Mol Neurobiol (2008) 38:123–128
DOI 10.1007/s12035-008-8028-x

# P2X7 Receptors in Oligodendrocytes: A Novel Target for Neuroprotection

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Received: 10 March 2008 / Accepted: 13 May 2008 / Published online: 14 August 2008


**Abstract** Intense ATP signaling through P2X7 purinergic receptors can lead to excitotoxicity, a feature which initiates neuronal demise in experimental paradigms relevant to ischemia and to traumatic injury. In addition, recent data provide evidence that oligodendrocytes also express P2X7 receptors that are activated under experimental pathological conditions involving white matter demise. Thus, this receptor subtype is a promising target for the development of new drugs to prevent white matter damage in acute and chronic diseases.

**Keywords** Oligodendroglia · Myelin · ATP · P2X7 · Ischemia · Multiple sclerosis

## Introduction

Oligodendrocytes are the major component of white matter, which, in the human brain, accounts for up to about 50% of the total central nervous system (CNS) [1]. Damage to this cell population compromises brain function in many neurological diseases including stroke, trauma, and demyelinating disorders [2]. Drug candidates that selectively protect neurons in experimental studies did not succeed in clinical trials [3], a feature which may be due, at least in part, to the failure of these drugs to protect white matter cellular elements including oligodendrocytes and axons from injury.

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Oligodendrocytes express most neurotransmitter receptors known to be present in neurons [for recent reviews, see, 2, 4–6]. In particular, cells of the oligodendrocyte lineage are endowed with functional ionotropic glutamate receptors of all kinds, in a region- and temporal-specific manner throughout development, thus providing a signaling substrate that underlies complex functions not elucidated yet. In turn, oligodendrocytes are vulnerable to increased levels of glutamate [7–9], an excitatory neurotransmitter that may reach toxic extracellular concentrations after intense activity or after injury [for reviews, see 2, 10].

Glutamate damages oligodendrocytes, like neurons, by excitotoxicity as a consequence of prolonged activation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), kainate, and *N*-methyl-D-aspartate (NMDA) receptors [2, 10]. In both cell types, glutamate receptor-mediated toxicity depends entirely on calcium overload of the cytoplasm and can be initiated by disruption of glutamate homeostasis [2, 11].

Like glutamate, ATP is co-released with other transmitters and thus contributes to neuronal excitability by activating ionotropic (P2X) and metabotropic (P2Y) receptors [12–16]. ATP-gated P2X channels have marked calcium permeability, equivalent to NMDA receptors, and are formed by P2X1–P2X7 subunits [14, 17]. P2X receptors are expressed in CNS neurons whereby they participate in fast synaptic transmission and modulation [18]. In addition, P2X7 receptors mediate immunomodulatory responses [19, 20] and signaling cascades leading to neurodegeneration after ischemia [21]. Recently, it has also been shown that spinal cord injury is associated with prolonged P2X7 receptor activation, which results in neuronal excitotoxicity [22].

In this short review, I will discuss evidence showing that ATP excitotoxicity can also contribute to oligoden-

drocyte damage and to the progression of acute and chronic neurodegeneration.

## P2X7 Receptors in the CNS

P2X receptors have two hydrophobic, putative membrane spanning segments outlining the channel-pore, which in most P2X channels is cation-selective and—like members of the nicotinic and ionotropic glutamate receptors—discriminate poorly among different cations [23].

P2X7 receptors are atypical P2X receptors. Although they can form functional heteromers [24] as other P2X receptors do, they require ATP concentrations an order of magnitude higher for activation than do other P2X family members. Furthermore, P2X7 receptors have a long intracellular C-terminal sequence that is involved in forming a membrane pore that is permeable to molecules as large as 900 Da during prolonged agonist activity [25].

P2X7 receptors are undoubtedly expressed in neurons whereby modulate synaptic function and influence neuronal survival [26]. However, the identification and localization of these receptors has been controversial because of limited pharmacological and immunochemical tools. As a consequence, a number of inconsistent data have been reported [26]. In spite of that, consensus criteria were recently proposed to characterize unequivocally the presence of P2X7 receptors in the CNS. These criteria include the known affinity of various agonists (ATP and 2′-3′-*O*-(4-benzoylbenzoyl)-ATP) and antagonists (periodate-oxidized ATP, Brilliant Blue-G; pyridoxal-5′-phosphate-6-azophenyl-2′,5′-disulfonic acid) to human and non-human recombinant P2X7 receptors as well as the use of available knock out mice to assess the presence of P2X7 [26].

In neurons, P2X7 receptors constitute a large source of transmitter-activated $Ca^{2+}$ influx [14, 27]. Because of that, presynaptic P2X7 receptors play a role in neurotransmitter release. In particular, these receptors mediate glutamate release in spinal cord [28] and stimulate both GABA and glutamate outflow in hippocampus [29]. In addition to presynaptic effects, recent evidence indicates that P2X7 receptors have postsynaptic effects mediating postsynaptic AMPA receptor insertion in the rat hypothalamic paraventricular nucleus [30].

