CNS Neuroscience & Therapeutics

REVIEW

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Oligodendrocyte Pathophysiology and Treatment Strategies in Cerebral Ischemia

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Keywords
Excitotoxicity; Hypoxia–ischemia; Oligodendrocyte; Oxidative stress; White matter.

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Received 20 January 2014; revision 6 March 2014; accepted 7 March 2014

SUMMARY

Oligodendrocytes (OLs), the myelin-forming cells of the central nervous system, form a functional unit with axons and play a crucial role in axonal integrity. An episode of hypoxia–ischemia causes rapid and severe damage to these particularly vulnerable cells via multiple pathways such as overactivation of glutamate and ATP receptors, oxidative stress, and disruption of mitochondrial function. The cardinal effect of OL pathology is demyelination and dysmyelination, and this has profound effects on axonal function, transport, structure, metabolism, and survival. The OL is a primary target of ischemia in adult-onset stroke and especially in periventricular leukomalacia and should be considered as a primary therapeutic target in these conditions. More emphasis is needed on therapeutic strategies that target OLs, myelin, and their receptors, as these have the potential to significantly attenuate white matter injury and to establish functional recovery of white matter after stroke. In this review, we will summarize recent progress on the role of OLs in white matter ischemic injury and the current and emerging principles that form the basis for protective strategies against OL death.

doi: 10.1111/cns.12263

Introduction

After an episode of cerebral hypoxia–ischemia (HI), early events include energy crisis, cell depolarization from the breakdown of transmembrane gradients, cytotoxic edema, reactive oxygen species (ROS) production, and endothelial dysfunction [1]. These events prompt a complex cascade resulting in neuronal and glial damage and death. OLs, the myelin-forming cells of the CNS, are acutely damaged by short periods of HI. Cell swelling occurs as early as 30 min after arterial occlusion, and large numbers of OLs die within 3 h [2]. It has been reported [3] that 30 min of oxygen–glucose deprivation (OGD) results in the death of 90% of OLs within 9 h. OL pathology results in demyelination and dysmyelination which have profound consequences for axonal function, transport, structure, metabolism, and survival [4–6]. The most devastating effects of HI on these cells occur in premature infants of <32 weeks' gestation, which show pathological symptoms of chronic myelination disturbance, leading to periventricular white matter injury [7]. The white matter of these infants is immature and poorly vascularized and contains oligodendrocyte progenitors (pre-OL) which are sensitive to ischemia and infection.

Research in neurological disorders is progressively embracing the concept of the neurovascular unit, which emphasizes that a successful neurorestorative therapy cannot exclusively target neurons, but must also encompass glial and endothelial cells [8]. Thus, therapeutic strategies that target OLs, myelin, and their receptors have the potential to significantly attenuate white matter injury in HI. This review highlights the mechanisms of OL injury and death in HI at all stages of development and focuses on the oligoprotective and oligorestorative therapies that have been investigated thus far.

Intrinsic Susceptibility of Oligodendrocytes to Hypoxic–Ischemic Damage

OLs display a number of features that render them more vulnerable to HI than other CNS glial cells, and in certain brain regions and stages of development, more vulnerable than neurons [9] (Figure 1).

Of all the cell types in the brain, OLs contain the highest levels of immobilized, protein-bound iron, which is a basic requirement for their function and oxidative metabolism, and for the synthesis of myelin components [10,11]. Apart from its important functional role, ferrous iron (Fe^{2+}) can be a potent cytotoxin

