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Review

Demyelination as a rational therapeutic target for ischemic or traumatic brain injury

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ABSTRACT

Previous research on stroke and traumatic brain injury (TBI) heavily emphasized pathological alterations in neuronal cells within gray matter. However, recent studies have highlighted the equal importance of white matter integrity in long-term recovery from these conditions. Demyelination is a major component of white matter injury and is characterized by loss of the myelin sheath and oligodendrocyte cell death. Demyelination contributes significantly to long-term sensorimotor and cognitive deficits because the adult brain only has limited capacity for oligodendrocyte regeneration and axonal remyelination. In the current review, we will provide an overview of the major causes of demyelination and oligodendrocyte cell death following acute brain injuries, and discuss the crosstalk between myelin, axons, microglia, and astrocytes during the process of demyelination. Recent discoveries of molecules that regulate the processes of remyelination may provide novel therapeutic targets to restore white matter integrity and improve long-term neurological recovery in stroke or TBI patients.

Contents

Abbreviations: AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; CNP, 2′,3′-cyclic nucleotide3′-phosphodiesterase; CNS, central nervous system; EAAT, excitatory amino acid transporters; IFN, interferon; IL, interleukin; MCT, monocarboxylic acid transporter; NMDA, N-methyl D-aspartate; NO, nitric oxide; OGD, oxygen glucose deprivation; OPC, oligodendrocyte precursor cell; OXPHOS, oxidative phosphorylation; PARP, poly[ADP]-ribose polymerase; PLP, proteolipid protein; ROS, reactive oxygen species; TBI, traumatic brain injury; TNF, tumor necrosis factor

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Introduction

Stroke and traumatic brain injury (TBI) are worldwide public health and socioeconomic problems (Gillum et al., 2011; Roozenbeek et al., 2013). With recent improvements in emergency care, greater numbers of patients are able to survive after stroke or TBI than before. Unfortunately, most of these survivors still develop physical disabilities due to the lack of effective therapies to restrict and/or repair brain damage. Understanding the mechanisms underlying progressive brain damage after stroke or TBI is therefore imperative for the development of novel therapies that successfully improve long-term neurological functions.

The human brain consists of both gray matter and white matter. Gray matter mainly contains neuronal cell bodies and unmyelinated axons. Gray matter serves as an information processor for the central nervous system (CNS). White matter, on the other hand, is mainly composed of bundles of myelin-ensheathed axons, myelin-producing oligodendrocytes, and other glial cells. White matter plays an essential role in signal transmission and communication between different brain regions. Although previous research on brain injuries emphasized the pathological alterations in neuronal cells within gray matter, recent studies also highlight the importance of white matter integrity in long-term recovery after stroke and TBI (Matute et al., 2013; Pham et al., 2012; Semple et al., 2013) White matter injury is an integral component of most human stroke or TBI events and usually accounts for at least half of the lesion volume (Ho et al., 2005; Hulkower et al., 2013). Unfortunately, the adult brain has very limited capacity for white matter repair. Thus, unrepaired white matter injury disrupts sensorimotor function and elicits profound neurobehavioral and cognitive impairments (Desmond, 2002).

Demyelination, or loss of the myelin sheath, is a major pathological component of white matter injury and contributes significantly to long-term sensorimotor and cognitive deficits (Pantoni et al., 1996). Oligodendrocytes are the primary cells responsible for generating and maintaining the myelin sheath under normal conditions and for remyelination after axonal damage (Nave, 2010a). However, myelinating oligodendrocytes are highly vulnerable to ischemic or traumatic insults (Back et al., 2007; Petito et al., 1998) and the loss of oligodendrocytes is known to be a significant factor underlying demyelination after injury (Caprariello et al., 2012).

Herein, we will describe the major causes of demyelination and oligodendrocyte death following acute injury in the adult brain, and discuss the crosstalk between myelin, axons, microglia, and astrocytes. We will also describe the toxic sequelae of demyelination, and highlight potential therapeutic strategies to target demyelination and improve long-term neurological function recovery in stroke or TBI patients.

