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An introduction to the roles of purinergic signalling in neurodegeneration, neuroprotection and neuroregeneration

By

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Abstract

Purinergic signalling appears to play important roles in neurodegeneration, neuroprotection and neuroregeneration. Initially there is a brief summary of the background of purinergic signalling, including release of purines and pyrimidines from neural and non-neural cells and their ectoenzymatic degradation, and the current characterisation of P1 (adenosine), and P2X (ion channel) and P2Y (G protein-coupled) nucleotide receptor subtypes. There is also coverage of the localization and roles of purinoceptors in the healthy central nervous system. The focus is then on the roles of purinergic signalling in trauma, ischaemia, stroke and in neurodegenerative diseases, including Alzheimer's, Parkinson's and Huntington's diseases, as well as multiple sclerosis and amyotrophic lateral sclerosis. Neuroprotective mechanisms involving purinergic signalling are considered and its involvement in neuroregeneration, including the role of adult neural stem/progenitor cells.

Keywords: ATP, Alzheimer's, Parkinson's, MS, ALS, stem cells.

Abbreviations: Aβ, β-amyloid; AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; APP, amyloid precursor protein; EAE, experimental autoimmune encephalomyelitis; GABA, γ-

amino butyric acid; BzATP, 2'- and 3'-O-(4-benzoylbenzoyl)-ATP; BBG, Brilliant Blue G; AP_4A, diadenosine tetraphosphate; ERK, extracellular signal-regulated protein kinase; HD, Huntington's disease; IL, interleukin; KO, knockout; NO, nitric oxide; MS, multiple sclerosis; NMDA, *N*-methyl-*D*-aspartate; 6-OHDA, 6-hydroxydopamine; OPs, oligodendrocyte progenitor cells; PD, Parkinson's disease; PK, protein kinase; PPADS, pyridoxalphosphate-6-azophenyl-2',4'-disulfonic acid; SOD1, superoxide dismutase 1; Treg, regulatory T cells; TNFα, tumour necrosis factor-α; WT, wild type.

1. Introduction

Purinergic signalling, adenosine 5'-triphosphate (ATP) acting as an extracellular signalling molecule, was proposed in 1972 (Burnstock, 1972). In 1976 the concept was introduced that ATP is a cotransmitter in most if not all nerves in the peripheral and central nervous system (CNS) (Burnstock, 1976; see Burnstock, 2014). Two families of receptors for purines were recognised in 1978, P1 receptors for adenosine and P2 receptors for ATP and adenosine 5'-diphosphate (ADP) (Burnstock, 1978). In the early 1990s, receptors for purines and pyrimidines were cloned and characterised (see Ralevic and Burnstock, 1998). Currently it is established that there are four subtypes of the adenosine P1 receptor (A_1, A_{2A}, A_{2B}, A_3), seven subtypes of the P2X ion channel receptor (P2X1-7) and eight subtypes of P2Y G protein-coupled receptor ($P2Y_1$, $P2Y_2$, $P2Y_4$, $P2Y_6$, $P2Y_{11}$, $P2Y_{12}$, $P2Y_{13}$, $P2Y_{14}$) (see Burnstock, 2007a). Ectoenzymes that hydrolyse ATP and adenosine released from cells have been identified (see Zimmermann, 2000; Yegutkin, 2014) and release of purines and pyrimidines from nerves and most non-neuronal cell types in response to mechanical stimulation described (see Burnstock, 1999; Lazarowski et al., 2011).

The actions of adenosine in the CNS were recognised early (see Phillis and Wu, 1981; Williams, 1984; Dunwiddie, 1985; Snyder, 1985), while consideration of the role(s) of ATP in the CNS received more attention later (see Bo and Burnstock, 1994; Burnstock, 1996, 2003, 2007b; Gibb and Halliday, 1996; Inoue et al., 1996; Abbracchio, 1997; Illes and Zimmermann, 1999; Masino and Dunwiddie, 2001; North and Verkhratsky, 2006). In particular, fast purinergic synaptic transmission has been clearly identified in the brain (Edwards et al., 1992; Bardoni et al., 1997; Nieber et al., 1997; Pankratov et al., 1999, 2002, 2009; Khakh, 2001; Mori et al., 2001; Robertson et al., 2001). Adenosine is the predominant, presynaptic modulator of transmitter release in the CNS (see Dunwiddie, 1985). However, ATP can also act presynaptically (Cunha

and Ribeiro, 2000). Local network behaviours are regulated by the balance between the effects of ATP, adenosine and ectonucleotidases on synaptic transmission (Kato et al., 2004; Matsuoka and Ohkubo, 2004). Adenosine is produced by ectoenzymatic breakdown of released ATP, but subpopulations of brain neurons and/or astrocytes have been claimed to release adenosine directly (Wall and Dale, 2007).

There are high concentrations of ATP within the brain, about 2 mmol/kg in the cortex to 4 mmol/kg in the putamen and hippocampus (Kogure and Alonso, 1978). Cortex and hippocampus synaptic membranes exhibit higher activities of NTPDase1 and NTPDase2 than cerebellum and medulla oblongata. Ecto-5'-nucleotidase and adenosine deaminase are found in most brain regions (Kukulski et al., 2004). There is heterogeneous distribution in the CNS of both P2X receptors (Llewellyn-Smith and Burnstock, 1998; Loesch and Burnstock, 1998; Kanjhan et al., 1999; Burnstock and Knight, 2004; Guo et al., 2008) and P2Y receptors (Moore et al., 2000; Morán-Jiménez and Matute, 2000; Burnstock, 2003; Miras-Portugal et al., 2007). A recent review discussed the roles of P2X receptors in the CNS in health and disease (Burnstock, 2015). P2X2, P2X4 and P2X6 receptors often form heteromultimers. P2X1 receptors are expressed in some regions of the brain, such as cerebellum, while P2X3 receptors are expressed in the brain stem. P2X7 receptors are probably largely presynaptic. The dominant adenosine receptor subtype in the brain is A_1, but A_{2B} and A_3 receptors have also been identified in some regions of the brain (Latini and Pedata, 2001). Nucleotides can act synergistically with growth factors to regulate trophic events (Neary et al., 1994; Rathbone et al., 1999; Burnstock and Verkhratsky, 2010). Some brain stem neurons appear to control autonomic functions via purinoceptors (see Burnstock, 2007b).

There is compelling evidence for the role of ATP as a cotransmitter with classical transmitters in the CNS. ATP is coreleased with acetylcholine from cortical synaptosomes and for a smaller number ATP is coreleased with noradrenaline (Potter and White, 1980). There is corelease of ATP with catecholamines from neurons in the locus coeruleus (Poelchen et al., 2001) and hypothalamus (Buller et al., 1996; Sperlágh et al., 1998). Corelease of ATP with γ-amino butyric acid (GABA) occurs in dorsal horn and lateral hypothalamic neurons (Jo and Role, 2002). Corelease of ATP with glutamate in the hippocampus (Mori et al., 2001) and with dopamine in the CNS (Krügel et al., 2003) has also been reported.