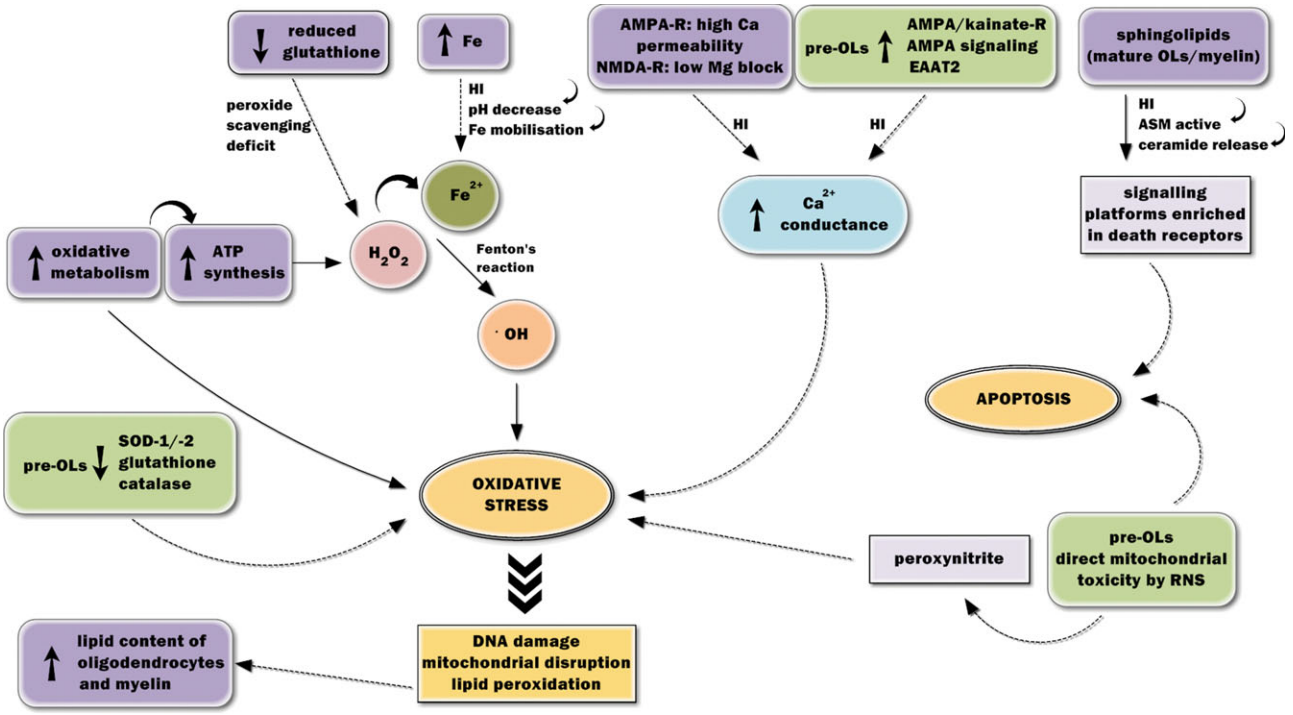

Figure 1 Features of oligodendrocytes (OLs) and pre-OLs which render them vulnerable to hypoxia–ischemia (HI). The amplified vulnerability of OLs to HI derives from their high iron content, low reduced glutathione content, high rate of oxidative metabolism, high lipid and sphingolipid content, and high permeability of glutamate receptors. Pre-OLs are even more vulnerable than their mature counterparts due to low levels of antioxidant enzymes, upregulation of AMPA/kainate receptors and enhanced AMPA/kainate signaling, increased expression of the glutamate transporter EAAT2, and a susceptibility to direct mitochondrial toxicity by reactive nitrogen species. In the event of HI, these properties lead to higher levels of oxidative stress and apoptosis, hence, severe damage, and death to cells of this lineage.

by catalyzing the conversion of hydrogen peroxide to hydroxyl radicals (OH), via the Fenton reaction [12,13]. In cerebral ischemia, an energy crisis leads to lactic acidosis, which results in mobilization of protein-bound iron stores. This increases the levels of free cytosolic Fe^{2+} that participates in the Fenton reaction to bring about oxidative stress [14,15]. This effect is further amplified in OLs by their low content of reduced glutathione (GSH) [16,17] which is an electron donor for the function of glutathione peroxidase, which in turn, scavenges peroxides. OLs contain less than half of the glutathione content of astrocytes and <15% of the glutathione peroxidase activity, which leads to a peroxide-scavenging deficit [17]. OLs also have the highest rate of oxidative metabolism by volume and can support a myelin membrane up to 100 times the weight of their cell bodies [4,11,18]. This high metabolic activity generates more ROS [18] and requires a correspondingly high consumption of oxygen and ATP, the synthesis of which generates hydrogen peroxide as a by-product [19–21].

The subunit composition of glutamate receptors in OLs continues to predispose them to injury during HI. Their AMPA receptors are especially permeable to Ca^{2+} [22,23], and their NMDA receptors are only weakly blocked by Mg^{2+}, enabling them to generate a substantial current even at resting membrane potential [22,24,25].

Sphingolipids, constituents of the myelin membrane, may also increase the susceptibility of OLs to damage under pathological conditions [4,26]. The simplest sphingolipid, ceramide, can activate the major pathways that govern cell death [27] and kill cells by limiting access to extracellular nutrients [28]. Many apoptotic stimuli activate acid sphingomyelinase, an enzyme that mediates ceramide release from biological membranes [29,30]. Ceramide-enriched signaling platforms that contain death receptors are formed in the plasmalemma, and these transmit apoptotic signals into the cell [29,31]. Ceramide released intracellularly also acts as a second messenger, leading to caspase-mediated OL apoptosis within hours [26,32,33].

