also regulated by P2X and P2Y receptors, including the propagation of inflammation due to the release of nucleotide agonists from damaged or diseased cells (Bours *et al.*, 2011; Ferrero, 2011; Fumagalli *et al.*,

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2011). This review describes the contributions of both P2X and P2Y receptors to cell specific functions in the CNS and focuses on the dual roles of the ionotropic P2X7 receptor (P2X7R) for ATP and the G protein-coupled $P2Y_2$ receptor ($P2Y_2R$) for ATP and UTP in the regulation of proinflammatory responses in the brain. Recent studies have found that the release of extracellular ATP from stressed or damaged cells of the CNS can activate microglial cell P2X7Rs, which increases cytokine release, *e.g.*, interleukin-1β (IL-1β), and the phagocytic activity of microglial cells (Bianco *et al.*, 2005b). Additionally, IL-1β has been shown to upregulate $P2Y_2R$ expression in neurons to promote neuroprotective responses (Kong *et al.*, 2009). These findings are reviewed in this paper and suggest that both P2X7 and $P2Y_2$ receptors are promising targets for the treatment of neurodegenerative and other inflammatory diseases.

P2X receptors in the Central Nervous System

P2X receptors (P2XRs) are ligand-gated, nonselective cation channels activated by extracellular ATP. Seven pharmacologically distinct P2XR subtypes have been identified, *i.e.*, P2X1–P2X7, and shown to be activated by ATP and its analogues (MacKenzie *et al.*, 1999; North and Surprenant, 2000). P2XRs range from 379–595 amino acids in length and, as shown in Figure 1, consist of two transmembrane domains, a large extracellular loop and intracellular N- and C-termini (Valera *et al.*, 1994). P2XRs share ~ 50% sequence homology with one third of the extracellular loop conserved, suggesting an ATP binding site (Vial *et al.*, 2004). P2X1 and P2X3 receptors rapidly desensitize (within milliseconds), whereas P2X2, P2X5, P2X6 and P2X7 receptors desensitize slowly (within seconds) upon activation by ATP (Ralevic and Burnstock, 1998). Depending on the subtype, P2XR subunits interact in a variety of homo- or heteromeric forms to regulate a wide range of cellular responses in the CNS under physiological and pathological conditions (Khakh and North, 2006; Koles *et al.*, 2007). The distribution of P2XR subtypes in the CNS is dependent upon species, brain region and cell type (Collo *et al.*, 1996; Vulchanova *et al.*, 1996; Kanjhan *et al.*, 1999; Vulchanova *et al.*, 1997; Collo *et al.*, 1997; Atkinson *et al.*, 2000; Deuchars *et al.*, 2001; Rubio and Soto, 2001; Sim *et al.*, 2004). The P2X2R, P2X4R and P2X6R appear to be abundantly expressed throughout the brain, whereas the remaining subtypes are expressed in distinct regions (Collo *et al.*, 1996; Tanaka *et al.*, 1996; Kanjhan *et al.*, 1999). In neurons, activation of P2XRs by extracellular ATP has been reported to have both presynaptic and postsynaptic effects including the modulation of transmembrane currents and neurotransmitter release (Nakatsuka and Gu, 2001; Watano *et al.*, 2004; Rodrigues *et al.*, 2005; Patti *et al.*, 2006; Jameson *et al.*, 2008; Illes *et al.*, 2011). All types of glia, *e.g.*, astrocytes, oligodendrocytes, Schwann cells and microglial cells express P2XRs where they can regulate inflammatory, neurodegenerative and neuroprotective responses (Illes *et al.*, 2011). Most notably, the P2X7R has gained recognition for its possible role in neurodegenerative disorders (Duan and Neary, 2006; Takenouchi *et al.*, 2010). The function of the CNS is dependent on neuronal-glial interactions and the complexity of P2XR signaling in both cell types adds to the difficulty in interpreting ATP-mediated events *in vivo*. The cell and tissue distribution and functional relevance of homomeric and heteromeric P2X receptors in the nervous system are summarized in Table 1.

P2X1Rs have been shown to cause contraction of neurogenic smooth muscle (Mulryan *et al.*, 2000; Vial and Evans, 2000), platelet activation (Hechler *et al.*, 2003; Mahaut-Smith *et al.*, 2004), and neuronal (Calvert and Evans, 2004; Watano *et al.*, 2004) and glial cell responses (Lalo *et al.*, 2008). Among the P2XRs, the P2X1R has the highest affinity for ATP (EC_{50} ~ 1 M) (Rettinger and Schmalzing, 2003). The P2X1R is often observed in a heteromeric complex with the P2X2R and P2X5R resulting in biophysical and pharmacological properties distinct from those observed when each of these receptor subtypes is expressed separately (Le *et al.*, 1997; Torres *et al.*, 1998; Haines *et al.*, 1999; Le

et al., 1999; Duckwitz *et al.*, 2006; Ase *et al.*, 2010). In superior cervical ganglia neurons, the P2X1R contributes to ATP-mediated responses by forming a heteromeric unit with the P2X2R (Calvert and Evans, 2004), whereas ATP-evoked biphasic membrane currents in mouse cortical astrocytes are regulated by P2X1R/P2X5R heteromeric channels (Lalo *et al.*, 2008).

P2X2Rs are widely expressed in the CNS with predominant expression in the cerebral cortex, cerebellum, striatum, hippocampus, habenula, substantia nigra, dorsal ganglia neurons, mesenteric ganglia neurons and glial cells (Kidd *et al.*, 1995; Vulchanova *et al.*, 1996; Pankratov *et al.*, 1998; Xiang *et al.*, 1998; Kanjhan *et al.*, 1999; Xiang and Burnstock, 2004; Brass *et al.*, 2011). The P2X2R is distinguished from other members of the P2XR family, since multiple splice variants exist in different mammalian species with diverse functional properties (Coddou *et al.*, 2011). Many studies have shown that P2X2Rs play a role in nociceptive transmission, hyperalgesia and allodynia, particularly when present as functional heterotrimers with P2X3Rs (Honore *et al.*, 2002; Jarvis, 2003; Xiang and Burnstock, 2004). The pharmacological properties of P2X2R/P2X3R are similar to the P2X3R, but the desensitization rate of the P2X3R is reduced by its interaction with the P2X2R (Koshimizu *et al.*, 2002). P2X2Rs and P2X2R/P2X3R have been implicated in pain processing (Wirkner *et al.*, 2007); however with chronic pain their functions are altered by the action of other P2XRs, especially those expressed in immune cells, such as microglia (Trang *et al.*, 2006). In addition to interactions with P2X2Rs, P2X3Rs also form homotrimeric receptors that are prominently expressed in primary sensory neurons where they enhance the release of glutamate and substance P (Gu and MacDermott, 1997; Vulchanova *et al.*, 1998; Nakatsuka *et al.*, 2001; Nakatsuka and Gu, 2001), which contribute to both acute and chronic pain sensation (Jarvis, 2003). *In vivo* studies using $P2X2R^{-/-}$, $P2X3R^{-/-}$ and $P2X2R^{-/-}/P2X3R^{-/-}$ mice have contributed significantly to our understanding of neuropathic and inflammatory pain sensation and have lead to the development of therapeutic antagonists to these receptors (Ford, 2011; Gum *et al.*, 2011). The P2X2R also has been suggested to play a role in pre- and postnatal neurogenesis (Cheung *et al.*, 2005).

The P2X4R is expressed throughout the central and peripheral nervous systems (Buell *et al.*, 1996; Rubio and Soto, 2001; Bo *et al.*, 2003; Calvert and Evans, 2004; Tsuda *et al.*, 2009). The P2X4R is upregulated in activated microglial cells after spinal cord or peripheral nerve injury where it appears to mediate the release of brain-derived neurotrophic factor and induce neuropathic pain (Ulmann *et al.*, 2008). Recent studies provide evidence that the functional expression of P2X4Rs in tissue-resident macrophages regulates inflammation-dependent prostaglandin E2 release (Ulmann *et al.*, 2010). Activation of homomeric P2X4Rs in hippocampal neurons has been suggested to contribute to synaptic strengthening and hypersensitivity to sensory stimuli (Tsuda *et al.*, 2009; Baxter *et al.*, 2011). In addition, hippocampal synaptic transmission and long-term potentiation were abolished in $P2X4R^{-/-}$ mice (Sim *et al.*, 2006). A unique characteristic of the P2X4R is its modulation by trace metals; copper inhibits whereas zinc and cobalt potentiate P2X4R activity (Coddou *et al.*, 2011). P2X4R activity has been shown to be modulated by the allosteric effector ivermectin (Coddou *et al.*, 2011). Heteromeric assembly of the P2X4R with the P2X1, P2X6 and P2X7 receptor subtypes has been described (Le *et al.*, 1998; Nicke *et al.*, 2005; Guo *et al.*, 2007), although the functional relevance of these complexes *in vivo* is currently unknown.