Multiple P1 and P2 receptor subtypes are expressed by astrocytes, oligodendrocytes and microglia (see Burnstock and Knight, 2004; Verkhratsky et al., 2009). ATP mediates both short-term calcium signalling events and long-term proliferation, differentiation and death of glia (Cotrina et al., 2000). Purinergic receptors have also been identified on adult neural stem cells (Mishra et al., 2006; Ulrich et al., 2012). Purinergic signalling is a major means of integrating functional activity between neurons, glial and vascular cells in the CNS (see Abbracchio and Burnstock, 1998; Fields and Burnstock, 2006; Parpura and Zorec, 2010; Matute and Cavaliere, 2011; Verderio and Matteoli, 2011).

A discussion of the involvement of purinergic signalling in neurodegeneration, neuroprotection and regeneration has been included in a number of reviews (Franke and Illes, 2006; Burnstock, 2007b, 2015; Abbracchio et al., 2009; Burnstock and Verkhratsky, 2012; Illes et al., 2012; Ulrich et al., 2012; Volonté and Burnstock, 2012). It is clear that the involvement of purinergic signalling is complex and involves the combined activity resulting from ATP release, receptor activation and ectonucleotide enzyme activity.

The involvement of ATP in peripheral (including enteric) nerve degeneration and regeneration has also been studied (see Tokui et al., 1994; Schäfer et al., 1995; Xu et al., 2013; Jung et al., 2014), but will not be covered in this review article, which is focussed on the CNS.

2. Trauma, ischaemia and stroke

Trauma, ischaemia and stroke lead to the release of ATP/adenosine from cells in the CNS (Neary et al., 1996; Abbracchio and Burnstock, 1998). These signalling molecules play two roles: partly to aggravate the neuronal and glial damage caused by mechanical trauma/metabolic limitation, and partly to serve as protective mechanisms (see Zimmermann, 1994; Fields and Stevens-Graham, 2002; Neary et al., 2003; Mêmе et al., 2004; Franke et al., 2006a ; Majumder et al., 2007). Pyridoxalphosphate-6-azophenyl-2',4'-disulfonic acid (PPADS), a P2 receptor antagonist, supports recovery from experimental stroke *in vivo* (Lämmer et al., 2011).

ATP release appears to be important in triggering cellular responses to trauma (see Franke et al., 2006a). Astrocytes sense the severity of damage in the CNS via ATP release from damaged cells and they can modulate the tumour necrosis factor-α (TNF-α)-mediated inflammatory response. Micromolar ATP activation of P2Y receptors boosts a moderate inflammatory response, while millimolar ATP activation of P2X receptors appears to prevent the

perpetuation of a comparatively large inflammatory response. Astrocytic release of ATP has been demonstrated *in vivo* to be essential in mediating the injury-induced defensive responses of microglial processes (Davalos et al., 2005). Upon traumatic brain injury, microglial processes rapidly converge on the site of injury without cell body movement. This chemotactic response can be mimicked by local injection of ATP and can be inhibited by blockers of P2Y receptors. Microglial cells orchestrate inflammatory brain responses to trauma and hypoxia. They are activated by purines and pyrimidines to release the inflammatory cytokines interleukin (IL)-1β and IL-6 and TNF-α. Resting microglia, characterised by a complex network of processes, migrate to the site of damage after brain trauma, where they are transformed into the activated amoeboid form; ATP has been shown to replicate this transformation (Xiang et al., 2006).

Cerebellar lesions produce up-regulation of P2X1 and P2X2 receptors in precerebellar nuclei (Florenzano et al., 2002). Stab wound injury in the nucleus accumbens led to increase in expression of subtypes of P2X and P2Y receptors (Franke et al., 2006a). A significant increase in ecto-NTPDase and ecto-5'nucleotidase activities occurs following cortical stab injury in rats, whereas in other brain areas only as increase in 5'-nucleotidase activity was seen (Nederljkovic et al., 2006). After stab wound injury, previously absent P2X1 and P2X7 receptor-immunoreactivity was observed on cells labelled for the astrocytic marker glial fibrillary acidic protein (Franke et al., 2001). Cortical stab injury induced rapid focal varicose swelling that developed into beading of NTPDase 3-positive fibres expressing P2X2 receptors (Bjelobaba et al., 2010). Changes in expression of ecto-5'-nucleotidase have been described in the rat model of cortical stab injury (Bjelobaba et al., 2011). $P2Y_1$, $P2Y_2$ and $P2Y_6$ receptor-immunoreactivity also became apparent on astrocytes around the stab wound (Franke et al., 2004b). Reduction of long-term neurologic injury after blunt spinal trauma is evoked by A_{2A} receptor agonists (Reece et al., 2004). ATP and nitric oxide (NO) play key roles in mediating neuronal responses after cell damage. Nitrergic and purinergic systems are activated after cerebellar lesion. Colocalisation of P2X1 and P2X2 receptors with neuronal NO synthase was observed in olivary and pontine neurons (Viscomi et al., 2004).The inhibitory effects of ATP on NO production correlates with activation of the transcription factor cyclic AMP response element-binding protein (Brautigam et al., 2005). After nerve injury P2X4 receptors induced in spinal microglia gate tactile allodynia (Tsuda et al., 2003).

P2X7 receptors are activated by ATP released during trauma and inflammation (Le Feuvre et al., 2002). Signalling via P2X7 receptors may allow cells to sense and respond to events occurring in the extracellular environment, modulate the genes involved in inflammatory responses and regulate cytokine responses in the CNS. P2X7 receptors play a role in mediating spinal cord injury (Wang et al., 2004). Since P2X7 receptors are highly expressed in spinal cord neurons, it was concluded that spinal cord injury is associated with prolonged activation of these receptors, which results in excitotoxicity-based neuronal degeneration. This study supports the role of ATP as an early danger signal in neurodegenerative damage. ATP-induced stimulation of P2X7 receptors releases not only ATP and glutamate, but also GABA from astrocytes of the brain (Wang et al., 2002). Thus the hypoxic release of ATP may exert both excitatory and inhibitory neuronal modulation via glutamate and GABA, respectively (Wirkner et al., 2005).

Receptor-positive neurons and glial cells in the rat nucleus accumbens showed significant increase in the number of $P2Y_1$ after injury and coexpression of $P2Y_1$ receptors and vesicular glutamate transporter immunopositive cells was observed (Franke et al., 2006b). The authors concluded that the enhanced sensitivity of neurons to purinergic signalling in trauma may be related to changes in glutamatergic transmission. Focal cerebral ischaemia induced by intraluminal occlusion of the right middle cerebral artery results in the release of ATP into the rat striatal microdialysate (Melani et al., 2005). Mechanical injury to the rat nucleus accumbens elevated the concentrations of both ATP and glutamate in the microdialysate (Franke et al., 2006b). The local increase in the ATP concentration may lead to the up-regulation of the ecto-nucleotidases hydrolyzing extracellular ATP (Braun et al., 1998). ATP together with glutamate may exert an excitotoxic action, thereby causing the death of previously uninjured neurons and astrocytes (Dallas et al., 2007). The hypoxia-induced outflow of glutamate may be the consequence of the release of ATP (Rodrigues et al., 2005; Zhang et al., 2006; Sperlágh et al., 2007).