Even more susceptible to injury than mature OLs are the $O4^+$/$O1^-$ late OL progenitors, which comprises about 90% of all OLs during the high-risk period for periventricular leukomalacia (PVL) [7,34]. This vulnerability is a consequence of:

1 Amplified oxidative damage that results from a developmental deficit in superoxide dismutases (SOD-1 and -2) and a hydrogen peroxide-scavenging deficit [35–37] combined with active iron acquisition [11].
2 Higher vulnerability to reactive nitrogen species attack by direct mitochondrial toxicity with translocation of apoptosis-inducing factor [38] and formation of peroxynitrite [39,40].
3 Significant developmental upregulation of non-NMDA glutamate receptors [41,42] accompanied by enhanced AMPA-mediated calcium signaling [43], which increases excitotoxicity. Furthermore, pre-OLs also exhibit a transiently increased expression of the glutamate transporter (GluT)

EAAT2, which may become a source of glutamate under pathological conditions [44].

Mechanisms of Oligodendrocyte Damage in HI

Neurotransmitter-Mediated Toxicity

OLs express neurotransmitter receptors that allow for axon-to-OL signaling and mediate their own development and function. The major excitatory neurotransmitters involved are glutamate and ATP [45,46]. These bind to their respective receptors on the OL plasmalemma and result in an influx of ions, most notably Ca^{2+}, which acts as a chemical signal under physiological conditions, triggering OL differentiation and myelination [47].

OLs are extremely sensitive to disruptions in intracellular calcium homeostasis [25]. In HI, energy crisis and metabolic stress lead to prolonged overstimulation of neurotransmitter receptors, resulting in a cytosolic Ca^{2+} surge which is worsened by the activation of voltage-gated calcium channels (VGCC) and the reversal of the Na^+/Ca^{2+} exchanger (NCX) [48]; (Figure 2). This Ca^{2+} is sequestered by mitochondria and leads to mitochondrial bioenergetic dysfunction, which is characterized by impaired oxidative phosphorylation, ROS generation, the release of apoptogenic proteins, such as cytochrome C, and cell death by apoptosis or necrosis [49].

Glutamate-Mediated Toxicity

Glutamate excitotoxicity is one of the major contributors toward ischemic injury in the CNS [50]. OLs are sensitive to glutamate-induced cell death [48] with an EC_{50} of 200 μM for a 24-h exposure period [51]. The glutamate signaling is governed by ionotropic and metabotropic glutamate receptors (iGluRs and mGluRs, respectively) and GluTs [52,53]. OLs express three main types of iGluRs: the AMPA and kainate receptors, predominantly located on their cell body, and NMDA receptors, clustered on their myelinating processes [25,54]. Pre-OLs strongly express all three groups of mGluRs, but these are downregulated in mature OLs [55]. GluTs are responsible