The expression of the P2X5R subtype in the mouse CNS is most abundant in the olfactory bulb, cerebral cortex, globus pallidum, hippocampus, thalamus, hypothalamus, cerebellar cortex, and mid- and hindbrain nuclei (Guo *et al.*, 2008). Although *in vitro* data have demonstrated ATP-evoked currents coupled to P2X5R activation, little is known about the physiological relevance of P2X5Rs in the CNS. Guo *et al.* speculate that P2X5R expression

in the molecular layer of the cerebral cortex could play a role in interconnection of local cortical areas and P2X5R expression in the olfactory bulb suggests a role in fast excitatory post-synaptic purinergic transmission (Guo *et al.*, 2009). *In vitro* studies have shown that activation of the homomeric P2X5R results in small, nondesensitizing currents, whereas activation of frequently observed heteromeric P2X5/P2X1 receptors results in slowly desensitizing ATP-evoked currents (Torres *et al.*, 1998; Le *et al.*, 1999). A $P2X5R^{-/-}$ mouse has not yet been developed; however, it will be critical for evaluating the role of the P2X5R *in vivo*. Interestingly, a recent study indicates that most humans express only a nonfunctional isoform of the P2X5R (Kotnis *et al.*, 2010).

In the CNS, the P2X6R is expressed in Purkinje cells in the cerebellum, pyramidal cells in the hippocampus and sensory ganglia (Collo *et al.*, 1996; Rubio and Soto, 2001; Robertson *et al.*, 2001; Burnstock and Knight, 2004; da Silva *et al.*, 2007). The ability of the P2X6R to form functional homomeric receptors is very low due to inefficient glycosylation of the N-terminus (Jones *et al.*, 2004; Ormond *et al.*, 2006). P2X6Rs readily form functional heteromers with P2X2 and P2X4 receptors, where activation of one subtype potentiates the activity of the other (Egan *et al.*, 2004). In the myenteric plexus, the P2X6R is expressed in Dogiel type II neurons where it likely regulates physiological responses to ATP as a heteromeric complex with P2X2Rs (Yu *et al.*, 2010).

Among the P2X receptor subtypes, the P2X7 receptor has gained prominent recognition as a regulator of inflammatory responses (Lister *et al.*, 2007). P2X7Rs are expressed in many types of cells, notably in immune cells where activation by ATP increases the release of proinflammatory cytokines and apoptotic cell death (Pelegrin and Surprenant, 2006; Ferrari *et al.*, 2006). The P2X7R was first cloned from rat brain (Surprenant *et al.*, 1996), and subsequently has been found to be expressed in microglia, neurons and astrocytes (Ballerini *et al.*, 1996; Brandle *et al.*, 1998; Ferrari *et al.*, 2006; Takenouchi *et al.*, 2010). The P2X7R requires high concentrations of ATP (> 0.1 mM) for activation, although the photoaffinity ligand BzATP is a more potent agonist (Gonzalez *et al.*, 1989; Erb *et al.*, 1990). Stimulation of the P2X7R regulates the gating of non-selective cation channels, mitochondrial and plasma membrane depolarization, the formation of plasma membrane pores, plasma membrane blebbing, and the production of reactive oxygen species (ROS), responses ultimately leading to cell death (Erb *et al.*, 1990; Schulze-Lohoff *et al.*, 1998; Morelli *et al.*, 2003; Verhoef *et al.*, 2003; Wang *et al.*, 2004; Adinolfi *et al.*, 2005; Lister *et al.*, 2007; Roger *et al.*, 2008; Bours *et al.*, 2011). P2X7R activity is dramatically potentiated by decreasing the divalent cation concentration, indicating that ATP^{4-} may be the active ligand (Steinberg and Silverstein, 1987; Weisman *et al.*, 1989; Hickman *et al.*, 1996). P2X7Rs have been shown to mediate the release of neurotransmitters, *e.g.*, glutamate, GABA, and ATP, and may be required for the induction of synaptic plasticity (Atkinson *et al.*, 2004; Gordon *et al.*, 2005; Duan and Neary, 2006). It also has been shown that P2X7R activation induces hypoxia- and caspase-dependent neuronal cell death (Kong *et al.*, 2005; Sugiyama *et al.*, 2010). Activation of P2X7Rs in glial cells results in the release of the proinflammatory cytokines TNFα, IL-1β and leukotrienes, thereby triggering or potentiating neuroinflammation (Hide *et al.*, 2000; Suzuki *et al.*, 2004; Ballerini *et al.*, 2005; Kataoka *et al.*, 2009), as described below. The P2X7R is upregulated in damaged nerves (Cavaliere *et al.*, 2004; Franke *et al.*, 2004a) and in nerves obtained from neuropathic pain patients (Chessell *et al.*, 2005). In a mouse model of neuropathic pain, hypersensitivity to pain stimuli was completely absent upon deletion of the P2X7R (Chessell et al. 2005). The P2X7R is also upregulated in microglia around β-amyloid plaques in a mouse model of Alzheimer's disease (AD) where it mediates superoxide production (Parvathenani *et al.*, 2003). Enhanced expression of P2X7Rs also was observed in microglia derived from postmortem AD brains compared with glia obtained from non-demented brains (McLarnon *et al.*, 2006). Furthermore, studies with a mouse model of Huntington's disease suggest that

P2X7Rs may play a role in disease pathogenesis (Diaz-Hernandez *et al.*, 2009). Therefore, the P2X7R receptor could represent a therapeutic target for treating neurodegenerative diseases.

P2Y Receptors in the Central Nervous System

P2Y receptors (P2YRs) are classical heterotrimeric G protein-coupled seven-pass transmembrane receptors, as shown in Fig. 1. The extracellular N-terminus contains several potential glycosylation sites and the C-terminus contains consensus phosphorylation sites for protein kinases (Nguyen et al., 1995; Erb *et al.*, 1995; Brinson and Harden, 2001; Flores *et al.*, 2005). The intracellular loops and C-terminus have structural diversity among P2YR subtypes, thereby influencing the degree of coupling with $G_{q/11}$, G_s, and G_i proteins (Abbracchio *et al.*, 2006). The length of human P2YRs varies from 328 ($P2Y_6R$) to 377 ($P2Y_2R$) amino acids and the composition reveals two structurally distinct subgroups within the P2YR family, the G_q-coupled $P2Y_1$, $P2Y_2$, $P2Y_4$, $P2Y_6$,and $P2Y_{11}$ receptors and the G_i-coupled $P2Y_{12}$, $P2Y_{13}$ and $P2Y_{14}$ receptors (Erb *et al.*, 2006; Abbracchio *et al.*, 2006). The degree of sequence homology among members of the human P2YR family ranges from 20 to 50%, suggesting a relatively high functional diversity (Shaver, 2001). It has been demonstrated that positively charged amino acids within transmembrane domains of P2YRs contribute to agonist binding (Erb *et al.*, 1995; Jiang *et al.*, 1997; Jacobson *et al.*, 1999). P2YRs, whose agonists are adenine and/or uridine nucleotides, are expressed in many cell types comprising the CNS and have been shown to regulate neurotransmission, inflammation, cell growth, and apoptosis (Burnstock *et al.*, 1972; Burnstock, 2009; Neary and Zimmermann, 2009; Burnstock and Verkhratsky, 2010). $P2Y_1$, $P2Y_{12}$, $P2Y_{13}$ and $P2Y_{14}$ receptors are activated by adenine nucleotides only, whereas the $P2Y_2R$ and rodent $P2Y_4R$ can be activated by either adenine or uridine nucleotides and the human $P2Y_4$ and $P2Y_6$ receptors are selective for uridine nucleotides (Abbracchio *et al.*, 2006). The $P2Y_{14}R$ subtype is activated by UDP-glucose (Sak and Webb, 2002; Burnstock and Knight, 2004; Abbracchio *et al.*, 2006). All eight P2Y receptor subtypes are expressed in primary rat astrocytes or astrocytoma cells (Fumagalli *et al.*, 2003; Abbracchio *et al.*, 2006; Kreda *et al.*, 2008; Brandenburg *et al.*, 2010), although the expression patterns vary with age (Lenz *et al.*, 2000; Jacques-Silva *et al.*, 2004). Rodent neurons express $P2Y_{1,2,4,6,12,13}$ receptors (Kong *et al.*, 2009; Espada *et al.*, 2010; Köles *et al.*, 2011). P2YRs are expressed at postsynaptic terminals where $P2Y_1$, $P2Y_2$ and $P2Y_4$ receptors are neuromodulators that have inhibitory roles in synaptic transmission (Rodrigues *et al.*, 2005; Rodrigues *et al.*, 2006; Sperlágh and Illes, 2007; Fischer and Krügel, 2007). The cell and tissue distribution, agonist specificities and functional relevance of P2Y receptors in the nervous system are summarized in Table 2.