Mechanical injury to the rat spinal cord caused an immediate, irreversible loss of tissue at the lesion site, as well as secondary extensive tissue damage over time (Wang et al., 2004; Peng et al., 2009). The secondary tissue damage was partially due to the release of ATP and its mediation by P2X7 receptors.

P2X7 receptors appear to be the main triggers of necrosis/apoptosis in mechanically or ischaemically damaged CNS cells, but other P2X receptor subtypes are probably also involved

(Franke and Illes, 2006; Volonté et al., 2003). Unilateral cerebellectomy axotomized precerebellar neurons, for example, either degenerated, or became immunopositive for P2X1 and P2X2 receptors (Florenzano et al., 2002). Also $P2Y_1$, P2X3 as well as P2X7 receptors played a detrimental role in neurotransmission in CA1 hippocampus during oxygen and glucose deprivation, causing downstream activation of extracellular signal-regulated protein kinase (ERK)1/2 that is involved in cell excitability and death (Traini et al., 2011). P2 receptor antagonists prevented the synaptic failure.

In cultured oligodendrocytes, in contrast to astrocytes and neurons, hypoxia/ischaemia down-regulates P2X7 expression (Wang et al., 2009). In healthy animals, P2X7 receptor-immunoreactivity was absent from microglia, but appeared after middle cerebral artery occlusion. The P2 receptor antagonist, reactive blue 2, reduced the ischaemic damage. Further, a P2Y receptor on microglia directed the convergence of these cells to the site of traumatic injury, establishing a barrier between the healthy and injured tissue (Davalos et al., 2005). The expression of P2X7 receptors, accompanying the activation of brain microglia after mechanical injury, is an early reaction, followed later by the appearance of these receptors on glial cells and probably also neurons (Franke et al., 2007).

There are changes in the second messenger mechanisms coupled to P2X and P2Y receptors activated by nucleotides following brain damage. For P2X receptors, a rapid increase of intracellular Ca^{2+} and activation of Ca^{2+}-dependent enzymatic pathways is the primary mediator of early and long-term cellular changes. P2Y receptor subtypes are linked to the protein kinase signalling pathways regulating cellular proliferation, differentiation and survival such as ERK and PKB/Akt (Neary and Kang, 2005; Neary and Zimmermann, 2009). After trauma, P2 receptor/protein kinase cascades are activated, induced by mechanical and ischaemic stress, leading to late responses of glial cells, including proliferation (glial scars) of astroglia and demyelination in the white matter of oligodendroglia.

Protein kinase (PK) B/Akt is a signalling molecule that regulates cell survival, growth and metabolism and inhibits apoptosis. Traumatic brain injury activates Akt. ATP was released when cortical astrocytes were subjected to mechanical strain, leading to Akt activation and PPADS attenuated the Akt activation (Neary et al., 2005). Mechanical strains comparable to those that occur in humans subjected to traumatic brain injury, cause release of ATP from astrocytes. Then there is activation of purinergic receptors coupled to protein kinase cascades

that regulate expression of genes involved in long-term, trophic actions (Neary et al., 2006). The activity of GSK-3, which is known to be involved in cell proliferation and survival, is regulated by ATP in astrocytes and is likely to be involved in the response of the brain to injury on release of ATP (Neary and Kang, 2006).

The significance of the hypoxia-induced release of ATP in the ventral medulla oblongata for respiratory control has been discussed (Rong et al., 2003; Gourine et al., 2005, 2010). There is evidence to support the view that adenosine regulation is a significant factor in the onset and recovery of traumatic brain injury and therapeutic strategies based on P1 receptor compounds are being explored (Lusardi, 2009). Hypoxic-ischaemic injury to perinatal brain is a major contributor to morbidity in children and adenosine has been claimed to play a role in its pathophysiology (Pimental et al., 2015). The authors highlighted the potential role played by adenosine deaminase inhibitors to increase adenosine at the sites of injury.

Inflammation and immunity are major elements in the pathobiology of stroke. ATP released during ischaemic damage activated P2X7 receptors on microglia leading to release of proinflammatory cytokines and activated microglia migrate and exhibit macrophage-like activity via $P2Y_6$ receptors (see Iadecola and Anrather, 2011; Figure 1). Recent reviews that discuss purinergic signalling and inflammation are available (Eltzschig et al., 2012; Fiebich et al., 2014; Idzko et al., 2014; Morandini et al., 2014). Ischaemic pathologies of white matter include a high proportion of stroke lesions (Fern et al., 2014).

3. Neurodegenerative diseases

Neurodegeneration is the basis of the wide range of neurodegenerative diseases, involving both neurons and glial cells and there is increasing evidence for the participation of purinergic signalling (see Burnstock, 2008; Burnstock and Verkhratsky, 2012). Microglia play an important role against infection in the CNS, but overstimulation of this immune reaction may accelerate the neuronal damage caused by neurodegenerative diseases and human immunodeficiency virus encephalopathy, which exhibit microglial proliferation and activation (Ogata et al., 2003). ATP inhibits cytokine release from lipopolysaccharide-activated microglia via P2Y receptors and it was suggested that P2Y agonists may be a potential treatment for toxic immunoreactions.

3.1. Alzheimer's disease (AD)

There is evidence for the involvement of both P1 and P2 receptors in AD. ATP release during neuronal excitation or injury enhances the inflammatory effects of cytokines and prostaglandin E_2 in astrocytes and contributes to the chronic inflammation seen in AD (Xu et al., 2003). Human brain tissue from patients who died with a confirmed diagnosis of AD consistently showed a loss of A_1 receptors, especially most clearly in the outer layers of dentate gyrus in hippocampus, the region of the brain most intimately involved in the processes of learning and memory (Jansen et al. 1990; Ulas et al. 1993). The levels of A_1 and A_{2A} receptors, however, increased in the frontal cortex, in parallel with an increased function of these receptors (Albasanz et al. 2008). In AD, a key role is played by abnormal metabolism of the amyloid precursor protein (APP), which is cleaved by β- and γ-secretases to generate the β-amyloid (Aβ) peptides, present in large amounts in the amyloid plaques of AD patients' brains. In post-mortem neocortical and hippocampal tissue from patients with AD, colocalization of A_1 receptors with Aβ in senile plaques was reported (Angulo et al., 2003). It was shown that, in human neuroblastoma cells, activation of A_1 receptors activated PKC, p21 Ras and ERK1/2, leading to increased formation of soluble Aβ fragments. These findings would implicate A_1 receptors in Aβ metabolism and suggest that agonists at these receptors might be useful drugs for the treatment of established or late-stage AD (see Stone et al., 2009).