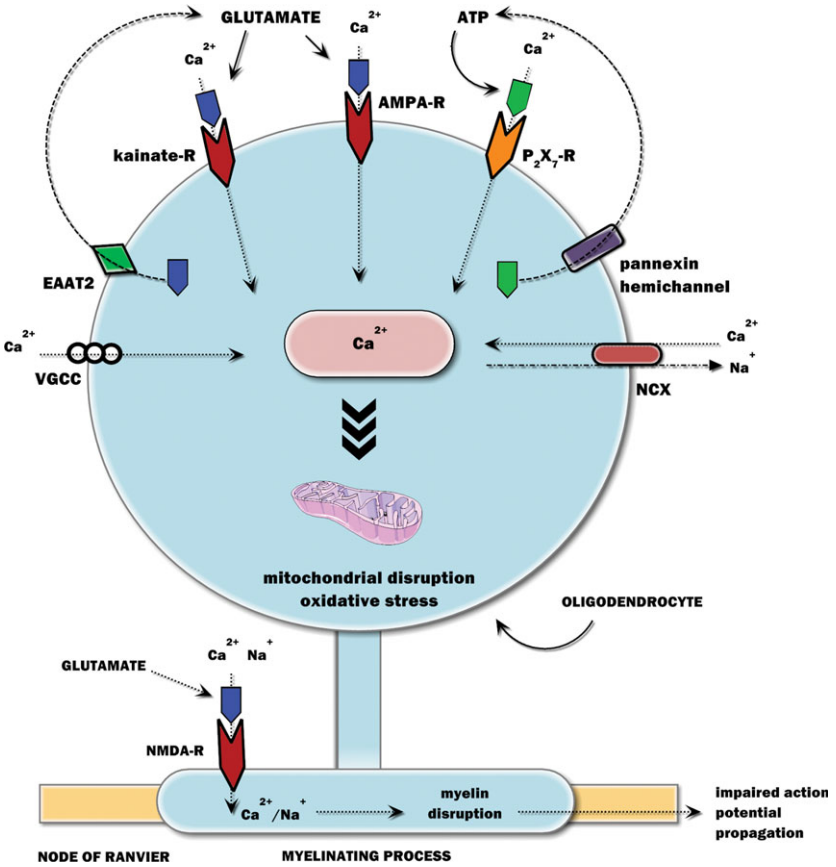

Figure 2 The major pathways governing neurotransmitter-mediated oligodendrocyte death in hypoxia–ischemia (HI). The glutamate surge that occurs during HI leads to the overactivation of AMPA/kainate receptors on oligodendrocyte somata and NMDA receptors on myelinating processes. ATP is also released in HI, partly from the oligodendrocyte itself via pannexin hemichannels, leading to the overactivation of purinergic P2X7 receptors and enhanced Ca^{2+} signaling. The Ca^{2+} surge leads to the activation of voltage-gated calcium channels (VGCC) and reversal of Na^+/Ca^{2+} exchanger (NCX), further increasing the intracellular Ca^{2+}. The glutamate transporter EAAT2 also starts to operate in reverse, contributing to the surge in extracellular glutamate. The excess cytosolic Ca^{2+} is sequestered in mitochondria where it leads to mitochondrial disruption and oxidative stress and eventual death to oligodendrocytes.

for the uptake of glutamate from the extracellular space and maintenance of low extracellular glutamate levels (1–2 μM). However, under conditions of energy failure that result from HI, GluTs on OLs, astrocytes and microglia operate in reverse, with release of glutamate into the extracellular space [48,56].

OLs have for a very long time, been known to be vulnerable to AMPA/kainate receptor-mediated excitotoxicity [57,58]. The AMPA receptors on mature, myelinating OLs contain subunits GluR3 and GluR4, but not GluR1 [59], and although mRNA for GluR2 is present, immunoprecipitation experiments indicate that GluR2 does not assemble with the other subunits [22,60], which renders them highly permeable to Ca^{2+} when activated [23,61]. In fact, Ca^{2+} influx via these receptors alone is enough to induce death of OLs by excitotoxicity in culture, [61] and blockade of AMPA/kainate receptors alone prevents death of OLs by OGD during cerebral ischemic injury [3]. Prolonged activation of these receptors leads to caspase-dependent and caspase-independent death pathways [62], and this toxicity is dose-dependent [58]. Recent work suggests the involvement of disturbed Zn^{2+} homeostasis in AMPA-induced excitotoxicity. It has been demonstrated [63] that activation of OL AMPA receptors leads to mobilization of intracellular Zn^{2+} and a surge in cytosolic Zn^{2+}, which contributes toward ROS production and mitochondrial depolarization, by a mechanism which is altogether separate from the Fenton reaction.

Oligodendrocytes express mRNA for the kainate subunits GluR6, GluR7, KA-1, and KA-2, but not for GluR5 [22]. Nontoxic concentrations of glutamate can sensitize these cells to complement attack, inducing OL death, in a process that is mediated exclusively by activation of kainate receptors. This complement-induced death of OLs occurs via formation of the membrane attack complex, which increases membrane conductance and leads to a Ca^{2+} surge [64].

Excitotoxic OL death was previously thought to be exclusively mediated by AMPA and kainate glutamate receptors. Three recent reports [24,54,65] have manifestly altered this view by showing *in vivo* that OLs and myelin possess NMDA receptors and that these are involved in ischemic injury. White matter OLs at all stages of development contain NR1, NR2C, and NR3A NMDA receptor subunits, allowing for inward currents upon binding of glutamate [66]. OL NMDA receptors are enriched with NR2C and NR3A subunits, which are blocked weakly by extracellular Mg^{2+} and allow for the generation of a current even at the cell's resting membrane potential [65–67]. As NMDA receptors are clustered on the myelinating processes of OLs, receptor activation leads to a drastic increase in ion concentration because of the small intracellular volume [25,54,68] with disruption of myelin structure and action potential propagation [69].

In pre-OLs, glutamate toxicity also occurs via a non-receptor-mediated mechanism, referred to as oxytosis, or oxidative glutamate toxicity [70]. This involves system x_c^-, a plasmalemmal antiport protein that transports cystine into the cytosol in exchange for glutamate to the extracellular space, in a 1:1 ratio [51]. Once in the cytosol, the cystine is converted to cysteine, which is used in the production of glutathione [71]. High extracellular glutamate concentrations can reverse the direction of this transport, promoting the efflux of cystine with consequent depletion of intracellular glutathione, and enhancement of oxidative stress [51,72]. Although this phenomenon is not exclusive to pre-OLs, they exhibit enhanced, maturation-dependent vulnerability because of low levels of glutathione peroxidase and SODs, especially SOD-2 [35–37].