The $P2Y_1R$ has a widespread distribution in mammalian brain, including the cerebral cortex, hippocampus, caudate nucleus, putamen, globus pallidus, habenula, subthalamic nucleus, midbrain and cerebellum, as demonstrated in autoradiographic and immunohistochemical studies (Simon *et al.*, 1997; Moore *et al.*, 2000; Morán-Jiménez and Matute, 2000). The $P2Y_1R$ is intensely expressed in Purkinje cells, in deep layers of the cerebral cortex and in areas of the hippocampus sensitive to ischemia (Morán-Jiménez and Matute, 2000). $P2Y_1R$ immunoreactivity has also been observed in oligodendrocytes and astrocytes in brain white matter tracts and optic nerves (Simon *et al.*, 1995; Fumagalli *et al.*, 2003). $P2Y_1Rs$ have been suggested to play important roles in glial cell functions (Morán-Jiménez and Matute, 2000). $P2Y_1R$ activation in astrocytes of hippocampal cultures has been suggested to provide neuroprotection from oxidative stress by increasing IL-6 release (Fujita *et al.*, 2009). $P2Y_1Rs$ are also expressed in microglial cells (Gotsch *et al.*, 1997; Simon *et al.*, 1997; Fumagalli *et al.*, 2003; Franke *et al.*, 2004a; Bianco *et al.*, 2005a), rat neuroprogenitor cells (Mishra *et al.*, 2006), and various sensory neurons such as dorsal root ganglia and dorsal horn neurons (Sanada *et al.*, 2002; Ruan and Burnstock, 2003; Kobayashi *et al.*, 2006).

Studies have suggested potential roles for $P2Y_1$Rs in brain development and repair (Mishra *et al.*, 2006) and sensory reception (Ruan and Burnstock, 2003; Gerevich *et al.*, 2005).

The contribution of the $P2Y_2$R subtype to CNS functions is becoming better understood (Franke and Illes, 2006; Inoue, 2008; Peterson *et al.*, 2010) and appears to be most relevant under pathophysiological conditions, such as inflammation and bacterial infection (Peterson *et al.*, 2010; Chen *et al.*, 2010). The mammalian $P2Y_2$R is equipotently activated by ATP or UTP (Weisman *et al.*, 2005; Abbracchio *et al.*, 2006) and is upregulated in many cell and animal models of inflammation or injury (Turner *et al.*, 1997; Koshiba *et al.*, 1997; Seye *et al.*, 2002; Shen *et al.*, 2004; Schrader *et al.*, 2005; Kong *et al.*, 2009), including acute and chronic stages of spinal cord injury (Rodríguez-Zayas *et al.*, 2010), brain ischemia, mechanical injury to the nucleus accumbens and brain trauma (Franke *et al.*, 2004a; Franke *et al.*, 2004b), suggesting that $P2Y_2$R upregulation represents a cellular response to tissue damage and inflammation. $P2Y_2$R expression under proinflammatory conditions is regulated by NF-κB binding to the *P2Y₂R* promoter (Degagne *et al.*, 2009), consistent with the established role of NF-κB activation in the induction of inflammation (Wullaert *et al.*, 2011). In addition to the typical G_q-coupled activation of the PLC/IP_3/PKC pathway, the $P2Y_2$R has a variety of structural motifs that enable it to activate integrin and growth factor receptor signaling cascades, as shown in Fig. 2. For example, $P2Y_2$R activation by ATP or UTP has been shown to induce phosphorylation of growth factor receptors which increases the activities of the MAP kinases ERK1/2 and the related adhesion focal tyrosine kinase (RAFTK) via a pathway dependent upon Src and Shc/Grb2 (Soltoff, 1998; Soltoff *et al.*, 1998; Seye *et al.*, 2004). However, other studies show that $P2Y_2$R-mediated EGFR phosphorylation is Src-independent, but requires the release of growth factors via $P2Y_2$R-dependent activation of the matrix metalloproteases ADAM10 and ADAM17 (Ratchford *et al.*, 2010). These differences appear to be due to cell type, *e.g.*, endothelial vs. epithelial. The $P2Y_2$R is unique among GPCRs in that it contains the consensus integrin-binding motif Arg-Gly-Asp (RGD) in a putative extracellular domain that enables the association of the $P2Y_2$R with $\alpha_v\beta_{3/5}$ integrins allowing activation of heterotrimeric G_o and G_{12} proteins that regulate the activities of the small GTPases Rho and Rac (Erb *et al.*, 2001; Bagchi *et al.*, 2005; Liao *et al.*, 2007), regulators of actin polymerization and cytoskeletal rearrangements required for cell migration (Xu *et al.*, 2003; Jang *et al.*, 2005). In addition, the $P2Y_2$R contains SH3-binding motifs in its C-terminal domain that can interact with the actin-binding protein filamin A (FLNa), another known regulator of cytoskeletal rearrangements, suggesting that the $P2Y_2$R may regulate migration of cells by both RGD-dependent interactions with integrins and C-terminal-dependent association with actin-binding proteins (Yu *et al.*, 2008). Moreover, the $P2Y_2$R has been reported to regulate migration of some cell types via transactivation of growth factor receptors (Bagchi *et al.*, 2005; Norambuena *et al.*, 2010), suggesting that a complex array of signaling events uniquely coupled to $P2Y_2$R activation may be required to optimize the cytoskeletal rearrangements whereby the $P2Y_2$R regulates cell-specific functions, *e.g.*, neurite outgrowth, phagocytosis, synapse formation and chemokinesis.

$P2Y_2$R expression in rat primary cortical neurons is upregulated in response to IL-1β (Kong *et al.*, 2009), a cytokine whose levels are elevated in the brains of AD patients (Xie *et al.*, 2004; Lee *et al.*, 2010). Subsequent activation of these upregulated $P2Y_2$Rs in neurons promotes neurite outgrowth (Pooler *et al.*, 2005) and generates the non-amyloidogenic soluble APPα peptide, rather than neurotoxic $A\beta_{1–42}$ peptide aggregates associated with AD (Kong *et al.*, 2009). In mouse primary microglial cells, the $P2Y_2$R is upregulated in the presence of $A\beta_{1–42}$ and when activated can increase the phagocytosis and degradation of neurotoxic forms of Aβ (Boucsein *et al.*, 2003; Peterson *et al.*, 2010; Kim *et al.*, 2012). In astrocytic cells, the $P2Y_2$R has been suggested to contribute to synaptic transmission through the regulation of intracellular calcium waves (Halassa *et al.*, 2009) and upregulates

anti-apoptotic protein expression to promote cell survival (Chorna *et al.*, 2004). Thus, $P2Y_2R$ upregulation in response to proinflammatory conditions likely serves a neuroprotective role in the CNS that requires contributions from both glial and neuronal $P2Y_2Rs$, as described in more detail below.