In turn, P2X7 receptors are also expressed in glial cells including Müller cells, astrocytes, microglia, and Schwann cells [14, 28] and contribute to the pathophysiology of these cells [31]. For instance, opening of the P2X7 pore in astrocytes can contribute to glutamate release, which is driven by the huge transmembrane gradient (millimolar versus micromolar concentrations, intra- and extracellular, respectively) and the inside negative membrane potential [32]. In addition, P2X7 receptor activation promotes the amplification of calcium signal transmission within the astrocytic network after exposure to low divalent cation solution [33]. Finally, microglial cells are also endowed with P2X7 [34], which can mediate the release of endocannabinoids and thus regulate inflammation [35].

## P2X7 Receptors in Oligodendrocytes

There is evidence showing that oligodendrocytes and their progenitors express P2X7 receptors in vitro [36–39]. Thus, ATP at high concentrations activated P2X receptor responses in optic nerve glia including oligodendrocytes that did not desensitize or saturate and was dependent on extracellular calcium [37]. In addition, benzoyl–benzoyl ATP (BzATP) also evokes an elevation in the cytosolic concentration of calcium, and the dye YO-PRO-1, which passes through pore-forming P2X7 receptors, is taken up by astrocytes, oligodendrocytes, and microglia [37]. Overall, these are characteristic properties of the P2X7 subtype, although they could be confounded by the presence in oligodendroglial cells of P2X2 and P2X4 receptors [40] that are also pore-forming in the presence of sustained high ATP concentrations [14].

Purinergic receptors have also been shown to participate in oligodendrocyte development [38, 41]. Thus, oligodendrocyte progenitors express different types of P2Y and P2X receptors, including P2X7, that induce calcium raises, stimulate their migration, inhibit the mitogenic response to platelet-derived growth factor PDGF and promote oligodendrocyte differentiation [38, 41]. However, the pharmacological profile of most of these ATP-induced effects corresponds to P2Y1 receptors, which play an important regulatory role in oligodendrocyte progenitors [38, 41].

Adding to and consistent with those previous results, we observed that differentiated oligodendrocytes have a robust expression of P2X receptors whose electrophysiological, pharmacological, and molecular properties in vitro and in vivo mostly correspond to that of the P2X7 subtype [Table 1; 40]. Thus, the $EC_{50}$ of the receptors response to ATP in oligodendrocytes is within the millimolar range and decreases by an order of magnitude in the absence of cations; receptor activation by ATP is blocked by Brilliant Blue-G (BBG) at submicromolar concentrations; and the immunochemical profile using two different antibodies to P2X7 indicate that this receptor type is expressed in vitro and in situ in oligodendrocytes and myelin in the optic nerve as well as in the spinal cord. As these antibodies can also stain neurons in P2X7 knock out mice [42], oligodendrocytes from these mice were also studied and showed much smaller responses to ATP, and absence of P2X7 as shown by immunoblotting and by immunostaining in cultures and optic nerve (see supplementary Fig. 1 in

**Table 1** Oligodendrocytes express P2X receptors with similar properties to those of recombinant P2X7 receptors

| | Recombinant P2X7 receptors (refs. [26, 27]) | Oligodendrocyte P2X7 receptors (ref. 40) |
|---|---|---|
| Agonists | | |
| ATP | $EC_{50}$=0.3–1.8 mM | $EC_{50}$=8.8 mM |
| BzATP | 10- to 30-fold more potent than ATP | $EC_{50}$=0.5 mM |
| No divalent cations | Increased affinity | Increased affinity |
| Antagonists | | |
| PPADS | > 50 μM | 100 μM |
| oATP | 100–300 μM (irreversible) | 1 mM (irreversible) |
| BBG | 10–100 nM | $IC_{50}$=17 nM |
| Calcium permeability | high (Pf %=4.6) | n.d. |
| Molecular weight | 75 kDa | 75 kDa |
| Location | n.a. | Soma, processes and myelin |
| Function | n.a. | n.d. |
| Pathophysiology | Excitotoxicity | Excitotoxicity and demyelination after EAE |

*BBG* Brilliant Blue-G, *BzATP* 20-30-*O*-(4-benzoylbenzoyl)-ATP, *EAE* experimental autoimmune encephalomyelitis, *oATP* periodate-oxidized ATP, *PPADS* pyridoxal-50-phosphate-6-azophenyl-20,50-disulfonic acid, *n.a.* not applicable, *n.d.* not determined yet, *Pf%* fractional calcium currents

[40]). Overall, these results indicate that matured oligodendrocytes have P2X7 receptors.

