

● PERSPECTIVE

Purinergic signalling in neuroregeneration

Purinergic signalling, adenosine 5'-triphosphate (ATP) as an extracellular signalling molecule, was proposed in 1972 (Burnstock, 1972). However, it was not generally accepted until the early 1990s when receptors for ATP and its breakdown product adenosine were cloned and characterised (Ralevic and Burnstock, 1998). Four P1 (adenosine) receptors are recognised (A_1 , A_{2A} , A_{2B} and A_3), seven P2X ion channel receptors (P2X1-7) and eight P2Y G protein-coupled receptors (P2Y₁, P2Y₂, P2Y₄, P2Y₆, P2Y₁₁, P2Y₁₂, P2Y₁₃, P2Y₁₄). The purinergic signalling field is now widely accepted and expanding in many different directions (Burnstock, 2012).

Purinergic signalling plays important roles in neurodegeneration, neuroprotection and neuroregeneration (Burnstock, 2015). Trauma, ischaemia and stroke result in release of ATP/adenosine from cells in the central nervous system (CNS), which can either enhance neuronal and glial cell damage or serve as neuroprotectors. Injury produces upregulation of both P2X and P2Y receptor expression, as well as ecto-nucleotidase activity. P2X7 receptors, expressed by both neurons and glia, are activated during trauma and inflammation, leading to neurodegeneration. P2X7 receptors are also involved in neurodegenerative diseases, including Alzheimer's, Parkinson's, and Huntington's disease, multiple sclerosis and amyotrophic lateral sclerosis (Burnstock, 2008). P2X7 receptor antagonists are claimed to be neuroprotective. P1 and P2Y₁ receptors also participate in neuroprotective mechanisms. A_{2A} receptor antagonists are being explored for the treatment of Parkinson's disease and P2Y-like GPR17 antagonists are promising for the treatment of multiple sclerosis.

ATP and its analogues are involved in tissue remodelling in response to injury and play a role in regulation of repair and regeneration (Burnstock and Verkhratsky, 2010). The weak regenerative capacity of injured neurons is an obstacle for neural repair, although the neonatal brain has a greater capacity for recovery than the adult brain. Purinergic drugs have been used to promote regeneration of injured and degenerating nerves in the brain and spinal cord. A signalling molecule, protein kinase B/Akt, regulates cell survival, growth and metabolism and inhibits apoptosis, and traumatic brain injury activates Akt. When cortical astrocytes were subjected to trauma or mechanical strain, ATP was released and there was Akt activation. PPADS, a P2 receptor antagonist, attenuated the Akt activation. Trauma-induced activation of purinergic signalling in astrocytes *via* P2Y₄ receptors stimulates the synthesis and release of thrombospondin-1, an extracellular matrix molecule that induces synapse formation during development. This may play a role in CNS repair and remodelling after injury.

Astroglial, the response of astrocytes to brain damage, is characterised by cell proliferation and remodelling of the neural circuitry. Astroglial is triggered by stimulation of purinoceptors in the CNS. Growth factors such as fibroblast growth factor, epidermal growth factor and platelet-derived growth factor combined with ATP can stimulate astrocyte proliferation, contributing to the process of reactive astroglial. P2Y receptors mediate reactive astroglial via induction of cyclo-oxygenase-2, and P2Y receptor antagonists reduce astroglial. Reactive astroglial limits brain damage, as well as promoting post-insult remodelling and recovery of neural function. Activation of P2Y₂ receptors can promote regeneration of nerves and glial cells in damaged brain (see Arthur et al., 2005). The P2Y-like GPR17 is a sensor of damage of the CNS, which participates in lesion repair in the rodent brain and in patients with traumatic brain injury (Franke et al., 2013).

When enteric nerve plexus was transplanted into the striatum of the brain, there was sprouting of central neurons (Tew et al., 1992) and synergistic actions of growth factors and ATP had been recognized in 1989 and evidence was presented to suggest that a growth factor released from enteric glial cells acted synergistically with ATP (and its breakdown product, adenosine) and nitric oxide. A similar

synergistic activity of purines and growth factors may be involved in stem cell activity (Burnstock and Ulrich, 2011).

Neural stem (progenitor) cells are involved in the development of the CNS and adult neural progenitor cells are involved in regeneration following injury (see Ulrich et al., 2012). Stem cell activation and the integration of newly formed neurons are involved in neuroregeneration in the diseased brain (Delic and Zimmermann, 2010). Pluripotent neural precursor cells derived from primary neural stem cells proliferate to form neurons, astrocytes and oligodendrocytes, while microglia are derived from immune-like cells. ATP is one of the factors causing proliferation of human neural stem cells. Adult neural progenitor cells in the mouse subventricular zone express functional P2X4 and P2X7 receptors. P2X7 receptor agonists and antagonists may provide novel tools for regeneration therapy in neurodegenerative diseases. Neural stem cells are present in the subventricular zone of the lateral ventricle and the subgranular zone of the hippocampal dentate gyrus in adult brains and neurogenesis continues throughout life. Proliferation of rapidly dividing stem cells in the subventricular region is promoted *via* P2Y₁ receptors.

Conclusion: There is growing evidence that purinergic signalling is involved in neuroregeneration, and drugs acting on purinoceptors are being explored to enhance regeneration. Activation of P2Y₂ receptors has been claimed to promote regeneration of nerves and glial cells and activation of the P2Y-like GPR17 receptor promotes regeneration of oligodendrocytes. Neural stem cell activation is involved in neuroregeneration and proliferation of neural stem cells involves ATP, probably acting *via* P2X4 and P2X7 receptors. However, the field is in its infancy and more studies are needed to establish the precise roles of purinoceptor subtype activation and antagonism in neuroregeneration.

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