The human $P2Y_4R$ is preferentially activated by uridine nucleotides, whereas the rat and mouse $P2Y_4Rs$ are stimulated equipotently by ATP and UTP (Webb *et al.*, 1998; Brunschweiger and Muller, 2006; Jacobson *et al.*, 2009). $P2Y_4R$ mRNA is highly expressed in human brain (Moore *et al.*, 2001). Single cell RT-PCR demonstrated the expression of $P2Y_4Rs$ in rat hippocampal pyramidal neurons (Rodrigues *et al.*, 2005). The expression of $P2Y_4Rs$ in astrocytes and microglial cells has been extensively documented (Webb *et al.*, 1998; Lenz *et al.*, 2000; Fumagalli *et al.*, 2003; Bianco *et al.*, 2005a). $P2Y_4Rs$, as well as $P2Y_2Rs$, are strongly expressed in glial endfeet in proximity to blood vessel walls (Simard *et al.*, 2003) where their activation by ATP has been postulated to regulate blood–brain barrier function, blood flow, metabolic trafficking and water homeostasis (Simard *et al.*, 2003; Zonta *et al.*, 2003).

The $P2Y_6R$ is activated by uridine 5'-diphosphate (UDP), and to a lesser extent UTP (Communi *et al.*, 1996). In 18 areas of the human brain, the level of $P2Y_6R$ mRNA expression was highest in the amygdala, cingulate gyrus, nucleus accumbens and putamen (Moore *et al.*, 2001). Single cell RT-PCR revealed $P2Y_6R$ mRNA in 2 of 12 pyramidal neurons of rat hippocampus (Rodrigues *et al.*, 2005). In addition, $P2Y_6R$ mRNA has been demonstrated in superior cervical ganglion (Calvert and Evans, 2004; Calvert *et al.*, 2004) and dorsal-root ganglion neurons (Sanada *et al.*, 2002; Ruan and Burnstock, 2003). Functional studies have revealed the presence of $P2Y_6R$ activity in cerebellar and cortical astrocytes (Fumagalli *et al.*, 2003; Bennett *et al.*, 2003). $P2Y_6R$ activation has been shown to increase phagocytotic activity of microglia, postulated to occur *in vivo* in response to UTP released from damaged cells (Koizumi *et al.*, 2007; Liu *et al.*, 2009). Consistent with this hypothesis, injury has been shown to induce increased $P2Y_6R$ expression in astroglial cells (Franke *et al.*, 2004a; Franke *et al.*, 2004b). In microglial cells stimulated overnight with bacterial lipopolysaccharide, $P2Y_6R$-mediated increases in the intracellular calcium concentration were observed, suggesting a role for the $P2Y_6R$ in neuroinflammation (Bianco *et al.*, 2005a).

The $P2Y_{11}R$ can couple to multiple G proteins to regulate the activity of two second messenger systems: adenylate cyclase-mediated cAMP production, and PLC-dependent production of IP_3 and DAG that modulate calcium release from intracellular storage sites and protein kinase C activation, respectively (Communi *et al.*, 1999). The $P2Y_{11}R$ is activated by ATP or ADP, but not by uridine nucleotides (Communi *et al.*, 1999). $P2Y_{11}R$ mRNA expression is prominent in nucleus accumbens, parahippocampal gyrus, putamen and striatum (Burnstock and Knight, 2004). The $P2Y_{11}R$ has been localized to single rat hippocampal pyramidal neurons and to Purkinje cells in adult rat cerebellum (Rodrigues *et al.*, 2005; Volonté *et al.*, 2006). Inhibition of the $P2Y_{11}R$ has been shown to delay ATP-induced neutrophil apoptosis, suggesting a role for the $P2Y_{11}R$ in the regulation of neuroinflammatory responses (Vaughan *et al.*, 2007).

The $P2Y_{12}R$ is widely distributed in the brain with a pattern consistent with expression in astrocytes (Hollopeter *et al.*, 2001; Kunapuli *et al.*, 2003). RT-PCR has demonstrated the presence of $P2Y_{12}R$ mRNA in single rat hippocampal pyramidal neurons (Rodrigues *et al.*, 2005). Cortical and cerebellar astrocytes and astrocytes in the rat nucleus accumbens also express $P2Y_{12}Rs$ (Fumagalli *et al.*, 2003; Franke *et al.*, 2004b; Carrasquero *et al.*, 2005). $P2Y_{12}Rs$ have been suggested to regulate the migration of microglial cells towards damaged neurons (Sasaki *et al.*, 2003). $P2Y_{12}R$ expression in microglia is robust in the 'resting' state,

but dramatically reduced in activated microglia, and $P2Y_{12}R^{-/-}$ mice have significantly diminished directional branch extension toward sites of cortical damage *in vivo* (Haynes *et al.*, 2006). In contrast, a recent study concludes that the expression of the $P2Y_{12}R$ in the CNS is restricted to oligodendrocytes (Amadio *et al.*, 2006). It also has been suggested $P2Y_{12}Rs$ contribute to the migration and adhesion of glial cell processes to axons during pre-myelination (Amadio *et al.*, 2006).

The $P2Y_{13}R$ is activated by ADP (Marteau *et al.*, 2003) and 2-methylthio ADP is a potent synthetic agonist (Burnstock, 2006b), similar to the $P2Y_{12}R$; however ATP and ATP analogues are inactive at the $P2Y_{13}R$ (Communi *et al.*, 1997). $P2Y_{13}R$ expression has been localized to brainstem astrocytes and glutamatergic neurons (Moore *et al.*, 2000; Moore *et al.*, 2001; Jiménez *et al.*, 2011). $P2Y_{13}Rs$, along with $P2Y_1$ and $P2Y_{12}$ receptors, have been shown to regulate Na^+ and Cl^--dependent synaptic glycinergic neurotransmitter transporters to increase transport of glycine from the synaptic cleft, thereby maintaining quantal glycine levels in inhibitory synaptic vesicles (Gomeza *et al.*, 2003; Jiménez *et al.*, 2011). The $P2Y_{13}R$ can also activate the glycogen synthase kinase-3 (GSK-3)-dependent phosphatidylinositol 3-kinase (PI3K)/Akt survival pathway to increase translocation of the GSK-3 substrate β-catenin to the nucleus, where it modulates expression of cell survival genes (Ortega *et al.*, 2008).

The $P2Y_{14}R$ is expressed in astrocytes (Moore *et al.*, 2001), and RT-PCR and single cell Ca^{2+} imaging has documented the functional expression of $P2Y_{14}Rs$ in rat cortical and cerebellar astrocytes (Fumagalli *et al.*, 2003; Carrasquero *et al.*, 2005). Agonists of the $P2Y_{14}R$ include UDP-glucose, UDP-galactose, UDP-glucuronic acid and UDP-N-acetylglucosamine, but not adenine or uridine nucleotides (Chambers *et al.*, 2000; Abbracchio *et al.*, 2003; Burnstock, 2006a). UDP-glucose has been shown to be released from a variety of cell lines, and UDP-glucose levels can exceed those of ATP under various conditions (Lazarowski *et al.*, 2003). Functionally, $P2Y_{14}Rs$ in primary microglial cells from rat brain have been shown to modulate the calcium response to bacterial lipopolysaccharide (Bianco *et al.*, 2005a). $P2Y_{14}Rs$ expressed in immature dendritic cells have been suggested to play a role in the immune system's anti-tumor response (Skelton et al., 2003; Fischer and Krügel, 2007).