Unfortunately, these findings do not provide hints regarding the physiological functions mediated by P2X7 receptors in mature oligodendrocytes. It is possible that their strategic location in the myelin sheath [40] is relevant to myelin formation and preservation as well as to sensing electrical activity in the axons they insulate.

## Relevance of P2X7 Receptor Signaling in Oligodendrocytes to Disease

Glutamate receptor-mediated excitotoxicity in neurons and oligodendrocytes is caused by calcium overload of the cytoplasm as a consequence of membrane depolarization and calcium influx [2, 11]. In like manner, P2X receptors in oligodendrocytes are highly permeable to calcium and prolonged activation of these receptors is lethal to differentiated oligodendrocytes in culture and to mature oligodendrocytes in isolated optic nerves in vitro and in vivo (Fig. 1, [40]). The pharmacological profile of this toxicity corresponds to that of P2X7 receptors (Table 1). Thus, cell death is maximal at concentrations of ATP close to the millimolar range, and it is prevented in the absence of calcium or by low concentrations of the P2X7 antagonist BBG. However, P2X2 and P2X4 receptors, which are also present in oligodendrocytes, may contribute as well to some of the observed ATP toxicity in these cells.

Consistent with those findings, excitotoxicity-based neuronal degeneration triggered by P2X7 receptors has been described after ischemia [21] and subsequent to spinal cord injury [22]. In the latter, the release of ATP around the damaged area results in cell death of nearby neurons and oligodendrocytes via activation of P2X7 receptors [22]. In addition, these data add to recent studies documenting that P2X7 receptors are involved in neurodegenerative processes by regulating intracellular calcium concentration, interleukin-1β processing and release, as well as caspase activation under pathological conditions such as inflamma-

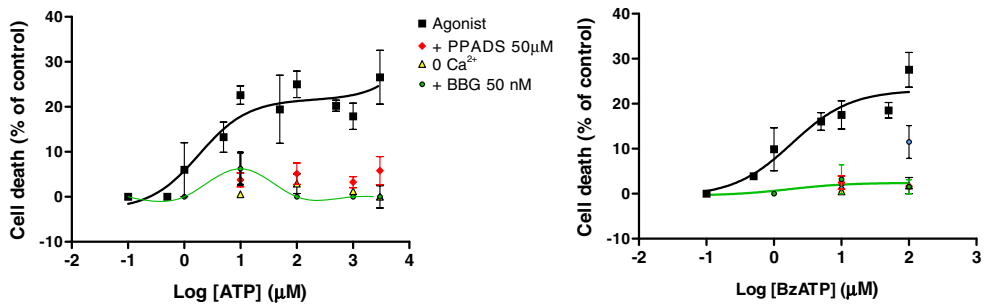


**Fig. 1** P2X receptor activation triggers oligodendrocyte death in vitro. **a** and **b** Toxicity of ATP and BzATP in optic nerve oligodendrocytes in culture, as measured 24 h later with calcein. Oligodendrocyte death is observed after exposure to ATP and BzATP at concentrations above 10 μM and 1 μM, respectively ($P$<0.05 for these concentrations or higher). This toxicity is prevented by co-application of the broad spectrum P2X antagonist PPADS, by P2X7 receptor antagonist BBG, and by $Ca^{2+}$ removal from the culture medium ($P$< 0.05 for each comparison between agonist and the various conditions). Modified from [40]

tion, mechanical injury, ischemia-reperfusion injury and stress [21, 43–45].

It is interesting to note that activation of P2X7 receptors in the optic nerve in vivo causes lesions reminiscent of those found in multiple sclerosis in that they have severe loss of oligodendroglia, intense microgliosis, demyelination, and axonal damage [40]. These features indicate that excess of extracellular ATP as a consequence of ongoing tissue damage in multiple sclerosis may in turn aggravate the progression of the disease. Indeed, treatment with P2X7 antagonists after the onset of experimental autoimmune encephalomyelitis (EAE), a well-established model of multiple sclerosis, ameliorates the course of the motor symptoms, reduces tissue damage, attenuates demyelination and restores normal conduction velocity in axons of the corticospinal tract [40]. Overall, these findings are consistent with the idea that sustained activation of P2X7 receptors can be deleterious to the CNS in pathological conditions including stroke and spinal cord injury [21, 22]. However, it should be noticed that EAE symptoms are exacerbated in P2X7-null mice [46], as a consequence of a disruption of the endocannabinoid neuroprotection system [47]. This apparent contradiction could be caused by adaptive changes in the immune response of P2X7 knock mice during the course of EAE and/or to altered repair mechanisms in CNS injury in these mice.