There is evidence implicating P2 receptors, in particular P2X7, in AD. In an early study, primary rat microglia stimulated with either ATP or 2'- and 3'-O-(4-benzoylbenzoyl)-ATP (BzATP) were shown to release copious amounts of superoxide primarily via the increased expression of P2X7 receptors (Parvathenani et al., 2003). ATP and BzATP also stimulated microglia-induced cortical cell death suggesting that this pathway contributes to neurodegeneration. P2X7 receptors were shown to be up-regulated around Aβ plaques in a mouse model of AD (Tg2576) (Parvathenani et al., 2003). Enhanced expression of P2X7 receptors in brain samples from six AD patients was reported (McLarnon et al., 2006). Prominent P2X7 receptor expression was observed in association with Aβ plaques on microglia. Cultured foetal human microglia cells exposed to amyloidogenic $A\beta_{1-42}$ peptide had significantly elevated levels of P2X7 receptors compared with untreated cells. Aβ triggers increases in intracellular Ca^{2+} concentrations, ATP release, IL-1β secretion and plasma membrane permeabilization in microglia from wild type (WT) but not from P2X7 knockout (KO) mice (Sanz et al., 2009). Similarly, intra-hippocampal injection of Aβ caused a large accumulation of

IL-1 in WT but not in P2X7 KO mice. This suggests that Aβ activates a purinergic autocrine/paracrine stimulatory loop involving P2X7 receptors. In the APPswe/PS1dE9 mouse model of AD, P2X7 immunoreactivity was predominantly found in activated microglia before Aβ plaque formation, suggesting a causative role in disease onset. Further, during disease development, upregulation of P2X7 and reactive oxygen species production in microglia paralleled Aβ increase and was associated with synaptotoxicity (Lee et al., 2011). Thus, P2X7 receptors mediate microglial purinergic inflammatory responses in AD brain. ATP reduces Aβ protein misfolding *in vitro* (Coskuner and Murray, 2014). Activation of P2X7 receptor-stimulated release of sAPPα from mouse and human neuroblastoma cells and from mouse primary astrocytes and neural progenitor cells was inhibited by P2X7 antagonists or by P2X7 receptor knockdown with siRNAs. This was not observed in neural cells from P2X7 KO mice. Other P2X receptor subtypes have been implicated in AD. $A\beta_{1-42}$ promoted accumulation of P2X4 receptors in neurons and induced caspase-3-mediated cleavage of the receptor that slowed channel closure times and prevented agonist-induced receptor internalization (Varma et al., 2009). Reduced expression of P2X4 receptors in primary rodent neurons attenuated $A\beta_{1-42}$-induced neuronal death. In contrast, induced P2X4 expression in a neuronal cell line that does not normally express P2 receptors enhanced the toxic effect of $A\beta_{1-42}$.

In AD brains, $P2Y_1$ receptors were localized to neurofibrillary tangles, neuritic plaques and neuropil threads (Moore et al., 2000). Activation of the $P2Y_2$ receptor expressed in human 1321N1 astrocytoma cells enhanced the release of sAPPα in a time- and dose-dependent manner (Camden et al., 2005). $P2Y_2$ receptor-activated sAPPα release was partially suppressed by ADAM10 or ADAM17/TACE, while treatment of cells with both ADAM10 and ADAM17/TACE siRNA completely abolished uridine 5'-triphosphate-activated sAPPα release. APP expression and release from astrocytes are regulated by nucleotides through activation of $P2Y_{2/4}$ receptors (Tran, 2011). The ATP synthase β subunit was identified as a new autoantigen in AD (Vacirca et al., 2010, 2011). A recent review presents evidence that there is a prominent role for P2Y receptors in AD pathology, including Aβ production and elimination, neuroinflammation, neuronal function and cerebral blood flow (Erb et al., 2015). Serum anti-ATP synthase autoantibodies were observed in 38% of patients with AD, but not in healthy subjects or in patients with Parkinson's disease (PD) or atherosclerosis. ATP synthase autoantibodies have been proposed as potential serum biomarkers for AD.

3.2. Parkinson's disease (PD)

The motor symptoms of PD are due to the degeneration of the dopaminergic neurons in the nigrostriatal pathway. A_{2A} receptors have been implicated in the pathophysiology of PD, due to its extensive interaction with the dopaminergic system in extrapyramidal areas (Morelli et al., 2010). An early event in PD is increased striatal A_{2A} receptor expression (Villar-Menéndez et al., 2014) and A_{2A} receptor antagonists are being explored for the treatment of PD (Antonini and Poewe, 2014; Gyoneva et al., 2014; Perez-Lloret and Merello, 2014; Zheng et al., 2014). Readers are referred to a number of authoritative reviews about the role of A_{2A} receptors in PD (Azam et al., 2009; Pinna, 2009; Jenner et al., 2009; Ciruela et al., 2011; Burnstock and Verkhratsky, 2012) that also draw our attention to the possible involvement of other purinergic receptors.

Data has implicated the P2X7 receptor in PD (Jun and Kin, 2004; Marcellino et al., 2010). Nigral P2X7 immunoreactivity was mainly found in microglia but also in astroglia in the unilateral 6-hydroxydopamine (6-OHDA) rat model of PD. The P2X7 antagonist 3-[[5-(2,3-dichlorophenyl)-1*H*-tetrazol-1-yl]methyl]pyridine (A-438079) significantly reduced the 6-OHDA-induced depletion of striatal dopamine stores. In conclusion, in addition to A_{2A} receptors, other purinergic receptors, in particular the P2X7 receptor, may be involved in PD. However, lack of neuroprotection for the survival of dopaminergic neurons in P2X7 receptor-deficiency or inhibition in toxin-induced animal models of PD was reported (Hracskó et al., 2011).

Transplanting foetal nigral grafts containing dopaminergic neurons into the brain of Parkinson’s patients has had limited success (Braak and Del Tredici, 2008). Transplanting enteric nerves (containing dopaminergic nerves) may be a promising alternative (Tew et al., 1992). Nucleotides affect neurogenesis and have the potential to produce dopaminergic neurons from neural progenitor cells derived from foetal mouse midbrain (Delic and Zimmerman, 2010).

3.3. Huntington's disease (HD)

HD is an inherited motor disorder, characterized by progressive striatal neurodegeneration. The mutation responsible for this disease is an abnormally expanded and unstable CAG repeat within the coding region of the gene encoding the huntingtin protein. GABAergic enkephalin neurons of the basal ganglia are the most vulnerable cells in HD. They show the highest levels of expression of adenosine A_{2A} receptors. This selective neuronal vulnerability occurs despite ubiquitous expression of mutant and normal huntingtin suggests that these receptors might play a

pathogenetic role in HD (Popoli et al., 2007, 2008). Changes in A_{2A} receptor expression and signalling in both experimental models of HD (Tarditi et al., 2006) and in peripheral blood circulating cells of HD patients (Varani et al., 2001, 2007) support this hypothesis. However, the functional significance of the aberrant A_{2A} receptor phenotype in HD is complicated by conflicting data about the potential neuroprotective and neurodegenerative effects of these receptors in the brain. In experimental models of HD, both A_{2A} receptor agonists and antagonists have shown beneficial effects (Popoli et al., 2008). A_{2A} receptor KO mice showed significantly worse motor performances and survival (Mievis et al., 2011).