Neuroinflammatory P2X7Rs Regulate Neuroprotective $P2Y_2R$ Expression

P2X7R activation contributes to neuroinflammation by promoting mitochondrial and plasma membrane depolarization, the formation of plasma membrane pores, plasma membrane blebbing, and the production of reactive oxygen species (ROS) (Schulze-Lohoff *et al.*, 1998; Morelli *et al.*, 2003; Verhoef *et al.*, 2003; Wang *et al.*, 2004; Adinolfi *et al.*, 2005; Lister *et al.*, 2007; Roger *et al.*, 2008; Bours *et al.*, 2011). In addition, P2X7R activation promotes neuroinflammation by causing the release of proinflammatory cytokines, such as IL-1β and TNF-α (Di Virgilio, 2007; Lister *et al.*, 2007; Tschopp and Schroder, 2010) and activation of MAP kinases and NF-κB, resulting in upregulation of proinflammatory gene products, including COX-2, chemokines and cell adhesion molecules (Pfeiffer *et al.*, 2004; Potucek *et al.*, 2006; Lister *et al.*, 2007; Lenertz *et al.*, 2009; Skaper *et al.*, 2009; Shiratori *et al.*, 2010) and the $P2Y_2R$ (Degagne *et al.*, 2009). Importantly, P2X7R-mediated pore formation initially increases ATP release through P2X7R interactions with a pannexin hemi-channel in cells (Pelegrin and Surprenant, 2006). P2X7R-mediated IL-1β and ATP release is a mechanism whereby the P2X7R regulates functional $P2Y_2R$ expression in neurons and provides agonist for the activation of the upregulated $P2Y_2R$ and other P2 receptors (Peterson *et al.*, 2010). ATP release also can occur from activated microglia and astrocytes in response to oxidative stress (Peterson *et al.*, 2010), following neuronal excitation (Bodin and Burnstock, 2001; Fields, 2011), via volume-activated anion channels (Fields, 2011), or

upon exposure of cells to fibrillar or oligomeric forms of amyloidogenic $A_{1–42}$ peptides (Inoue, 2008; Sanz *et al.*, 2009; El Khoury and Luster, 2008; Kim *et al.*, 2012). Thus, P2X7 and $P2Y_2$ receptors may represent promising targets to control inflammatory responses associated with neurodegenerative diseases. Indeed, mice deficient in the P2X7R ($P2X7R^{-/-}$ mice) exhibit decreased inflammatory responses (Labasi *et al.*, 2002; Chessell *et al.*, 2005; McGaraughty *et al.*, 2007; Lucattelli *et al.*, 2011), including a reduction in pulmonary fibrosis in a mouse model of lung inflammation (Lucattelli *et al.*, 2011) and the absence of pain hypersensitivity in mouse models of chronic inflammation and neuropathic pain (Chessell *et al.*, 2005). Phase I and II clinical trials for selective P2X7R antagonists are presently underway for the treatment of rheumatoid arthritis and other inflammatory diseases (Friedle et al. 2010; Arulkumaran et al. 2011).

Upregulation of the $P2Y_2R$ in response to P2X7R activation appears to promote neuroprotective responses. The ability of the $P2Y_2R$ to stimulate neuroprotective responses depends upon the coupling of the receptor to intracellular signaling pathways that are distinct among the P2YR family (see Fig. 2). These responses associated with $P2Y_2R$ upregulation include the outgrowth and stabilization of dendritic spines (Jang *et al.*, 2005; Bamburg and Bloom, 2009; Peterson *et al.*, 2010), which requires RGD-dependent $P2Y_2R$/α_v integrin interaction to stimulate Rac and Rho and induce cytoskeletal rearrangements (Bagchi *et al.*, 2005; Liao *et al.*, 2007) and upregulation of neurofilament M and neurofilaments that promote neurite outgrowth (Pooler *et al.*, 2005). $P2Y_2Rs$ also require Src to co-localize with the tyrosine receptor kinase A (TrkA) in the presence of nerve growth factor, a pathway that regulates neurite outgrowth and cell division via the activation of p38 and ERK1/2 MAP kinases (Arthur *et al.*, 2005, 2006a). In neural progenitor cells isolated from the subventricular zone of adult mouse brain, $P2Y_2R$ activation was shown to induce proliferative responses such as the transient activation of the epidermal growth factor receptor (EGFR), the MAP kinases ERK1/2 and the transcription factor CREB (Grimm *et al.*, 2009). Other studies indicate that the $P2Y_2R$ mediates the activation of PI3-kinase/Akt and MAP kinases to inhibit apoptosis of PC12 pheochromocytoma cells and dorsal root ganglion neurons (Arthur *et al.*, 2006a; Arthur *et al.*, 2006b). $P2Y_2R$ upregulation by IL-β1 and subsequent activation in primary cortical neurons increases amyloid precursor protein (APP) processing via activation of matrix metalloproteases (*i.e.*, α-secretases), a neuroprotective response that produces a non-amyloidogenic soluble APP peptide (*i.e.*, sAPPα) rather than neurotoxic amyloidogenic Aβ peptide (Kong *et al.*, 2009). IL-1β is known to stimulate neuronal synthesis of APP and increase the release of neurotoxic Aβ, which further enhances IL-1β production (Walker *et al.*, 1995). We postulate that upregulation of the $P2Y_2R$ induced by IL-1β *in vivo* counteracts the potential neurotoxic effects of IL-1β-dependent elevations in APP levels by promoting generation of non-toxic sAPPα instead of Aβ. Thus, $P2Y_2R$ upregulation in the CNS may delay the progression of neurodegeneration associated with reactive gliosis and chronic inflammation in AD and other neurological disorders.

Glial cells, including astrocytes and microglia, play important neuroprotective roles. Astrocytes contribute to the maintenance of the blood-brain barrier (BBB) (Sudo *et al.*, 1998; Shlosberg *et al.*, 2010; Barreto *et al.*, 2011), which prevents invasion of pathogenic, neurotoxic substances into the brain from the circulation (Takenouchi *et al.*, 2009; Sugama *et al.*, 2009). Astrocytes also release neurotrophic factors that regulate neuronal survival and sprouting and supply energy substrates to neurons (Giaume *et al.*, 2010). Astrocytes have been shown to release ATP under a variety of pathological conditions (Butt, 2011; Hamilton *et al.*, 2008; Hamilton *et al.*, 2010) and ATP levels are elevated sufficiently by inflammation *in vivo* to activate P2 nucleotide receptors (Butt, 2011). $P2Y_2Rs$ are upregulated in reactive astrocytes of the rat cortex and nucleus accumbens in response to mechanical injury (Franke *et al.*, 2004a; Franke *et al.*, 2004b) and have been suggested to enhance astrocyte survival

(Chorna *et al.*, 2004; Burgos *et al.*, 2007). In addition, interactions between the $P2Y_2R$ and integrins have been demonstrated to regulate the migration of astrocytes (Wang *et al.*, 2005; Bagchi *et al.*, 2005; Liao *et al.*, 2007). It also has been shown that P2X7R activation increases the expression of $P2Y_2Rs$ in rat astrocytes (D'Alimonte *et al.*, 2007) likely via P2X7R-mediated IL-1β release (Chakfe *et al.*, 2002; Suzuki *et al.*, 2004; Choi *et al.*, 2007; Mingam *et al.*, 2008; Sanz *et al.*, 2009; Takenouchi *et al.*, 2009).

Microglia have important immunoregulatory functions in the CNS. Injury or other insults to the CNS trigger transformation of quiescent microglia into activated phenotypes, *i.e.*, phagocytic macrophages (Kreutzberg, 1996; Streit, 2002). Activated microglia have neuroprotective functions (Streit, 2002; Butovsky *et al.*, 2005; Turrin and Rivest, 2006; Lalancette-Hébert *et al.*, 2007; El Khoury *et al.*, 2007), although sustained activation can be neurotoxic (Butovsky *et al.*, 2005; Boillée *et al.*, 2006; Streit, 2006; Neumann and Takahashi, 2007). Microglial cell activation by proinflammatory cytokines has been shown to increase cell motility and proliferation (Brown and Neher, 2010), responses associated with reactive gliosis in neurodegenerative diseases. Adenine and uridine nucleotides have been shown to increase the motility of microglial cells (Honda *et al.*, 2001; Haynes *et al.*, 2006; Koizumi *et al.*, 2007) via activation of $P2Y_2$ and $P2Y_{12}$ receptors (Haynes *et al.*, 2006; Chen *et al.*, 2006) and ATP release can significantly increase microglial process extension towards a site of injury (Davalos *et al.*, 2005). The endogenous expression of $P2Y_2Rs$ has been reported in mouse microglia (Shigemoto-Mogami *et al.*, 2001; Crain *et al.*, 2009) where they have been shown to regulate responses associated with reactive gliosis (Chorna *et al.*, 2004; Franke *et al.*, 2004b; Wang *et al.*, 2005; Weisman *et al.*, 2005; Burgos *et al.*, 2007; Peterson *et al.*, 2010). For example, the $P2Y_2R$ agonists UTP and ATP released from apoptotic cells have been shown to induce migration of phagocytic cells (Elliott *et al.*, 2009), which presumably serves to enhance the clearance of cellular debris. Microglial cells exposed to Aβ also have been shown to release ATP (Rogers and Lue, 2001; Sanz *et al.*, 2009). Studies using peritoneal macrophages in mice have shown that stimulation of $P2Y_2$ and $P2Y_{12}$ receptors induces the formation of lamellipodia in membrane protrusions which is required for cell motility (Kronlage *et al.*, 2010). Co-activation of $P2Y_2$ and $P2Y_6$ receptors in human monocytes enhances migration, a response shown to involve toll-like receptor-induced IL-8 release (Ben Yebdri *et al.*, 2009; Kukulski *et al.*, 2010). We have found that $P2Y_2R$ activation increases mouse microglial cell migration and phagocytic activity, such as the uptake of neurotoxic oligomeric $A_{1–42}$, responses that are absent in microglia from $P2Y_2R^{-/-}$ mice (Kim *et al.,* 2012). Both activated astrocytes and microglia internalize and degrade A (Chung *et al.*, 1999; Wyss-Coray *et al.*, 2001; Pihlaja *et al.*, 2008; Mandrekar *et al.*, 2009; Kong *et al.*, 2010), a pathway that reduces Aβ toxicity in neurons that is postulated to play a role in the progression of AD. We speculate that $P2Y_2Rs$ in glial cells contribute to the phagocytosis and degradation of neurotoxic forms of Aβ *in vivo* under conditions where elevated levels of ATP release and IL-1β generation occur (Ferrari *et al.*, 1997; Di Virgilio *et al.*, 1998).