Molecular mechanisms underlying oligodendrocyte death and demyelination

Oligodendrocytes are highly sensitive to various stimuli, including oxidative stress (Husain and Juurlink, 1995), excitotoxicity (McDonald et al., 1998; Salter and Fern, 2005), and inflammation, all of which induce oligodendrocyte cell death and contribute to demyelination after stroke or TBI. Below we discuss the molecular mechanisms underlying oligodendrocyte cell death and demyelination.

Glutamate excitotoxicity

Glutamate toxicity is a major cause of cell death in oligodendrocytes and their progenitor cells in diverse CNS injuries (McDonald et al., 1998; Salter and Fern, 2005). Under conditions of energy breakdown, reversal of excitatory amino acid transporters (EAATs) may lead to unchecked extracellular glutamate release, which induces glutamate excitotoxicity through glutamate receptors on the surface of oligodendrocytes (Fern et al., 2014). Intracellular calcium overload from glutamate excitotoxicity is a significant cause of oligodendrocyte and myelin damage (Benarroch, 2009). Glutamate receptor overstimulation opens Na^+/Ca^{2+} channels on oligodendrocytes, not only allowing the influx of calcium but also depolarizing the cell membrane (Tong et al., 2009). This membrane depolarization activates voltage-dependent Ca^{2+} channels, which could further increase intracellular Ca^{2+} levels. In addition, the decreased Na^+ gradient across the cell membrane caused by the glutamate surge may reduce the capacity of the Na^+ gradient-dependent antiporter to remove intracellular Ca^{2+}. In addition, Ca^{2+} can be released from its intracellular storage sites upon glutamate stimulation in oligodendrocytes. It has been reported that Ca^{2+} release from the endoplasmic reticulum through ryanodine receptors (RyRs) and from mitochondria through inositol triphosphate receptors (IP(3)Rs) is important for α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor-mediated excitotoxicity in oligodendrocytes (Ruiz et al., 2010). All of these mechanisms might contribute to the accumulation of cytosolic Ca^{2+}, which in turn can trigger oligodendrocyte toxicity (Benarroch, 2009).

There are three types of glutamate receptors on oligodendrocytes: AMPA, kainate, and N-methyl D-aspartate (NMDA) receptors (Butt, 2006; Salter and Fern, 2005). Glutamate receptors might be directly activated by glutamate released from damaged axons (Kukley et al., 2007; Ziskin et al., 2007). It has been shown that extracellular glutamate levels surge several hours after CNS injuries (Kolodziejczyk et al., 2010; Lai et al., 2014; Matute et al., 2006), leading to the over-activation of AMPA/kainate and NMDA receptors in the brain.

Previous studies have demonstrated that oligodendrocytes are highly vulnerable to AMPA/kainate receptor-mediated excitotoxicity (Alberdi et al., 2002). Blockade of this receptor reduces oligodendrocyte death in vivo (Tekkok and Goldberg, 2001) and in vitro (McDonald et al., 1998). Recent work further suggests that Zn^{2+} dysregulation is important in AMPA-induced excitotoxicity (Mato et al., 2013). The activation of AMPA receptors results in the cytosolic accumulation of Ca^{2+}, which in turn induces Zn^{2+} mobilization and accumulation in the cytosol (Mato et al., 2013). Excessive Zn^{2+} is known to activate ERK1/2 signal transduction cascades and induce oligodendrocyte death in a poly[ADP]-ribose polymerase 1 (PARP-1)-dependent manner (Baxter et al., 2014; Domercq et al., 2013). NMDA receptors are expressed on the myelin sheath of oligodendrocyte processes and are similarly involved in oligodendrocyte cell death (Karadottir et al., 2005; Micu et al., 2006; Salter and Fern, 2005). Activation of these receptors leads to a drastic increase in ion concentrations (Benarroch, 2009; Butt, 2006; Salter and Fern, 2005; Song and Yu, 2014) and the disruption of myelin structure (Bakiri et al., 2008). Thus, excess glutamate released from damaged axons after CNS injuries may elicit calcium-induced excitotoxicity and zinc dysregulation in oligodendrocytes through AMPA and NMDA receptors.

Mitochondrial dysfunction and oxidative stress

Mitochondria are double membrane-bound organelles responsible for more than 80% of total ATP production within the cell. ATP production in mitochondria is achieved through the oxidative phosphorylation (OXPHOS) complexes embedded in the inner mitochondrial membrane. NADH and FADH2 are produced through the