The P2X7 receptor also appears to be involved in HD. Increased P2X7 receptor levels and altered P2X7 mediated calcium permeability in somata and terminals of HD neurons were shown using transgenic mice HD models (Díaz-Hernández et al., 2009). Also, cultured neurons expressing mutant huntingtin exhibited increased susceptibility to apoptosis triggered by P2X7 receptor stimulation. Administration *in vivo* of Brilliant Blue G (BBG), a P2X7 antagonist, to HD mice prevented neuronal apoptosis and attenuated body weight loss and motor-coordination deficits.

3.4. Multiple sclerosis (MS)

Both P2X7 and P2Y receptors have been shown to be involved in MS. Nucleotides, which are released in high amounts under inflammatory conditions and following cell death, may regulate remyelination processes in demyelinating diseases. Different types of P2 receptors expressed by oligodendrocyte progenitor cells (OPs), cells that give rise to mature myelinating oligodendrocytes, were described (Agresti et al., 2005b). Nucleotide-induced Ca^{2+} raises in these cells are mainly due to the activation of P2X7 and $P2Y_1$ receptors. ATP and ADP stimulated migration but inhibited the mitogenic response of OPs to platelet derived growth factor. Decreased levels of $P2Y_{12}$ receptors were observed in proximity to demyelinating lesions in sections of cerebral cortex from post-mortem MS brains (Amadio et al., 2010). This was correlated with the extent of demyelination found in gray matter cortical plaques and subcortical white matter.

There was a marked increase of P2X7 immunoreactivity in reactive astrocytes of autopsy brain tissues from MS patients (Narcisse et al., 2005). In human MS specimens, the density of P2X7 receptors on microglial cells was significantly increased in affected regions. P2X7 receptor

blockade prevented ATP excitotoxicity in oligodendrocytes, reduced demyelination and ameliorated neurological symptoms in experimental autoimmune encephalomyelitis (EAE), a model of MS (Matute et al., 2007). Moreover, development of this model was suppressed in P2X7 KO mice (Sharp et al., 2008). In brain homogenates of EAE rats there was increased levels of P2X7 receptor protein (Grygorowicz et al., 2011). In another study, patients with relapsing-remitting MS showed strikingly reduced numbers of blood regulatory T (Treg) cells expressing CD39. Activated Treg cells are able to abrogate ATP-related effects, which is consistent with the hypothesis that there is an increase in P2X7 receptor-mediated cell cytotoxicity in MS (Borsellino et al., 2007). However, P2X7 receptor KO mice were shown to develop more severe clinical and pathological expression of EAE than WT controls (Chen & Brosnan 2006).

GPR17, a P2Y-like receptor, was shown to be involved in repair of demyelinating wounds in two distinct stages of early slowly proliferating OPs that are present in the parenchyma of the adult brain (Lecca et al., 2008). Mature oligodendrocytes no longer expressed GPR17, suggesting that the receptor has to be down-regulated to allow cells to proceed to terminal differentiation. Activation of GPR17 by uridine 5'-diphosphate (UDP) or UDP-glucose caused progression of immature OPs towards mature myelinating oligodendrocytes (Ceruti et al., 2011; Fumagalli et al, 2011). GPR17 inhibition or knockdown by siRNAs impaired the normal differentiation of OPs (Fumagalli et al., 2011). Lymphocytes from MS patients upregulate A_{2A} receptors that mediate anti-inflammatory actions (Vincenzi et al., 2013).

3.5. Amyotrophic lateral sclerosis (ALS)

The involvement of purinergic signalling in ALS, in particular P2X4 and P2X7 receptor subtypes, has been proposed. The density of P2X7 microglial cells/macrophages was significantly increased in human ALS specimens (Yiangou et al., 2006). Up-regulation of P2X4, P2X7 and $P2Y_6$ receptors and down-regulation of ATP-hydrolyzing activities was reported in microglia from transgenic mice over-expressing human superoxide dismutase 1 (SOD1), an animal model of ALS (D'Ambrosi et al., 2009). In SOD1 astrocyte cultures, repeated stimulation by ATP or BzATP caused astrocytes to become neurotoxic, inducing death of motor neurons and P2X7 receptor involvement was supported by BBG inhibition of the ATP and BzATP effects (Gandelman et al., 2010). Increased ATP-dependent proliferation and a basal increase in extracellular ATP degradation was also seen in SOD1 astrocytes. Thus purinergic activation of

both astrocytes and microglia in ALS may constitute a route involved in disease progression.

High P2X4 receptor expression was shown to be selectively localised on degenerating motoneurons in the ventral horn of the spinal cord in a transgenic rodent model of ALS, the $SOD1^{G93A}$ (Casanovas et al., 2008). P2X4 receptors were also seen on degenerating neurons in the locus coeruleus, reticular formation and Purkinje cells in the cerebellum. P2X4 receptor antibodies cross-react with misfolded forms of mutant SOD1 that is present in neurons, but not in glial cells (Hernández et al., 2010). It was concluded that neuronal $SOD1^{G93A}$ conformers with P2X4 receptor immunoreactivity may have pathogenic relevance in the promotion of neuroinflammation.

It has been claimed that the death of motoneurons in ALS can be reduced by adenosine A_{2A} receptor antagonists (Mojsilovic-Petrovic et al., 2006). It was concluded in a review that purinergic signalling plays complex roles in ALS, a multifactorial and multisystemic disease involving participation of microglia, astrocytes, muscle and T cells, as well as neurons in different places (Amadio et al., 2011).

P2X7 receptor activation increases the pro-inflammatory actions of microglia in the $SOD1^{G93A}$ mouse model of ALS and in P2X7 KO mice where there is increased gliosis and motoneuron death (Apolloni et al., 2013). However, spinal cord injury is reduced by P2X7 receptor antagonists in the SOD1-mutant mouse model (Apolloni et al., 2014). A comparison was made of microRNAs transcriptional profiling of non-transgenic and ALS microglia in resting conditions and after inflammatory activation by a P2X7 receptor agonist (Parisi et al., 2013).

4. Neuroprotection

Protection against neural damage caused by trauma, ischaemia, stroke and neurodegenerative diseases is the focus of many current investigations. Reviews have been published concerned with the roles in neuroprotection of adenosine (Stone, 2005; Chen et al., 2007; Ribeiro, 2008; Williams-Karnesky and Stenzel-Poore, 2009; Gomes et al., 2011) and of ATP (Skaper, 2007, 2011; Peterson et al., 2010; Burnstock et al., 2011; Burnstock and Verkhratsky, 2012; Watts et al., 2013; Corps et al., 2015). In the Editorial about the Hot Topic Issue of CNS & Neurological Disorders-Drug Targets entitled ‘Pharmacology and Therapeutic Activity of Purinergic Drugs for Disorders of the Nervous System’, attention is drawn to the variety of drugs acting on P2X and

P2Y receptor subtypes being explored for the treatment of neurodegenerative diseases (Volonté and Burnstock, 2012).