ATP-Mediated Toxicity

ATP activates ionotropic P2X and metabotropic P2Y purinoreceptors, both of which are expressed by OLs [73]. P2X receptors consist of P2X1-7 subunits that are most permeable to Ca^{2+} ions [74,75]. During ischemia, ATP-mediated toxicity to OLs occurs mainly via P2X7 receptor subtypes, the sustained activation of which induces cell death, myelin damage, and white matter injury [53,76,77].

During situations of metabolic stress, such as cerebral ischemia, anoxic depolarization causes ATP to be released from glial cells, leading to a surge in the extracellular ATP concentration [78]. It has been suggested [76] that OLs may release ATP during ischemia via pannexin hemichannels, resulting in depolarization of mitochondria and release of ROS. ATP released from dying cells can continue to aggravate P2X7-mediated injury [6]. Functional P2Y and P2X receptors are also expressed by pre-OLs [79], the latter of which exhibit postischemic downregulation [80].

ATP-mediated toxicity leads to apoptosis or necrosis of OLs, the mode of cell death being determined by the intensity of the Ca^{2+} surge, which, in turn, depends on the intensity of the ischemic insult [6]. Prolonged stimulation of P2X7 receptors also leads to several enzyme and secondary messenger cascades, with release of cytokines such as interleukin-1β and activation of mitogen-activated protein kinase (MAPK) and nuclear factor-κB, among others [75,81].

Mitochondrial Disruption and Oxidative Stress

Oxidative damage is a cardinal consequence of neurotransmitter-mediated toxicity. HI rapidly causes oxidative stress in OLs, which is characterized by enhanced production of the superoxide radical (O_2^-), lipid peroxidation, and reduction of Fe^{3+} to the oxidant Fe^{2+} [82]. The exposure of OLs to systems which generate free radicals, or free radical donors, such as O_2^- and NO, leads to their rapid necrosis or apoptosis [5,83].

The drastic rise in cytoplasmic Ca^{2+} that occurs during HI has profound consequences for mitochondria, which sequester this cation in large amounts and generate ROS at levels dependent on Ca^{2+} uptake [84]. The oxidative stress that ensues activates several signaling pathways that modulate the functions of enzymes and transcription factors. These signals cause changes in gene expression that influence the cell's survivability [85]. O_2^- and NO radicals are particularly toxic to mitochondria as they interact with and block several key proteins of the respiratory chain [18]. These radicals also lead to a diffusion-limited generation of peroxynitrite, which causes death of OLs by lipid peroxidation, release of Zn^{2+}, activation of extracellular signal-regulated kinases and of 12-lipoxygenase, and formation of additional ROS [86].

Auxiliary Mechanisms

Kinins are peptides produced at sites of tissue injury or inflammation [87]. They activate specific B_1 or B_2 receptors, which mediate a number of signaling transduction mechanisms [88]. In the CNS, kinins act as neuromediators [89]. They also promote the synthesis of other pro-inflammatory mediators, including cytotoxins and prostanoids, which lead to tissue damage and blood–brain barrier breakdown [88,90]. Functional kinin receptors are expressed by OLs, and their activation leads to a cytosolic Ca^{2+} surge, inflammation, and turnover of phosphoinositide [1,91]. Following ischemia, expression of B1 and B2 kinin receptors is upregulated, and the concentrations of bradykinin and kallidin also increase and result in damage and death of neural and glial tissue. Because of this, B1R and B2R receptor antagonists may be useable as neuroprotective and glioprotective agents during stroke, especially because they target multiple mechanisms that are involved in different stages of brain pathology [1].

The activation of dopamine D2 and D3 receptors [92], $GABA_A$ receptors [22] and adenosine A_{2A} receptors [93] has also been implicated in ischemic damage of OLs. Moreover, A_1 adenosine receptors are found on pre-OLs, and their activation in HI inhibits maturation of these cells [94], with consequent shortage of myelinating OLs.

The Role of Neighboring Glia

Neighboring glia cause bystander damage to OLs in HI. Glutamate activates AMPA/kainate receptors in both resting and activated microglia at the site of injury and thereby enhances production and release of the cytokine, tumor necrosis factor-α [95]. This can kill OLs by apoptosis and by potentiation of interferon γ toxicity and is more toxic to pre-OLs than to mature OLs [96,97]. Reactive microglia also release interleukin-1β, glutamate [98], and reactive oxygen and nitrogen species, such as peroxynitrite [40], which further inhibit glutamate uptake and amplify excitotoxic damage [99].