Recent studies suggest that peripheral leukocytes and hematopoietic cells that differentiate into microglia have important functions in the CNS (Gate *et al.*, 2010), particularly in response to tissue injury (Hawkes and McLaurin, 2009). $P2Y_2Rs$ in endothelial cells that form the BBB may also regulate the migration of leukocytes across the BBB towards sites of injury or disease in the brain. Activation of the endothelial $P2Y_2R$ has been shown to enhance the diapedesis of neutrophils towards the chemoattactant lipopolysaccharide of gram-negative bacteria (Kukulski *et al.*, 2010) through a mechanism involving Rho kinase activation, suggesting that $P2Y_2R$ associations with integrins may be involved (Bagchi *et al.*, 2005; Liao *et al.*, 2007). Microglia derived from bone marrow have been shown to phagocytose Aβ deposits in the brain of AD mice to a greater extent than resident brain microglia (Simard *et al.*, 2006). Thus, diapedesis of microglia across the BBB, in addition to

neurite outgrowth, non-amyloidogenic APP processing and phagocytosis of neurotoxic forms of Aβ may comprise a neuroprotective phenotype linked to $P2Y_2R$ activation in several cell types that comprise the brain (*i.e.*, neurons, glial cells and endothelium). The neuroprotective pathways by which P2X7R-mediated upregulation and activation of $P2Y_2Rs$ are suggested to contribute to neuroprotection in the brain are shown in Fig. 3.

Conclusion

This review summarizes data indicating that seven ionotropic P2X and eight G protein-coupled P2Y receptors for extracellular nucleotides are expressed in cell types comprising the CNS and these P2X and P2Y receptor subtypes have been shown to regulate diverse physiological and pathological responses under a variety of conditions. Recent studies indicate that activation of the P2X7R rsubtype during inflammation causes upregulation and activation of $P2Y_2Rs$ to promote neuroprotective responses. These findings suggest that ATP released from injured or stressed cells in the CNS can activate P2X7Rs in microglial cells to increase the release of proinflammatory cytokines, such as IL-1β, that increase the expression of the $P2Y_2R$, particularly in neurons. Other studies indicate that both P2X7R and $P2Y_2R$ activation can increase phagocytosis of neurotoxic forms of Aβ and that activation of the $P2Y_2R$ increases non-amyloidogenic APP processing, neuroprotective responses that are postulated to delay the onset or retard the progression of neurodegenerative diseases, such as Alzheimer's disease. In addition, $P2Y_2R$ activation in neurons has been shown to increase neurite outgrowth. The $P2Y_2R$ contains multiple motifs that enable its activation to directly couple to integrin and growth factor receptor signaling pathways that play a role in cell proliferation and differentiation and cytoskeletal rearrangements that are critical for tissue repair. Thus, the studies described in this review suggest that the P2X7R and $P2Y_2R$ are promising targets for the treatment of neurodegenerative diseases.

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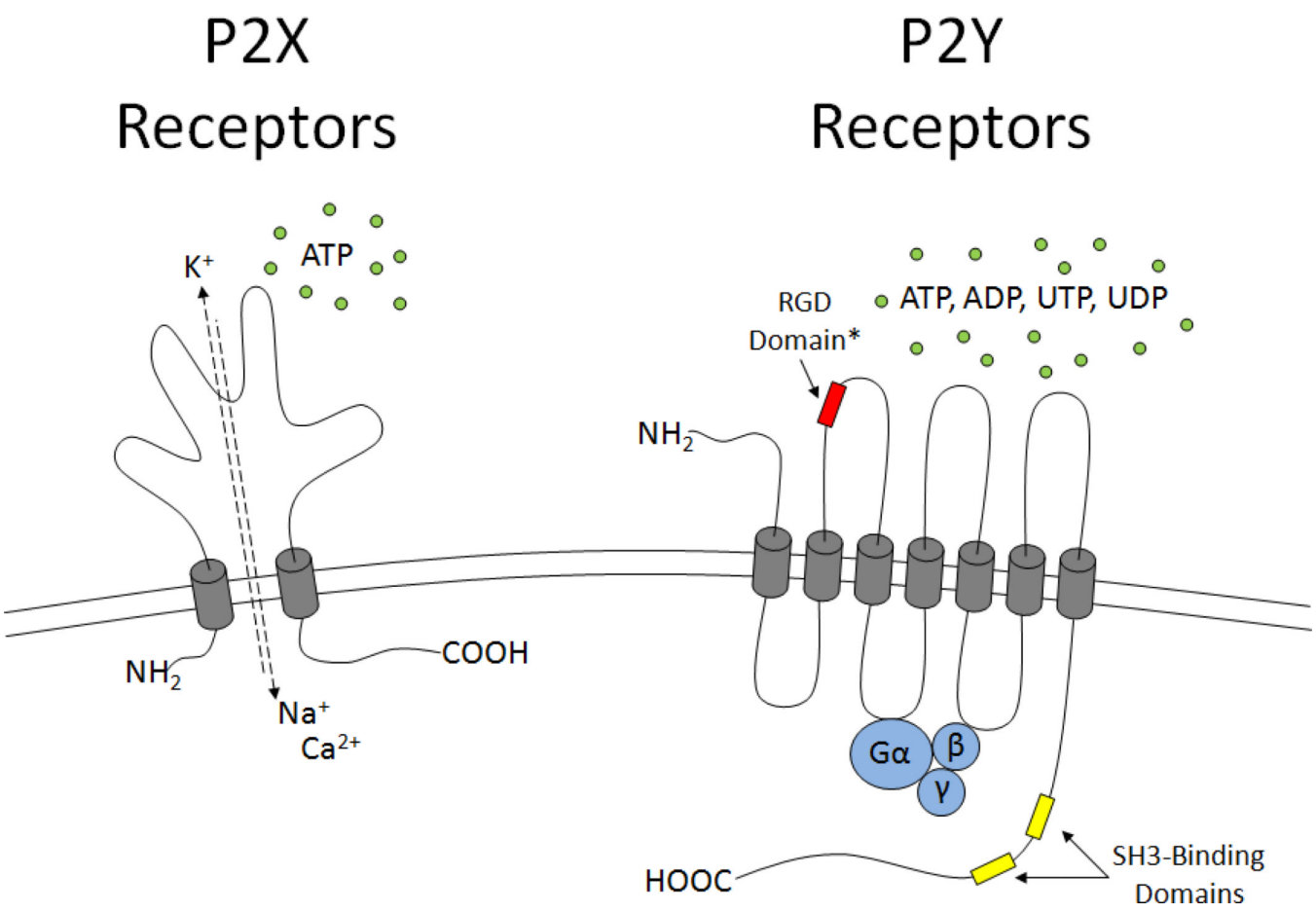

Fig. 1. Structural Features of P2X and P2Y Receptors

Based on structure and function, P2 nucleotide receptors can be divided into two classes. The P2X receptors are nonselective ligand-gated cation channels featuring two transmembrane domains and a large extracellular loop. P2X receptors interact in a wide variety of homo- and heteromeric forms depending on tissue-specific expression and receptor subtype (*i.e.*, P2X1–7) and they are activated by extracellular ATP. The P2X7R has received much attention due to its capacity for intracellular signaling via a large C-terminal tail and its participation in inflammatory processes. The P2YRs are classical G protein-coupled receptors featuring an extracellular N-terminus, 7 transmembrane domains, and an intracellular C-terminus that is structurally diverse between P2Y receptor subtypes. The G_q-coupled $P2Y_{1,2,4,6,11}$ and the G_i-coupled $P2Y_{12,13,14}$ receptors are activated by adenine and uridine tri- and dinucleotides with pharmacologically distinct efficacies and potencies. The $P2Y_2R$ subtype has been shown to associate with integrins via an extracellular RGD domain and to transactivate growth factor receptors via the binding of Src to Src-homology-3 (SH3) domains located within the C-terminus.