ATP, released during trauma, acts via P2 receptors to inhibit the release of the cytotoxic excitatory transmitter, glutamate, and stimulates release of the inhibitory transmitter, GABA, from hippocampal nerves, thus serving a protective role (Inoue, 1998). Excessive activation of glutamate receptor systems is implicated in neuronal cell death associated with stroke and neurodegenerative diseases such as AD, PD, HD and ALS (Zona et al., 2000). Guanine nucleotides inhibit N-methyl-D-aspartate (NMDA)- and kainate-induced neurotoxicity and may be used to antagonise glutamate receptor-mediated neurotoxicity (Morciano et al., 2004). The P1 receptor antagonist, caffeine, is claimed to have beneficial actions in both AD and PD (Ribiero et al., 2003). P2 receptors have been claimed to mediate neuroprotective effects in the cerebellum, suggesting the use of P2 receptor agonists as neuroprotective agents (Volonté et al., 2003). It has been suggested that adenine is involved in the control of Purkinje cell survival (Watanabe et al., 2003).

4.1. Neuroprotection against trauma, ischaemia and stroke

The release of adenosine is considered to be a neuroprotective factor during traumatic and hypoxic/ischaemic CNS injury (Nieber et al., 1999; Sebastião and Ribeiro, 2009; Stone et al., 2009). Both neuronal morphology and behavioural tests revealed full preservation of spatial memory and learning ability. *In vivo* studies indicated a beneficial effect of A_1 receptor stimulation in cerebral ischaemia, but the therapeutic value was limited by the wide receptor-distribution on neuronal and non-neuronal cells in the CNS (Stone et al., 2009).

The protective effect of A_{2A} receptor agonists in ischaemia may be largely due to reduced glutamate outflow, particularly from glial cells (Popoli et al., 1995, 2003; Pedata et al., 2007). Decreased activation of mitogen-activated protein kinases that are involved in neuronal death may also contribute to neuroprotection by A_{2A} antagonism (Kawasaki et al., 1997). A_{2A} receptors trigger the actions of neurotrophic factors involved in axonal outgrowth or synaptic plasticity (Sebastião and Ribeiro, 2009), so blockade of A_{2A} receptors may reduce the effects of neurotropic factors, favouring neuronal survival and regeneration. In neurodegenerative disorders astrocyte death may occur and complicate the outcome of brain ischaemia. A_{2A} receptor antagonists SCH 58261 (Monopoli et al., 1998) and 8-(3-chlorostyryl)caffeine (Von

Lubitz et al., 1995) were protective in global or focal cerebral ischaemia in both rats and gerbils (Pedata et al., 2005). Also cerebral infarction was significantly attenuated in A_{2A} receptor KO mice (Chen et al., 1999). A_{2A} receptor antagonists were also beneficial for rabbit spinal cord reperfusion injury (Cassada et al., 2001). The A_3 receptor agonist chloro-N^6-(3-iodo-benzyl)-adenosine-5'-N-methyluronamide decreased experimentally-induced cerebral infarction in gerbils and rats (Chen et al., 2006; Von Lubitz et al., 1994). The protective role of A_1 adenosine receptors in hypoxia/ischaemia *in vitro* in brain slice preparations was also reported (e.g. Fujiwara et al., 1987; Nieber et al., 1995; Krnjevic, 1999).

Potential benefits of P2X7 receptor antagonism in rodent studies of brain and spinal cord injury and neurodegenerative diseases have been described (Wang et al., 2004; Bartlett et al., 2014; Sperlágh and Illes, 2014). This has prompted the use of drugs targeting the P2X7 receptor for the treatment of human CNS disorders. However, these studies are facing problems, partly due to the many polymorphic variations of the human P2X7 receptor. Microglial cells possess P2X7 receptors which become activated in a rat model of focal cerebral ischaemia to participate in the early defence reaction (Melani et al., 2006). P2X7 receptor antagonists adenosine 5'-triphosphate-2',3'-dialdehyde (oxidized ATP) or BBG even 15 minutes after spinal cord injury resulted in recovery of hind limb motor function (Peng et al., 2009). In the cerebral cortex of spontaneously hypertensive rats, there was up-regulation of P2X7 receptor immunoreactivity in the penumbra surrounding the necrotic region (Franke et al., 2004a). In ATP-induced secondary damage, via stimulation of P2X (probably P2X7) receptors in the penumbra, both suramin and PPADS reduced the infarct volume and accelerated functional recovery in behavioural tests (Kharlamov et al., 2002; Lämmer et al., 2006, 2011). P2X7 receptor-activated microglia protect neurons against glutamate toxicity (Suzuki et al., 2004). PPADS, a P2 receptor antagonist, confers neuroprotection against glutamate/NMDA toxicity (Lin et al., 2005). It has been claimed that P2X7 receptor antagonists are neuroprotective for their ability to inhibit assembly of inflammasome in glial cells (Murphy et al., 2012). Cerebral ischaemia-reperfusion injury is a primary cause of ischaemic stroke and ischaemic postconditioning is considered as an important technique to contain ischaemia-reperfusion injury, which involves the activation of P2X7 receptors (Bindra et al., 2014). Cortical spreading depression is a model of preconditioning that provides tolerance to a subsequent ischaemic event in the brain. It appears to be due to release of ATP via connexin-36 hemichannels into the extracellular space (Schock et al., 2008). The ATP,

via activation of P2Y receptors and new protein synthesis, causes ischaemic tolerance and enhances neuronal survival in cultured primary cortical neurons.

P2Y receptor antagonists are potential neuroprotective agents in the cortex, hippocampus and cerebellum by modulation of kainate- and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid-induced currents. Inhibition of apoptosis by $P2Y_2$ receptor activation has been claimed to be a novel pathway for neuronal survival (Arthur et al., 2006). $P2Y_1$ receptor antagonists improve recovery from traumatic brain injury (Choo et al., 2013). A recent paper reports that neuroprotection against genotoxic stress is elicited by $P2Y_{13}$ receptor activation (Morente et al., 2014). The P2Y-like receptor, GPR17, is a sensor of brain damage and reacts to the release of nucleotides and cysteinyl leukotrienes in a focal ischaemia model (Lecca et al., 2008). It is expressed on OPs, but not astrocytes and is a potential target for stroke and spinal cord injury induced by acute compression (Ceruti et al., 2009). The *in vivo* knock-down of GPR17 by an antisense oligonucleotide strategy markedly reduced tissue damage. It has been claimed that $P2Y_2$ receptors activate neuroprotective mechanisms in astrocytes (Chorna et al., 2004).