Activation of microglia is a major source of damage to pre-OLs in PVL, especially as the number of microglia in cerebral white matter peaks during the period of highest vulnerability to PVL [100]. Reactive astrocytes, microglia, and macrophages also damage pre-OLs in PVL, by the release of interferon γ [101], which leads to an increase in inducible nitric oxide synthase (iNOS) that becomes upregulated during HI [102]. iNOS generates NO, which injures pre-OLs by peroxynitrite formation and nitrosative damage. Antimicroglial agents, such as minocycline and melatonin, provide promising routes to the attenuation of pre-OL damage and demyelination in PVL [97].

Recovery from Trauma and Role of Adult Oligodendrocyte Progenitor Cells (OPCs)

An important task of the adult CNS after an episode of HI is the replacement of affected OLs and the remyelination of affected axons, to restore saltatory conduction, improving motor function [103]. *In vivo* rodent models of stroke have demonstrated that a few days following an insult, OLs surrounding the infarct tend to increase in number [104]. Axons that have been demyelinated as a result of trauma or disease can be remyelinated by immature cells that "respond to demyelination by differentiating into myelinating OLs" [105]. These cells, now referred to as adult OPCs, form part of a larger subtype of glial cells, NG2+ glia, which express the NG2 proteoglycan and platelet-derived growth factor-alpha (PDGF-α) receptors [106]. Also known as polydendrocytes, these cells are closely intermingled with other glial cells in the CNS, but nonetheless represent a distinct cell population [107].

Adult OPCs are not pre-OLs but mature cells which develop after birth. They become activated during axonal inflammation and/or demyelination and develop into mature, myelinating OLs [108]. Many chemical signals appear to be responsible for their activation, including axonal signals released on demyelination, growth factors and cytokines from other activated glial cells, as well as other injury-induced stimuli, such as ATP and glutamate surges [4]. It is of interest that, although TNF-α causes death of OL by apoptosis [96], lack of TNF-α leads to a delay in remyelination and a reduction in the population of proliferating adult NG2+ OPCs, which is followed by a decrease in the number of myelinating OLs. Apparently, the binding of this cytokine to TNF receptor 2 (TNFR2) is critical for the regeneration of OLs after trauma [109].

Recently, several therapies have been evaluated to target the protection or multiplication of these progenitors and allow for replacement of OLs and remyelination. Sun et al. [110] report that the synthetic cannabinoid agonist WIN55, 212-2, has been shown to reduce injury to NG2+ glia cells and to promote their multiplication in the stroke penumbra. Adenosine was found to accelerate the maturation of OPCs in culture [111] and erythropoietin to stimulate oligodendrogenesis and maturation *in vivo* [112]. The transplantation of predifferentiated human embryonic stem cells, which develop into myelinating OPCs, has also been proposed [103].

In PVL, pre-OLs and immature OLs also exhibit a defensive reaction in response to HI. These cells typically take the form of an enlarged soma with elaborate, thickened processes that are not typical of OLs at this stage of development and with a concentrated distribution around areas of injury [34]. HI also promotes accelerated maturation of pre-OLs to immature OLs, which are less vulnerable to ischemia [7].

Protective Strategies for Oligodendrocyte Injury in HI

Numerous neuroprotective agents have been developed and tested for their ability to block specific cell damaging pathways in the ischemic cascade. Although many of these gave promising results in animal models, clinical trials have been, for the most part, disappointing, because of a lack of efficacy and/or clinical safety concerns. This failure may be explained, in part, by the histological and morphological differences between human and rodent brains [113]. Ginsberg [114] also suggests that many agents may have been taken to clinical trials without sufficient preclinical evidence of efficacy. More rigorous experimentation is necessary to elucidate efficacious and clinically safe neuroprotective and glioprotective agents, with a focus on

targeting multiple biochemical cascades and CNS cell types, and combinatorial therapies. A summary of the agents that have been deemed most promising in conferring protection to OLs is provided in Table 1.

Protection Against Neurotransmitter-Mediated Injury

Excitotoxic OL, pre-OL, and neuronal injury can be attenuated by administration of the AMPA antagonist NBQX, which preserves white matter structure and improves motor deficits [3,42,115], although this compound may not be clinically safe [116]. Topiramate, a clinically safe anticonvulsant, protects pre-OLs against HI when administered postinsult, as does NBQX [117]. SPD 502, a competitive AMPA antagonist, protects both gray and white matter, including OLs, when administered intravenously 15 min before the insult, and for 4 h after the insult [118]. Other AMPA antagonists that have been shown to protect OLs against excitotoxic damage include GYKI 52466 [3] and CNQX [58]. Dihydrokainic acid, an inhibitor of glutamate release via reverse transport, significantly protected immature OLs from ischemic injury in culture [119].

