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Invited review

CNS remyelination as a novel reparative approach to neurodegenerative diseases: The roles of purinergic signaling and the P2Y-like receptor GPR17

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Chemical compounds:
2′-Deoxy-N^6-methyladenosine 3′,5'-bisphosphate ammonium salt (MRS2179)
3-(2-carboxy-4,6-dichloro-indol-3-yl) propionic acid (MDL29,951)
3-[4-[2-[[6-amino-9-[(2R,3R,4S,5S)-5-(ethylcarbamoyl)-3,4-dihydroxy-oxolan-2-yl]purin-2-yl]amino]ethyl]phenyl] propanoic acid (CGS21680)
7-(2-phenylethyl)-5-amino-2-(2-furyl)-pyrazolo-[4,3-e]-1,2,4-triazolo[1,5-c] pyrimidine (SCH58261)
Adenosine
ADP
ATP
Brilliant blue G (BBG)
Leukotriene D4 (LTD_4)
Montelukast
N6-cyclohexyladenosine (CHA)
Oxidized ATP (oxATP)
Rapamycin
UDP
UDP-Glucose

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ABSTRACT

Oligodendrocytes are the myelin-forming cells in the CNS. They enwrap axons, thus permitting fast impulse transmission and exerting trophic actions on neurons. Demyelination accompanied by neurological deficit is a rather frequent condition that is not only associated with multiple sclerosis but has been also recognized in several other neurodegenerative diseases, including brain trauma and stroke, Alzheimer's disease and amyotrophic lateral sclerosis. Recently, alterations of myelin function have been also reported in neuropsychiatric diseases, like depression and autism. Highly relevant for therapeutic purposes, oligodendrocyte precursor cells (OPCs) still persist in the adult brain and spinal cord. These cells are normally rather quiescent, but under specific circumstances, they can be stimulated to undergo differentiation and generate mature myelinating oligodendrocytes. Thus, approaches aimed at restoring myelin integrity and at fostering a correct oligodendrocyte function are now viewed as novel therapeutic opportunities for both neurodegenerative and neuropsychiatric diseases. Both OPCs and mature oligodendrocytes express purinergic receptors. For some of these receptors, expression is restricted at specific differentiation stages, suggesting key roles in OPCs maturation and myelination. Some of these receptors are altered under demyelinating conditions, suggesting that their dysregulation may contribute to disease development and could represent adequate new targets for remyelinating therapies.

Here, we shall describe the current literature available on all these receptors, with special emphasis on the P2Y-like GPR17 receptor, that represents one of the most studied receptor subtypes in these cells.

Contents

Abbreviations: AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; ATX, autotaxin; CNS, central nervous system; DRG, dorsal root ganglion; EAE, experimental autoimmune encephalomyelitis; GDNF, glial cell derived neurotrophic factor; GRK, G-protein receptor kinase; MBP, myelin basic protein; MCAo, middle cerebral artery occlusion; MS, multiple sclerosis; mTOR, mammalian target of rapamycin; OPC, oligodendrocyte precursor cell; PDGF, platelet derived growth factor; PVL, periventricular leukomalacia.

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1. Introduction

The myelin sheath is the fatty insulating layer wrapped around neuronal axons that is essential to increase the speed and efficiency of nerve impulse conduction and maintain axonal integrity. In the CNS, it is produced by specialized glial cells, the oligodendrocytes, which ensheath axons with concentrically multi-lamellar sheets of plasma membrane comprised of specific proteins and lipids (Baumann and Pham-Dinh, 2001).