ATP-$MgCl_2$ decreases lipid peroxidation in spinal cord injury and protect the spinal cord from secondary injury after trauma. It was concluded that ATP-$MgCl_2$ should be explored for the treatment of spinal cord injuries in conjunction with other treatments (Cakir et al., 2003). After spinal cord injury, topical application of ATP significantly improved locomotor function (Shields et al., 2004).

4.2. Neuroprotection against neurodegenerative diseases

Data from animal models of AD and in samples from AD patients, support the concept that $A\beta_{1-42}$-induced synaptic dysfunction and neuronal death may involve abnormalities in purinergic receptor signalling, with the most convincing evidence for P2X7 receptors (see Takenouchi et al., 2010). Processing of APP is regulated by two different nucleotide receptors, P2X7 and $P2Y_2$, with opposite effects on α-secretase activity (León-Otegui et al., 2011). It was suggested that activators of the $P2Y_2$ receptor in combination with P2X7 receptor antagonists could have beneficial effects by reducing amyloid plaques (Wurtman et al., 2009). Block of P2X7 receptor-mediated activity with BBG was shown to be neuroprotective in an animal model of AD (Ryu and McLarnon, 2008). Activation of microglia by Aβ requires P2X7 receptor expression and it

was suggested that Aβ microglia stimulation may open new avenues for the treatment of AD (Sanz et al., 2009). ATP, released from astrocytes, protects Aβ-induced impairment of synaptic plasticity (Jung et al., 2012). P2X7 may also have beneficial effects via the stimulation of non-amyloidogenic processing of APP by α-secretases, leading to proteolytic cleavage within the Aβ peptide sequence and shedding of the soluble APP ectodomain (sAPPα), exerting neuroprotection (Delarasse et al., 2011).

Antagonists of the A_{2A} receptor alleviate symptoms in PD patients. Ongoing research programs in this area, and orally efficacious A_{2A} receptor antagonists, have been advanced into clinical development (see Shah and Hodgson, 2010). Several xanthines and non-xanthine compounds possessing good affinity have been introduced. BIIB014, preladenant and ST-1535 are new adenosine A_{2A} receptor antagonists currently in use. A_{2A} antagonists may also be neuroprotective under certain toxicity paradigms (see Stone et al., 2009). There are Phase I and II clinical trials for evaluation of their efficacy in PD patients (Pinna, 2009). All these compounds were safe and well tolerated. Results from the Phase II trial showed that BIIB014 and preladenant were effective in reducing the waking time spent in OFF state in patients at the late stage of PD treated with L-DOPA. BIIB014 was also effective as monotherapy in patients at the early stage of PD and ST-1535 displays a promising potential in experimental models of PD and in clinical studies. The therapeutic effects of A_{2A} receptor antagonists appear to act via a reduction of the inhibitory output of the basal ganglia indirect pathway. This possibility has been validated in patients treated with the A_{2A} antagonist SYN115 (Black et al., 2010). Neuroprotective mechanisms also include blockade of A_{2A} receptor-mediated glutamate release from neurons, inhibition of microglia-induced inflammation. However, there is conflicting data on the protective and detrimental roles reported for A_{2A} receptors in the CNS. Diadenosine tetraphosphate (AP_4A), an endogenous diadenosine polyphosphate, also has protective effects in the unilateral 6-OHDA rodent model of PD (Wang et al., 2003). AP_4A also reduced TUNEL in the lesioned nigra 2 days after 6-OHDA administration, implying inhibition of apoptosis.

Therapeutic potential of P2X7 receptor antagonists for the treatment of HD was discussed (Díaz-Hernández et al., 2009). Decrease in stimulated A_1 and A_{2A} receptors has also been implicated in HD (Bauer et al., 2005; Popoli et al., 2007). Alterations of P2X7 receptor activity could contribute to HD pathogenesis and highlight the therapeutic potential of P2X7 receptor antagonists. A_{2A} receptor agonists protect neurons derived from induced pluripotent stem cells of

patients with HD (Chern et al., 2014). The level of 5'-nucleotidase increased in synaptosomes from the cerebral cortex of rats that were experimentally demyelinated (Spanevello et al., 2006).

An early feature of MS and its animal model of EAE is neuronal pathology. Lesional accumulation of P2X receptors on macrophages in rat CNS in the EAE model has been reported (Guo and Schluesener, 2005). P2X7 expression is elevated in axon tracts in patients with MS and ATP can kill oligodendrocytes by activating P2X7 receptors (Domercq et al., 2010). Patients exhibiting the remitting/relapsing form of MS have strikingly reduced numbers of NTPDase1-positive Treg cells, suggesting that purines might be involved (Borsellino et al., 2007). A regulatory role of $P2Y_1$ receptor signalling in OPs has been described (Agresti et al., 2005a). It was suggested that high ATP released in inflammatory conditions might act on $P2Y_1$ receptors to influence the remyelination processes in MS. In the lesioned cerebral cortex of MS patients $P2Y_{12}$ receptor expression has also been identified (Amadio et al., 2010). GPR17 is a key regulator of OP differentiation. GPR17 dysfunctions seem be present in MS, setting the background for future GPR17-based remyelination therapies (Chen et al., 2009).

The protective effect mediated by both ATP and ivermectin for ALS is by potentiation of ATP action on P2X4 receptors (Andries et al, 2007). Preincubation of motor neurons with a low concentration of ATP protected cells against excitotoxic stimulation, while high concentrations of ATP were toxic. To study the relevance of these findings for ALS, $SOD1^{G93A}$-mice were treated with ivermectin. This led to an increase of the life span of these mice by almost 10%. The increased expression of P2X1 receptors on axotomized facial motoneurons was impaired in $SOD1^{G93A}$-mutant mice (Kassa et al., 2007). It was suggested that the release of ATP from mutant motor neurons is altered after damage.

5. Neuroregeneration: neural stem/progenitor cells

A major obstacle for neural repair is the weak regenerative capacity of injured neurons, although the neonatal brain has a greater capacity for recovery than the adult brain (Pekovic et al., 2006). There are a number of reports about the role of purinergic drugs promoting regeneration of injured and degenerating nerves in the brain and spinal cord. Both A_1 and A_2 receptors mediate proliferation of microglia (Gebicke-Haerter et al., 1996). Inosine has been shown to stimulate axonal growth in the rat corticospinal tract after injury (Benowitz et al., 1999, 2001). PKB/Akt is a signalling molecule that regulates cell survival, growth and metabolism and inhibits apoptosis.

Traumatic brain injury activates Akt. ATP is released when cortical astrocytes were subjected to mechanical strain, leading to Akt activation and PPADS attenuated the Akt activation (Neary et al., 2005). Mechanical strains, comparable to those that occur in humans exposed to traumatic brain injury, cause release of ATP from astrocytes. Then there is activation of purinergic receptors coupled to protein kinase cascades that regulate expression of genes involved in long-term, trophic actions (Neary et al., 2006). Activation of purinergic signalling in astrocytes via $P2Y_4$ receptors induced by trauma stimulates the synthesis and release of thrombospondin-1, an extracellular matrix molecule that induces synapse formation during development and may play a role in CNS repair and remodelling after injury (Tran and Neary, 2006).