Table 1 Therapeutic candidates for oligoprotection in hypoxia–ischemia

Mechanism	Oligoprotective agent	Oligodendrocyte maturation stage	Experimental model	References
AMPA antagonist	NBQX	Mature	Brain slices (mouse)	3
		Pre-OLs	*In vivo*(rat)	42
	Topiramate	Pre-OLs	*In vivo*(rat)	117
	SPD502	Mature	*In vivo* (rat)	118
	GYKI52466	Mature	Brain slices (mouse)	3
	CNQX	Mature	Optic nerve oligodendrocyte culture	58
NMDA-antagonist	D-AP5	Mature	Live adult rat optic nerve	24
		Pre-OLs, immature, mature	Brain slices (rat)	65
	MK801	Mature	Live rat optic nerve	24
		Pre-OLs, immature, mature	Brain slices (rat)	65
	Memantine	Mature	Brain slices (rat)	69
		Pre-ols	*In vivo* (rat)	120
	7-CKA	Mature	Live adult rat optic nerve	24
Reverse glutamate transport inhibitor	Dihydrokainic acid	Immature	Cultured rat OLs	119
P2X7 antagonist	BBG	Mature	Rat optic nerve oligodendrocyte culture + isolated optic nerve	53
	Oxidized ATP			
P2X antagonist	PPADS			
ATP degrader	Apyrase			76
Pannexin hemichannel blocker	Mefloquine			
Adenosine receptor antagonist	SCH58261	Mature	*In vivo* (rat)	93
	Caffeine	Pre-OLs	*In vivo* (mouse)	94
Antioxidant/radical scavenger	Mangiferin	Mature	Optic nerve oligodendrocyte culture	84
	Morin			
	N-acetyl cysteine	Pre-OLs	Rat oligodendrocyte progenitor cultures	124
	Edaravone	Mature	*In vivo* (rat)	127
		Mature	Clinical trial	128
	α-phenyl-tert-butyl-nitrone	Mature	*In vivo* (rat)	126
	Vitamin K	Pre-OLs	Cultured rat OLs	129
	Ebselen	Mature	*In vivo* (rat)	130
		Mature	Clinical trial	133
	Erythropoietin	Pre-OLs	*In vivo* (sheep)	135
	Melatonin	Pre-OLs	*In vivo* (rat)	136,137
	Estradiol	Mature	*In vivo* (mouse)	138
Iron chelator	Deferoxamine	Mature	Cultured rat OLs	134
Antiapoptotic agent	IGF-1	Pre-OLs	*In vivo* (rat)	97,140
		Pre-OLs	*In vivo* (lamb)	97,141
		Mature	*In vivo* (mouse)	142
	CNTF	Pre-OLs	*In vivo* (mouse)	97,143
	Estradiol	Pre-OLs	Cultured rat OL + *in vivo* (rat)	97,144
Antimicroglial agent	Minocycline	Pre-OLs	*In vivo* (rat)	97,145
Cannabinoid agonist	WIN55, 212-2	OPCs	*In vivo* (rat)	110

BBG, brilliant blue-G; OLs, oligodendrocytes; OPC, oligodendrocyte progenitor cell.

NMDA receptors are excellent targets for antagonists because they contain several sites at which ligands can bind in a subunit-selective manner, such as glutamate-binding sites, ion-channel pores, and allosteric sites on the N-terminal domain. NMDA receptor antagonists that target NR3A and NR2C subunits have the potential of acting as major therapeutic targets for white matter preservation in stroke [67]. The NMDA antagonists, D-AP5, and MK801 protect OLs and myelin from excitotoxic death, but are not clinically safe [24,65,72]. Memantine, a clinically safe, uncompetitive NMDA receptor blocker is also effective against injury in both OLs and pre-OLs [72,120], and 7-CKA protects OLs and myelin during chemical ischemia *in vitro* [24]. Of interest is that blockade of NMDA receptors or removal of extracellular Ca^{2+} worsens, rather than improves, functional recovery in aging animals [121], which emphasizes the importance of age-specific stroke treatment.

Another possible therapeutic route is the upregulation of GluTs, as these allow for ischemic tolerance subsequent to ischemic preconditioning. EAAT2 promoters, such as valproic acid, can protect glia against ischemia by enhanced removal of glutamate from the extracellular space [122–124].