*- only present in the $P2Y_2$ receptor

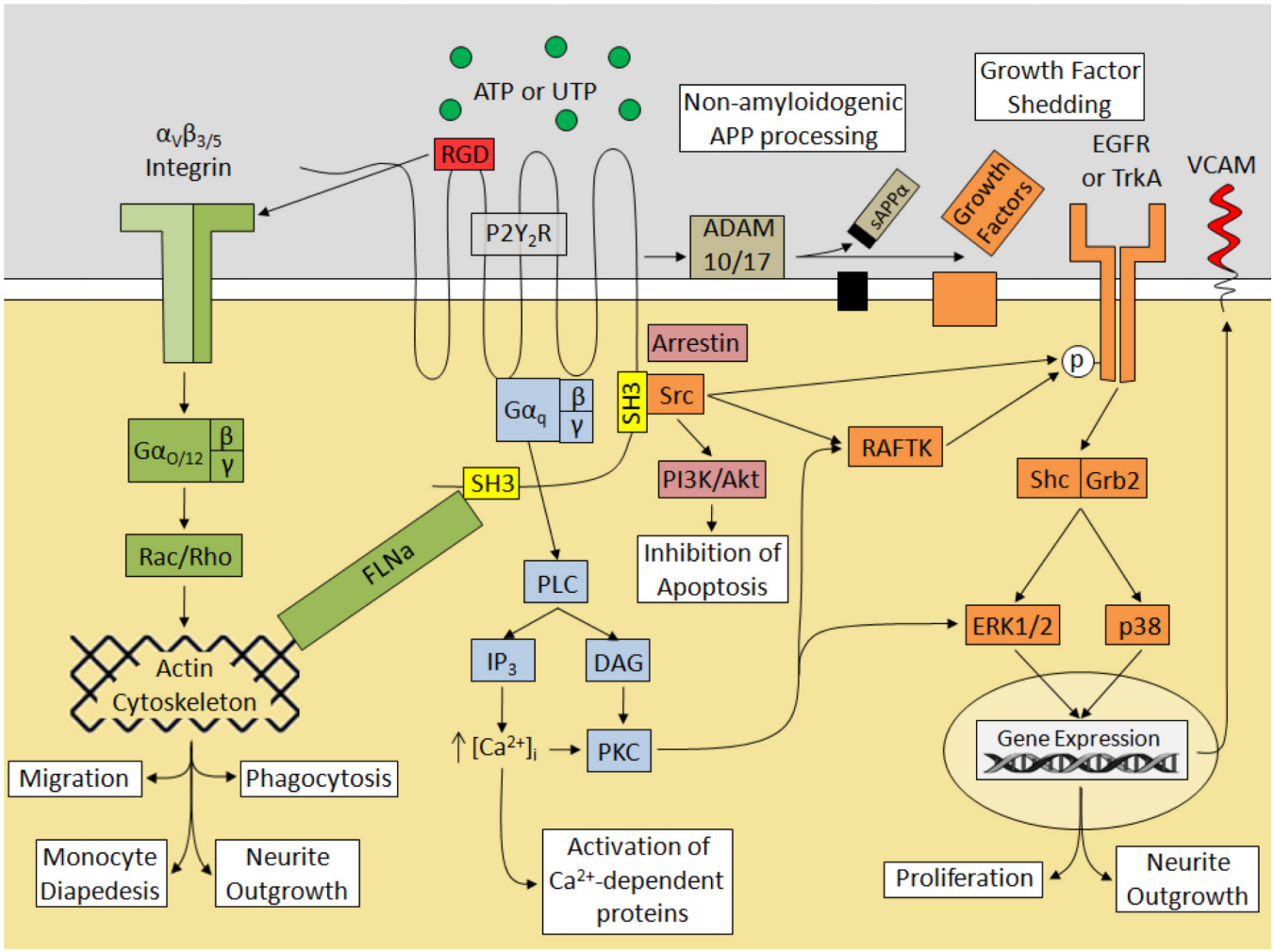

Fig. 2. $P2Y_2R$ Signaling Pathways

The $P2Y_2R$ modulates a variety of cellular processes through classical G protein-coupled receptor pathways and unique receptor motifs. Activation of the $P2Y_2R$ by ATP or UTP stimulates the G_q-dependent activation of PLC leading to the generation of IP_3 and DAG. IP_3 triggers a release of Ca^{2+} from intracellular stores leading to an increase in $[Ca^{2+}]_i$ and the activation of Ca^{2+}-dependent proteins, whereas DAG serves to activate PKC leading to activation of a variety of downstream proteins including RAFTK; also known as Pyk2) and the MAP kinases ERK1/2. The Src-homology-3 (SH3) domains in the C-terminus allow the $P2Y_2R$ to stimulate Src-dependent transactivation of growth factor receptors and their downstream signaling molecules Shc and Grb2 leading to ERK1/2 and p38 activation of cell proliferation and neurite outgrowth. The $P2Y_2R$ also has been shown to upregulate VCAM-1 through a pathway involving VEGFR-2. Furthermore, $P2Y_2R$ activation has been shown to stimulate the PI3K/Akt pathway to inhibit apoptosis in neurons, a response that was dependent on Src activation. SH3 domains also allow the $P2Y_2R$ to interact with the actin cytoskeleton via the actin-binding protein filamin A (FLNa). Alternatively the $P2Y_2R$ can access the actin cytoskeleton through an extracellular RGD domain that interacts with $\alpha_v\beta_{3/5}$ integrins to enable activation of G_o and G_{12} proteins allowing the $P2Y_2R$ to stimulate cell migration, phagocytosis, neurite outgrowth, and diapedesis by activating the cytoskeletal regulators Rac and Rho. Lastly, the $P2Y_2R$ is able to activate the matrix

metalloproteases ADAM10 and ADAM17 to induce non-amyloidogenic APP processing and shedding of growth factors.