ATP and its analogues are involved in tissue remodelling in response to injury and have a key role in regulation of repair and regeneration (Burnstock and Verkhratsky, 2010). Stimulation of purinoceptors in the CNS triggers astrogliosis, the response of astrocytes to brain damage, which is characterised by cell proliferation and remodelling of the neural circuitry (Giaume et al., 2007). In combination with growth factors such as fibroblast growth factor, epidermal growth factor and platelet-derived growth factor, ATP can stimulate astrocyte proliferation, contributing to the process of reactive astrogliosis (Abbracchio and Burnstock, 1998; Ishibashi et al., 2006; Neary et al., 2006). P2Y receptors are claimed to mediate reactive astrogliosis via induction of cyclo-oxygenase-2, and P2Y receptor antagonists reduce astrogliosis (Brambilla et al., 1999). Reactive astrogliosis is instrumental for limitation of brain damaged area, as well as for the post-insult remodelling and recovery of neural function. Initial events in astroglial responses to purinergic signalling appear to be associated with $P2Y_1$ and $P2Y_2$ receptor-mediated Ca^{2+} astroglial signalling (Kirischuk et al., 1995). It has been claimed that activation of $P2Y_2$ receptors can promote regeneration of nerves and glial cells in damaged brain (see Arthur et al., 2005; Franke, 2011). Intraneural injection of Aβ has been shown to stimulate regeneration of primary sensory axons in the spinal cord (Wu et al., personal communication). The P2Y-like GPR17 has been identified as a sensor of damage of the CNS and participates in lesion repair in the rodent brain and in patients with traumatic brain injury (Franke et al., 2013).

Synergistic actions of ATP and growth factors were recognised in 1989 (Huang et al., 1989). Sprouting of central neurons was shown in experiments in which the enteric nervous system was transplanted into the striatum of the brain (Tew et al. 1992). It was suggested that a growth factor released from enteric glial cells acts synergistically with ATP (and its breakdown

product, adenosine) and NO (Höpker et al. 1996). A similar synergistic activity of purines and growth factors may be involved in stem cell activity (Burnstock and Ulrich, 2011). Purines and pyrimidines released from damaged cells stimulate astrocyte proliferation *in vitro* and may contribute to astrocyte proliferation *in vivo* following injury to the CNS (Christjanson et al., 1993). Co-operation of guanosine 5' triphosphate and nerve growth factor in neural differentiation and neurite outgrowth has also been described (Gysbers et al., 2000; Guarnieri et al., 2004).

Neural stem (progenitor) cells are heavily involved in the development of the CNS and adult neural progenitor cells are also involved in regeneration following injury (Shih et al., 2001; Zimmermann, 2006; Lin et al., 2007; Trujillo et al., 2009; Ulrich et al., 2012). It has been reported that stem cell activation and the integration of newly formed neurons can be applied for neuroregeneration in the diseased brain (Martino and Pluchino, 2006; Omerod et al., 2008; Delic and Zimmermann, 2010). Neural pluripotent precursor cells derived from primary neural stem cells proliferate to form the three main cell types constituting the neurons, astrocytes and oligodendrocytes, while microglia are derived from immune-like cells. ATP causes proliferation of human neural stem cells (Ryu et al., 2003). Adult neural progenitor cells in the mouse subventricular zone express interacting functional P2X4 and P2X7 receptors (Messemer et al., 2013a, b) and it has been proposed that P2X2 and P2X7 receptor agonists and antagonists may provide novel tools for regeneration therapy in neurodegenerative diseases (Glaser et al., 2013). In adult brains, neural stem cells are present in the subventricular zone of the lateral ventricle and the subgranular zone of the hippocampal dentate gyrus, where neurogenesis continues throughout life. Purinergic signalling promotes proliferation of rapidly dividing stem cells in the subventricular region via $P2Y_1$ receptors (see Suyama et al., 2012). ATP was shown to promote locomotor recovery after spinal cord injury (Sun et al., 2013).

6. Conclusions

The P2X7 receptor subtype appears to be the dominant receptor involved in CNS disorders, which is upregulated after trauma and ischaemia and in inflammatory conditions. P1 and $P2Y_1$ receptors also participate in neuroprotective mechanisms. P2X7 receptor antagonists are being explored for the treatment of neurodegenerative diseases, including AD, HD, MS and ALS. A_{2A} receptor antagonists are promising for the treatment of PD (see Table 1).

For major advances to be made in our knowledge of the roles of purinergic signalling in neurodegeneration and neuroregeneration there is an urgent need for novel compounds to be developed, including purinoceptor subtype agonists and antagonists and inhibitors of ectonucleotidases and ATP transport, that are orally bioavailable, stable *in vivo* and can cross the blood brain barrier. There are questions to be raised about the viability of some of the animal models currently available to replicate human CNS diseases.

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Conflict of Interest

The author declares no conflict of interest.

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Table 1

Pathology	Main P1/P2 receptor subtypes involved
Trauma: injury, stroke, ischaemia	A_{2A}, P2X7, $P2Y_1$, $P2Y_2$
Alzheimer's Disease	A_1, A_{2A}, P2X7, $P2Y_1$
Parkinson's Disease	A_{2A}
Huntington's Disease	A_{2A}, P2X7
Multiple Sclerosis	P2X7, $P2Y_1$, GPR17
Amyotrophic Lateral Sclerosis	A_{2A}, P2X4, P2X7

Figure Legends

Figure 1

Resolution of inflammation and tissue repair. Clearing of dead cells and suppression of inflammation are key events in brain repair. Find-me signals (UTP, ATP) attract microglia and macrophages through $P2Y_2$ receptors. Eat-me signals include UDP, which acts on $P2Y_6$ receptors to stimulate microglial phagocytosis, and phosphatidylserine (PtdSer), which is translocated to the outer leaflet of the plasma membrane of apoptotic cells. PtdSer-binding proteins involved in the clearance of dead cells include milk fat globule epidermal growth factor 8 protein on microglia and T cell immunoglobulin and mucin domain-containing molecule 4 (TIM4) on macrophages. Immunoglobulins directed against CNS antigens, which appear after stroke, may also promote phagocytosis by engaging Fc receptors on phagocytic cells. Phagocytosis promotes secretion of IL-10 and TGF-β, which, in turn, suppress antigen presentation, promote Treg formation, inhibit expression of adhesion molecules in endothelial cells and production of proinflammatory cytokines. TGF-β and IL-10 are also neuroprotective and may facilitate brain repair processes. In addition, lipoxins, resolvins and protectins, metabolites of arachidonic acid and omega-3 fatty acids that play an active part in the resolution of inflammation in other organs, could also contribute to suppress postischemic inflammation. Growth factors and MMPs produced by endothelial cells, neurons, astrocytes, oligodendrocytes and microglia are key molecules driving tissue reorganization and repair. (Reproduced from Iadecola and Anrather, 2011, with permission from The Nature Publishing Group.)