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Invited review

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

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N-methyl-*D*-aspartate (NMDA) (PubChem CID: 22880)
Pyridoxalphosphate-6-azophenyl-2′,4′-disulfonic acid (PPADS) (PubChem CID: 6093163)

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.

This article is part of the Special Issue entitled 'Purines in Neurodegeneration and Neuroregeneration'.

Contents

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.

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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