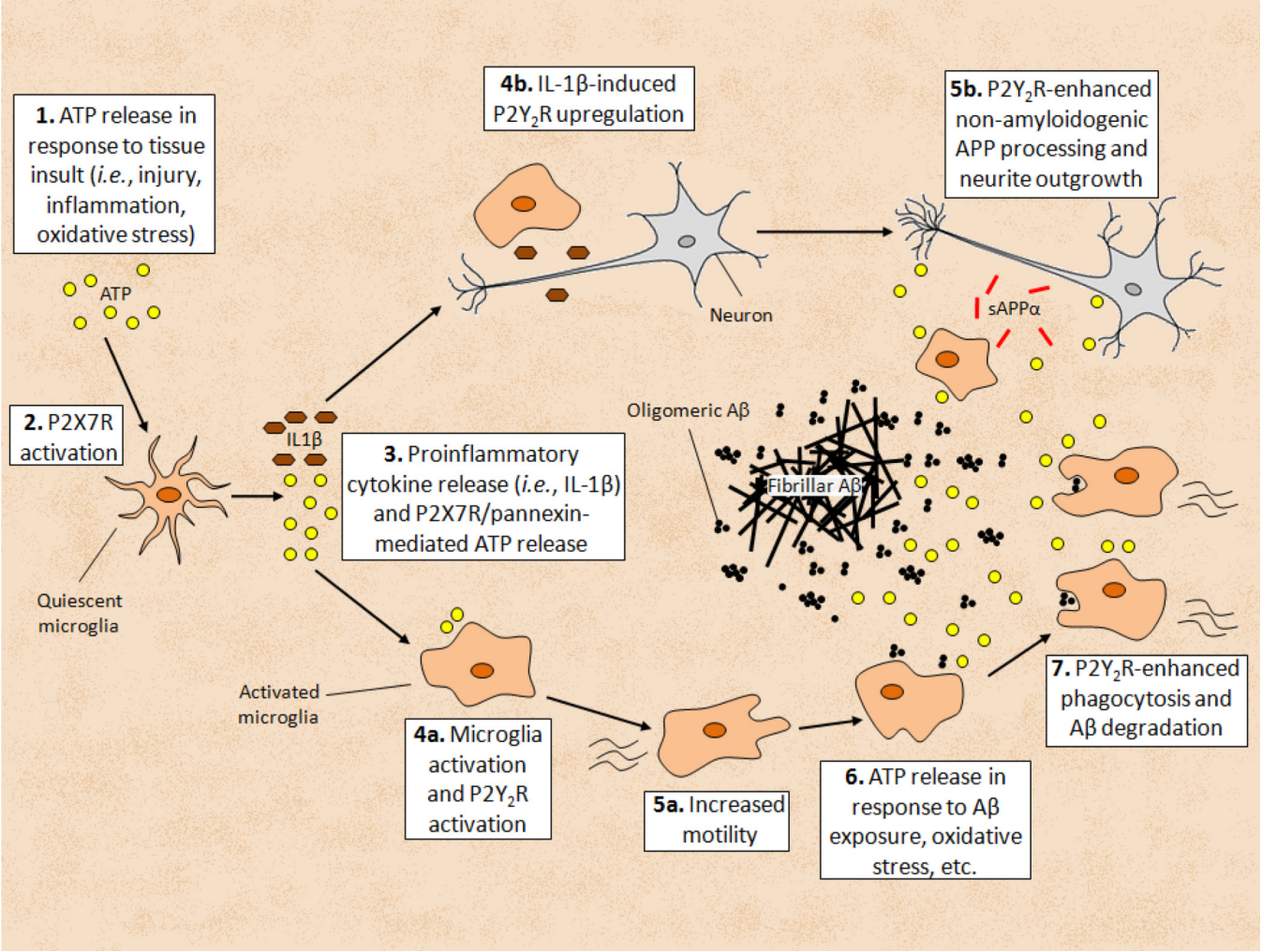

Fig. 3. P2X7R-mediated Neuroinflammation Stimulates $P2Y_2R$-mediated Neuroprotective Responses

(1) ATP released under neuroinflammatory conditions can (2) activate the P2X7R to stimulate (3) the release of proinflammatory cytokines, including interleukin-1β (IL-1β), and further ATP release via interaction of the P2X7R with pannexin hemi-channels. In response to the proinflammatory environment, quiescent microglia take on an (4a) activated phenotype and $P2Y_2R$ activation by extracellular ATP increases (5a) cell motility. In addition, (4b) IL-1β upregulates $P2Y_2R$ expression in neurons and glia through NF-κB activation. (6) ATP release (from Aβ exposure, cytokine exposure, oxidative stress, etc.) provides agonist for the (5b) $P2Y_2R$ to stimulate non-amyloidogenic APP processing and neurite outgrowth through $P2Y_2R$ interactions with matrix metalloproteases and the actin cytoskeleton, respectively. Another neuroprotective response to (7) $P2Y_2R$ activation in microglial cells is increased phagocytosis and degradation of neurotoxic oligomeric $A\beta_{1–42}$.

Table 1

P2X Receptors in the Nervous System

The expression and function of P2X receptor subtypes in the nervous system are summarized in Table 1. This table highlights the information presented in this review article and is not considered to be comprehensive.

Receptor Subtype	Expression		Function
Homomeric	**Cell Type**	**Region**	
P2X1	Neurons, astrocytes, microglia	Cerebral cortex, superior cervical ganglia	Neurogenic smooth muscle contraction, platelet activation, neuron and glial responses
P2X2	Neurons, astrocytes	Cerebral cortex, cerebellum, hippocampus, striatum, habenula, substantia nigra, dorsal root ganglia, mesenteric ganglia	Nociceptive transmission, hyperalgesia, allodynia, pre- and postnatal neurogenesis
P2X3	Neurons	Dorsal root ganglia, spinal cord	Enhance glutamate and substance P release, neuropathic pain sensation
P2X4	Neurons, astrocytes	Cerebellum, hippocampus, brainstem, spinal cord	Release of brain-derived neurotrophic factor, induce neuropathic pain, prostaglandin E2 release, synaptic strengthening, hypersensitivity to sensory stimuli
P2X5	Neurons	Cerebral cortex, cerebellum, hippocampus, hypothalamus, thalamus, olfactory bulb, globus pallidum, midbrain and hindbrain	Interconnection of cortical areas, post-synaptic purinergic transmission
P2X6	Neurons, astrocytes	Cerebellum, hippocampus, purkinje neurons, pyramidal neurons, sensory ganglia	Rarely forms functional homomeric receptors
P2X7	Neurons, astrocytes, microglia	Cerebral cortex, hippocampus, brainstem, nucleus accumbens, spinal cord	Release of proinflammatory cytokines, apoptosis, membrane pore formation, glutamate release, ATP release, induction of synaptic plasticity
Heteromeric			
P2X1/P2X2	Neurons	Superior cervical ganglia	ATP-mediated physiological responses
P2X1/P2X5	Astrocytes	Cerebral cortex	ATP-evoked membrane currents
P2X2/P2X3	Neurons	Dorsal root ganglia	Similar to P2X3, but with reduced desensitization
P2X2/P2X6	Neurons	Dogiel type II neurons in myenteric plexus	ATP-mediated physiological responses

Table 2

P2Y Receptors in the Nervous System

The agonists, expression and function of P2Y receptor subtypes in the nervous system are summarized in Table 2. This table highlights the information presented in this review article and is not considered to be comprehensive.

Receptor Subtype	Agonist	Expression		Function
		Cell Type	Region	
$P2Y_1$	ADP, ATP	Neurons, astrocytes, microglia, oligodendrocytes	Cerebral cortex, cerebellum, hippocampus, midbrain, caudate nucleus, putamen, globus pallidus, habenula, subthalamic nucleus, dorsal root ganglia, dorsal horn	Synaptic transmission modulation, provides neuroprotection by stimulating IL-6 release from astrocytes, brain development and repair, sensory reception
$P2Y_2$	ATP, UTP	Neurons, astrocytes, microglia	Cerebral cortex, cerebellum, hippocampus, nucleus accumbens, spinal cord	Promote neurite outgrowth, stimulate α-secretase-dependent processing of amyloid precursor protein, increase phagocytosis of Aβ peptide, regulation of intracellular calcium waves, stimulate proliferation, modulate pain sensation, increase cell motility
$P2Y_4$	ATP, UTP	Neurons, astrocytes, microglia	Cerebral cortex, hippocampus	Synaptic transmission modulation, regulation of blood-brain barrier function, blood flow, metabolic trafficking, water homeostasis
$P2Y_6$	UDP, UTP	Neurons, astrocytes, microglia	Cerebral cortex, cerebellum, hippocampus, amygdala, cingulate gyrus, putamen, nucleus accumbens, superior cervical ganglia, dorsal root ganglia	Stimulate phagocytic activity, neuroinflammatory responses
$P2Y_{11}$	ATP, ADP	Neurons	Cerebellum, hippocampus, parahippocampal gyrus, putamen, striatum, nucleus accumbens	Neuroinflammatory responses
$P2Y_{12}$	ADP	Neurons, astrocytes, microglia, oligodendrocytes	Cerebral cortex, cerebellum, hippocampus, nucleus accumbens	Regulation of migration and chemotaxis
$P2Y_{13}$	ADP	Neurons, astrocytes	Brainstem	Modulation of synaptic transmission, modulates expression of cell survival genes
$P2Y_{14}$	UDP-glucose	Astrocytes, microglia	Cerebral cortex, cerebellum	Modulation of immune system's anti-tumor response