Ischemia-induced mitochondrial depolarization and oxidative stress are partially reversed by P2X7 receptor antagonists, by the ATP-degrading enzyme apyrase, and by pannexin hemichannel blockers such as mefloquine. P2X7 receptor antagonists do not interfere with normal physiological function because of their selective activation [76,77]. The P2X7 antagonists Brilliant Blue-G (BBG), oxidized ATP (oATP), and the nonselective P2X antagonist PPADS prevent ATP-mediated OL toxicity [53]. The calmodulin antagonist calmidazolium has been shown to inhibit P2X7-receptor evoked glutamate release and may therefore have potential in oligoprotection during ischemia [125]. The administration of the selective adenosine A_{2A} receptor antagonist SCH58261 also protects OLs against cerebral ischemia by reducing the activation of the MAPK, JNK [93]. Caffeine, an adenosine receptor antagonist, was found to be protective in PVL as it promotes the maturation of pre-OLs after HI [94].

Protection Against Oxidative Stress

Antioxidants are potent therapeutic candidates for oxidative damage to OLs in cerebral ischemia. Mangiferin and morin, two natural antioxidant polyphenols, protect OLs from excitotoxic insult by free radical scavenging and cytosolic Ca^{2+} handling [84]. N-acetyl cysteine also attenuates AMPA/kainate OL cytotoxicity by increasing intracellular glutathione levels [124]. Pretreatment with the spin-trap agent α-phenyl-tertbutyl-nitrone (PBN) reduced the number of damaged OLs by 55%, 40 min after the insult [126]. The radical scavenger edaravone protects all components of the neurovascular unit against oxidative stress [8,127,128], while Vitamin K prevents oxidative damage to pre-OLs and neurons during HI, with clinical safety [129]. 12-lipoxygenase inhibitors may also be of protective value to OLs at all stages of development, as 12-lipoxygenase is a potent generator of ROS [97].

Ebselen, a mimic of glutathione peroxidase and phospholipid hydroperoxide glutathione peroxidase, exerts potent antioxidant effects on OLs and neurons [130–132]. When administered intravenously, 2 h after stroke onset, it can salvage damaged tissue without major side effects [130]. In a clinical trial, ebselen demonstrated a significant improvement in stroke patients who started ebselen treatment within 24 h of onset of the insult [133]. The iron chelator deferoxamine protects OLs from cytotoxic effects induced by H_2O_2 and suppresses free radical formation [134]. In clinical trials for PVL, erythropoietin, an antiinflammatory, antiapoptotic, antioxidant, and neurotrophic agent was found to reduce injury and preserve myelination in infants with moderate damage, without significant adverse effects [135]. Melatonin, a free radical scavenger and up-regulator of SOD, catalase, and glutathione peroxidase, has been found to promote pre-OL maturation after perinatal brain damage [136] and decreases white matter inflammation, promoting myelination after neonatal stroke [137]. The administration of the hormone 17β-estradiol was recently shown to attenuate OL loss in the corpus callosum of male mice, and results in decreased demyelination and microglial activation [138], by a quinol-based cyclic antioxidant mechanism [139].

The ability to visualize OLs in living brain through cell type-selective transfer of genes encoding fluorescent proteins [146] provides new opportunities to understand cell–cell interactions of recovery in diseases of the myelinating unit.

Conclusion

Largely ignored for many years, the importance of OLs in the pathophysiology of a variety of neurological disorders has become evident. We now know that OLs are major targets of cerebral ischemia, both in the case of adult-onset stroke and especially in PVL, which means that treatment strategies that exclusively target neuronal recovery cannot be optimally successful. This has led and should continue to lead researchers to make new links and explore new pathways of investigation, with the objective of treating cerebral ischemia in a more comprehensive manner.

New, groundbreaking research on oligodendrocyte pathophysiology in ischemia is constantly being made available. A notable example is the relatively recent discovery of functional NMDA receptors on OLs, antagonists of which are now being considered a possibly valid and valuable therapeutic route. Further work should continue to elucidate the exact underlying mechanisms of oligodendrocyte pathophysiology and to shed light on therapies that simultaneously target multiple mechanisms of injury and multiple components of the neurovascular unit. Therefore, it is hoped that future investigations should continue to work toward generating animal models of white matter stroke along with well-designed clinical trials to extrapolate the findings on experimental animals to human neurological disease. These therapies are expected to be more innovative, more extensive, and more clinically viable.

Acknowledgments

This study was supported in part by University of Malta research funding, coordinator M. Valentino. The authors thank EU COST Action CM1103 "Structure-based drug design for

diagnosis and treatment of neurological diseases: dissecting and modulating complex function in the monoaminergic systems of the brain."

Conflict of Interest

The authors have no conflict of interest.

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