The formation of myelin is a complex process by which oligodendrocyte progenitors (OPCs) maturate to myelinating cells through phenotypic and morphological changes, reorganization of cytoskeleton, cell polarization and assembly of specialized membrane domains (Bauer et al., 2009; Bin ame et al., 2013). During myelination, OPCs follow an intrinsic program of proliferation, migration and differentiation through specific developmental stages, which are controlled by exogenous signals, including axonal cues, and the activation of specific intracellular signaling pathways (Ahrendsen and Macklin, 2013; Gonsalvez et al., 2015; Mitew et al., 2014). Recent review articles have extensively discussed the balance existing among inhibiting and promoting molecules that finally regulates myelin formation, its plasticity and the reciprocal interactions between myelinating glial cells and axons (Emery, 2010; Nave and Werner, 2014).

In this respect, extracellular ATP and uracil nucleotides have been identified as important, activity–dependent axonal signals, that, when non-synaptically released from electrically stimulated axons or from nearby astrocytes, activate purinergic P2 receptors on neighboring oligodendrocytes (Fields and Burnstock, 2006; Fields and Stevens, 2000). Functional P2X and P2Y receptors (P2XRs and P2YRs), including the P2Y-like receptor GPR17, have been identified on myelinating glial cells at specific developmental stages both *in vitro* and *in vivo* by means of different approaches (Burnstock, 2011, 2015; Fumagalli et al., 2011; Verkhratsky et al., 2009). Of note, the multiple effects of released ATP are not only exerted through purinergic P2 receptors, but also through extracellular ectonucleotidases capable of regulating extracellular ATP, ADP, AMP and adenosine concentrations (Zimmermann et al., 2012). This is particularly important in light of data showing that adenosine is also crucially involved in modulation of OPC proliferation, migration and myelination (Stevens et al., 2002). The large number of purinergic receptors identified on both OPCs and mature oligodendrocytes, the different signaling pathways modulated by them and the combined activity of ectonucleotide enzymes make this system highly complex.

Here, we shall summarize some crucial aspects of the purinergic regulation of oligodendrocyte functions to shed light on the role of purinergic signaling in myelination. We will also analyze how the purinergic system is dysregulated in diseases characterized by either myelin deterioration or malfunction of myelinating cells. These key issues will be discussed also based on the more recent discovery that myelinating oligodendrocytes do not only electrically insulate axons, but they also exert a trophic effect and contribute to energy supply of myelinated axons by delivering pyruvate/lactate (Funfschilling et al., 2012; Lee et al., 2012; Nave, 2010). This support is essential for normal axonal function *in vivo* and it is of particular relevance for longer axons in which some segments are far away from the neuronal soma, but in close contact to local glial cells (Hirrlinger and Nave, 2014). Axonal metabolic need is also sustained by oligodendrocytes through the release of neurotrophic factors, such as glial cell derived neurotrophic factor (GDNF), and by the presence of gap-junction-forming connexins, that may provide routes for the passage of small metabolites (Wilkins et al., 2003). Of interest, in addition to classical means of cell-to-cell communication, the transfer of vesicles from oligodendrocytes to neuronal endings has been proposed to be a very rapid and efficient means by which these cells may contribute to sustain axonal homeostasis and integrity (Fruhbeis et al., 2013a, 2013b).

Thus, myelinating oligodendrocytes protect and promote neuronal activity and survival, and the loss of these cells, in diseases such as multiple sclerosis (MS), results in demyelination of axons. Without an intact myelin sheath and glial support, axons become vulnerable to irreversible and cumulative degeneration. It appears clear that strategies aimed at implementing oligodendroglial support and remyelination, namely the myelination of demyelinated axons should result in axon preservation (Franklin and Ffrench-Constant, 2008). In this respect, the discovery that adult parenchymal OPCs are recruited and proliferate in the demyelinating area has raised the possibility of repairing lesions by implementing the spontaneous endogenous remyelination mediated by these cells (Nishiyama et al., 2009). OPCs, which express the proteoglycan NG2 (and for this reason are also known as NG2-glia) and the platelet-derived growth factor receptor-α (PDGFRα), indeed persist in the adult CNS, constituting the main proliferative cell type of the intact CNS (Dawson et al., 2003). At adult stage, they can be engaged into

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