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Invited review

Pharmacological approaches to intervention in hypomyelinating and demyelinating white matter pathology

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ABSTRACT

White matter disease afflicts both developing and mature central nervous systems. Both cell intrinsic and extrinsic dysregulation result in profound changes in cell survival, axonal metabolism and functional performance. Experimental models of developmental white matter (WM) injury and demyelination have not only delineated mechanisms of signaling and inflammation, but have also paved the way for the discovery of pharmacological approaches to intervention. These reagents have been shown to enhance protection of the mature oligodendrocyte cell, accelerate progenitor cell recruitment and/or differentiation, or attenuate pathological stimuli arising from the inflammatory response to injury. Here we highlight reports of studies in the CNS in which compounds, namely peptides, hormones, and small molecule agonists/antagonists, have been used in experimental animal models of demyelination and neonatal brain injury that affect aspects of excitotoxicity, oligodendrocyte development and survival, and progenitor cell function, and which have been demonstrated to attenuate damage and improve WM protection in experimental models of injury. The molecular targets of these agents include growth factor and neurotransmitter receptors, morphogens and their signaling components, nuclear receptors, as well as the processes of iron transport and actin binding. By surveying the current evidence in non-immune targets of both the immature and mature WM, we aim to better understand pharmacological approaches modulating endogenous oligodendroglia that show potential for success in the contexts of developmental and adult WM pathology.

1. Introduction

Oligodendrocytes have essential roles in the function of a healthy nervous system. They are, however, also among the most vulnerable of neural cell types in the CNS, and as a result, central myelin abnormalities are found in a wide variety of neurological disorders. White matter pathologies are found in many neurologic diseases, including genetic leukodystrophies (Costello et al., 2009), brain injury (Kinnunen et al., 2011), endocrine and metabolic abnormalities (Sievers et al., 2009; van der Werff et al., 2014), and psychiatric (Ladouceur et al., 2012) and neurodegenerative conditions (Mascalchi, 2005). These heterogeneous pathologies range from abnormal myelin structure to the virtual absence of myelin, and can arise directly from lack of myelin production or indirectly from damage to myelin. In white matter pathologies, insults such as oxidative stress, mechanical injury and inflammation ultimately lead to the degenerative loss of myelin (demyelination) or inadequate or abnormal formation of myelin (hypomyelination/dysmyelination). Primary mechanisms of myelin damage include

Abbreviations: CNS, Central nervous system; WM, white matter; OPC, oligodendrocyte progenitor cell; OL, oligodendrocyte; SVZ, subventricular zone; EAE, experimental autoimmune encephalitis bromodeoxyuridine; BrdU, bromodeoxyuridine; i.p., intraperitoneal; GFAP, glial fibrillary acidic protein; MBP, myelin basic protein; MAG, myelin associated glycoprotein; MOG, myelin oligodendrocyte glycoprotein; PLP, proteolipid protein; CNP, 2′,3′-cyclic nucleotide 3′-phosphodiesterase; APC, adenomatous polypolysis coli; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; NMDA, N-methyl-D-aspartic acid; NBQX, 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo[f]quinoxaline-2,3-dione; PDGF, platelet derived growth factor; bFGF, basic fibroblast growth factor; NT-3, neurotrophin-3; BDNF, brain derived neurotrophic factor; IGF, insulin-like growth factor; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; RXR, retinoid X receptor; RAR, retinoic acid receptor; THR, thyroid hormone receptor; PKB, protein kinase B; MAP, mitogen-activated protein kinase; SHH, Sonic Hedgehog; BMP, bone morphogenetic protein.

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destruction of the myelin sheath and oligodendrocyte (OL) death (Merrill and Scolding, 1999), failure of progenitor cell recruitment and/or differentiation during remyelination (Kremer et al., 2015; Shi et al., 2015), or in the case of neonates, delayed OPC maturation and defective ensheathment of myelinated axons (Jablonska et al., 2012; Ritter et al., 2013; Scafidi et al., 2014). As WM supports multiple axonal functions besides saltatory conduction, WM injury invariably leads to, or is associated with, devastating neurological disabilities, including motor and cognitive impairment.

In the adult CNS, approaches to intervention and protection against demyelination include attenuation of immune-mediated, excitotoxic and oxidative stress-mediated damage, as well as cell engraftment, direct protection of endogenous OLs and enhancement of repair by oligodendrocyte progenitor cells (OPCs). The success of cell replacement therapy is dictated by the lesion environment (Blakemore et al., 2002), so that an understanding of the multitude of factors in remyelination failure is needed not only for success of the graft, but also for stimulating repair by endogenous progenitor cells.

In the developing brain, perinatal WM damage, for which there is currently no cure, constitutes an important component of injury to the cerebrum that includes neurons and axons. Many of these insults occur in utero, as a consequence of preterm birth, or with complications of delivery (Silbereis et al., 2010). With improved antenatal care, the incidence of tissue degeneration from cystic lesions of the WM has declined, whereas the predominant lesion has now become more diffuse (Silbereis et al., 2010). As with the adult, the mechanisms which result in injury may also be excitotoxic, inflammatory and oxidative (Van Steenwinckel et al., 2014), and may either impact OLs directly, their synapses with axons (Shen et al., 2012), or other cells such as microglia (Kaur et al., 2012) and astrocytes (Deng et al., 2014).