Overall, these findings suggest that blockade of P2X7 receptors can alleviate the symptoms of multiple sclerosis and delay its progression. However, the relevance of these findings to the etiology of multiple sclerosis is not known. On an intriguing note, P2X7 expression is increased in oligodendrocytes of non-lesioned, apparently normal, axonal tracts in postmortem tissue from patients with multiple sclerosis [40]. Enhanced levels of P2X7 in oligodendroglia may render this cell population vulnerable to ATP excitotoxicity and thus contribute to the onset and/or progression of multiple sclerosis (Fig. 2). Moreover, inter-individual variability in regions regulating the expression of the gene encoding P2X7 receptors may add to the genetic background predisposing to multiple sclerosis. Alternatively, genetic polymorphisms resulting in P2X7 receptor gain of function [48] may also elevate the sensitivity of oligodendrocytes to excitotoxicity.

## Concluding Remarks

The new findings have identified oligodendrocyte P2X7 receptors as a new intermediary of axon to myelin signaling. The location of these receptors in oligodendrocytes and myelin sheaths renders these sites particularly vulnerable to excitotoxic insults in spinal cord traumatic

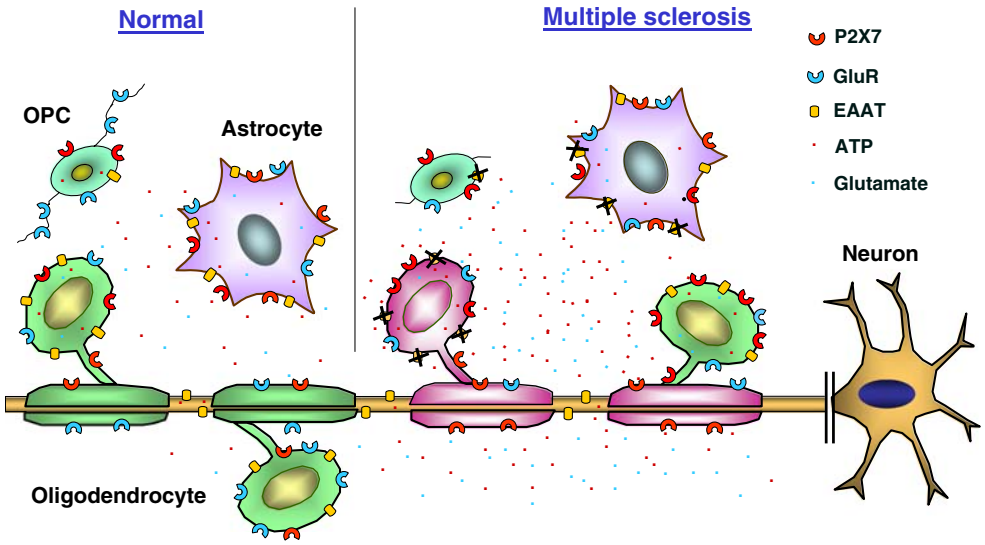


**Fig. 2** P2X7 receptors and oligodendrocyte excitotoxicity in multiple sclerosis. The identification of oligodendrocyte P2X7 receptors adds additional complexity to the mosaic of neurotransmitter-mediated interactions among glial cells and axons in white matter tracts. Astrocytes and oligodendrocytes and their myelin sheaths express glutamate receptors and transporters as well as P2X7 receptors. In normal conditions, glutamate is taken up by glutamate transporters, which prevent overactivation of glutamate receptors in oligodendrocyte progenitors (OPC), oligodendrocytes, and myelin, and cell damage by excitotoxicity. In multiple sclerosis, increased extracellular levels of glutamate as a result of oxidative stress, which impairs glutamate uptake (illustrated with an X on the glutamate transporter), can lead to excitotoxic damage of oligodendrocytes and myelin (illustrated in pink) and the release of ATP from destroyed cells. In turn, the increased expression of P2X7 receptors observed in oligodendrocytes in multiple sclerosis augments the vulnerability of these cells to ATP. In conjunction, enhanced signaling by both glutamate and ATP in oligodendrocytes may contribute to the progression of tissue damage in multiple sclerosis. EAAT, glutamate transporter; GluR, receptor; OPC, oligodendrocyte progenitor cell. Microglia have been omitted for simplicity. Scheme is based on data from [2, 5, 49, 50]

injury, ischemia-reperfusion damage, and multiple sclerosis. P2X7 receptor-mediated tissue damage may well occur in other disease conditions including cerebral palsy and chronic neurodegenerative diseases. A deeper knowledge of the functions mediated by these receptors and their pathophysiological significance will undoubtedly provide new therapeutic tools to treat acute and chronic damage to white matter.

**Acknowledgments** Research in my laboratory is supported by CIBERNED, Universidad del País Vasco, Gobierno Vasco, Ministerio de Educación y Ciencia y Ministerio de Sanidad y Consumo. Support by the European Leukodistrophy Association is also gratefully acknowledge.

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