This article aims to review pharmacological approaches to attenuate WM damage through efforts to promote remyelination in the adult, and reduce or prevent developmental delay in the neonate. Neuroprotection will not only help to preserve saltatory axonal conduction, but also aid in the maintenance of axonal metabolism and integrity, thus improving overall connectivity. Interestingly, white matter integrity and connectivity are impacted in conditions besides primary demyelinating disease, such as psychiatric (Chew et al., 2013) and neurodegenerative disorders (Mascalchi, 2005). Since anti-psychotic and anti-depressant therapies have been found to additionally attenuate myelin damage, targeted approaches for promoting or preserving myelination in a wide variety of neurological conditions would be justified (Bartzokis, 2012). Many neurological diseases are strongly associated with inflammation. Not surprisingly, some therapeutic reagents which have been found to protect the OL cell from damage have been shown to possess immunomodulatory properties. However, as continuous oligodendrogenesis is now considered a central component of brain plasticity and remodeling throughout life (Young et al., 2013), we have chosen an emphasis on non-immune therapeutic targets employed to improve myelination and remyelination by endogenous OPCs. By reviewing reports of pharmacological intervention in experimental models of demyelination and hypomyelination/dysmyelination, we hope to identify overlapping mechanisms that show the potential to benefit neonatal and adult WM pathologies.

1.1. Animal models of WM damage

Experimental models of adult WM damage involve viral, chemical, and immune-mediated demyelination paradigms, as well as spinal cord injury. These systems are well described in laboratory rodents (Tanaka and Yoshida, 2014). Briefly, gliotoxic chemicals that are injected into the WM to generate localized lesions include ethidium bromide that kills OLs by intercalating into the minor groove of DNA, and lysolecithin/lysophosphatidylcholine (Hall, 1972) which specifically disrupts myelin sheaths. Cuprizone (biscyclohexanone-oxaldihydrazone), a copper chelator that causes OL apoptosis by impairing metabolic function and inhibiting cellular support of myelin, is administered via the diet. It causes diffuse demyelination that is most notable in, but not restricted to (Skripuletz et al., 2008), WM regions (Matsushima and Morell, 2001). Remyelination is initiated by resuming a cuprizone-free diet for 2 weeks. None of these toxin-based methods of demyelination mimics the dynamics and pathogenesis of human disease, but they are useful to understand many aspects of damage and remyelination, such as preferential vulnerability of myelin without significant axonal loss, properties of the cellular response in recovery, the biological factors regulating these processes, and therapeutic regimens that improve cellular repair. The focal lesion provides rapid (48 h) demyelination that is circumscribed, so that secondary inflammation (Hall, 1972; Miron et al., 2013) and directed progenitor recruitment may be studied, using the lesion as an endpoint destination (Jablonska et al., 2010). In addition, unilateral lesions allow internally controlled sampling (Aguirre et al., 2007). However practical considerations of consistency in lesion size and location, applicable to quantitative analysis by histological and biochemical methods, add to the technical demands of this approach. These models are most valuable to study cellular responses during remyelination after myelin loss and injury, but because they lack the autoimmune component of MS, cannot be considered ideal animal models of MS. The interested reader is referred to comprehensive chapters and articles that further discuss MS models (Croxford et al., 2011; Merrill, 2009; Ransohoff, 2012).

Diffuse demyelination is also observed in an immune-mediated model, experimental autoimmune encephalitis, or EAE. EAE has remained the most influential in our understanding of inflammatory demyelination (Robinson et al., 2014). EAE may be produced in both mice and rats, and can be generated by 1) passive immunization with WM tissue homogenate, or 2) immunization with MBP or MOG. A third method, the adoptive transfer of T cells isolated from myelin peptide primed animals, allows the selection or in vitro manipulation of T cells before transfer to naive recipients to produce EAE (Robinson et al., 2014). Another inflammatory model of demyelination utilizes viruses – Theiler's murine encephalomyelitis virus (TMEV), or neurotrophic variants of the mouse hepatitis virus (MHV) – that stimulate the activity of T cells to induce chronic demyelination (Lane and Buchmeier, 1997; Templeton and Perlman, 2007). Immune mediators secreted by T cells and macrophages/microglia have been suggested to contribute to virally-induced demyelination due to dysregulation or death of oligodendrocyte lineage cells (Marro et al., 2014). These models are often considered alongside autoimmune-based models such as EAE, as they are useful for the characterization of infectious events leading to CNS immune responses (Baker and Amor, 2015; Fazakerley and Walker, 2003). Although EAE is powerful and remains most commonly used MS model, it is recognized that its limitations for MS therapy (Constantinescu et al., 2011) stem from a dependence on the artificial induction of the immune response (Mecha et al., 2013), unreliable predictability of treatments, a spinal cord preference over brain lesions, difficulty in analyzing remyelination of stochastic lesions and inconsistency of clinical functional progression (Ransohoff, 2012). On the other hand, proponents of viral models of demyelination note an inside-out axon-first degeneration, the presence of brain demyelination and progressive disease with viral spread (Mecha et al., 2013). Given the

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