

# Advances in Oligoprotection

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## ABSTRACT

*Oligodendrocytes, the myelinating glial cells of the nervous system, in various disease states display great vulnerability to excitotoxic damage, oxidative stress, and inflammatory cytokines. Besides demyelinating diseases where oligodendrocyte injury is primarily implicated, damage to them also occurs secondarily in various neuropathies. Oligoprotection should, therefore, be looked into something not just as a means for protecting oligodendrocytes alone but also as a common target of protecting neurons and the neurogliovascular unit as a whole. In this review, we provide a description on oligodendrocytes, the reasons for their vulnerability, the evolving new concepts of protecting neurovascular unit and recently neurogliovascular unit; the various diseases where oligodendrocyte injury is implicated with a brief idea on different injury mechanisms of oligodendrocytes. Finally, we present the summary of the drugs that have shown promising results in protecting oligodendrocytes or in protecting white matter as a whole in different in vivo and in vitro models.*

**Keywords:** *Oligodendrocytes, Neurovascular Unit, Oxidative Stress, Excitotoxicity, Demyelinating Diseases, Stroke, Spinal Cord Injury, Neuropharmacology*

## 1. Introduction

Neurobiology has been a field of ever-growing interest with more and more researchers working aimed at preventing or curing various neurological diseases like Multiple Sclerosis (MS), Alzheimer's disease (AD), Parkinson's disease (PD). The incidence of these diseases is on the rise with the increasing elderly population. Our high paced life style has increased auto-accidents and the cases of traumatic brain injury (TBI) and spinal cord injury (SCI) which leads to loss of lives or debilitating conditions lifelong.

Research focused in central nervous system (CNS) pathologies in the yesteryears focused centrally on neuronal mechanisms. However, the concept of neuroprotection alone failed to prove optimal therapeutic strategy hence the neuron-based model has taken a paradigm shift to integrate the non-neuronal cells which maintain the homeostatic environment for neurons. It has widened to embrace much wider concept of Neurovascular unit (NVU) which itself has remolded into Neurogliovascular unit [1,2]. The neurovascular unit has been recently defined as a unit that comprises neurons and non-neuronal

cells such as vascular cells (endothelia, pericytes and vascular smooth muscle cells) and glia (astrocytes, microglia and oligodendrocytes), along with an extracellular matrix that maintains the integrity of brain tissue [3]. Also the concept of oligovascular niche has emerged which includes the main cell types comprising white matter—the neuronal axon, oligodendrocyte (myelin), astrocyte, and endothelial cell [1].

Oligodendrocytes (OLGs) are the myelinating glial cells of the CNS. OLGs in the nervous system are analogous to the Schwann cells in the peripheral nervous system in providing support for quick transfer of neuronal signals. OLGs not only myelinate axons but also maintain their functional integrity and survival thorough oligodendrocyte specific proteins and/or trophic factor release by secreting soluble factors. Factors like Brain derived neurotrophic factor (BDNF), Neurotrophin-3 (NT-3), Nerve growth factor (NGF), and Platelet derived growth factor (PDGF) are reported as oligodendrocyte-axon signaling mediators [1]. They differ greatly morphologically based on their function and subtypes [4].

Myelin sheath, the protective covering of the nerve fibers insulating the axons, is responsible for transmission of the electrical signals with high velocity and without the loss of signal strength. The myelin sheath produced by OLGs is up to 600 × surface area and 100 × weight of

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soma and therefore their energy requirement is 2-3 times more than other brain cells [5]. These facts make OLGs the most vulnerable cells in the brain coupled with highest rate of metabolism, high reactive oxygen species (ROS) formation, low levels of antioxidant glutathione; high iron stores for cholesterol and lipid synthesis required for myelin formation; high levels of polyunsaturated fatty acids (PUFA) which react with ROS triggering lipid peroxidation [5-7]. OLGs are damaged as a result of adverse environmental signals and stress situations, such as oxidation, which may retard or inhibit myelination [8]. Neurons require assistance of glial cells for maintaining brain homeostasis from extracellular concentrations of ions, neurotransmitters and neurohormones for provision of an uninterrupted metabolic support [9]. The denuding of axons following oligodendrocyte death leads to functional loss of neurons and eventually their death, moreover, with a single oligodendrocyte myelinating numerous axons, death of a single oligodendrocyte exposes multiple neurons to risk [9].

## 2. Oligodendrocytes in Disease States

### 2.1. Multiple Sclerosis (MS)

MS is an autoimmune demyelinating disease with a neurodegenerative component most commonly diagnosed in patients 20 - 40 years of age [10]. In MS, the immune system attacks the white matter of the brain and spinal cord, causing multifocal demyelination leading to disability and/or paralysis. In acute MS, oligodendrocytes die mainly by apoptosis, however, in chronic MS lesion apoptosis was absent or rare which could be because of the rapid removal of apoptotic cells *in vivo* [11]. Oxidative stress plays an important role in oligodendroglial death in MS [12]. Macrophages from MS patients show increased production of superoxide radicals and H<sub>2</sub>O<sub>2</sub>; while CSF displays significantly high level of NO metabolites, nitrite and nitrate compared to controls [13]. As the MS lesion formation starts, locally produced ROS induce tight junction and cytoskeletal changes in brain endothelial cells which facilitate transendothelial monocyte migration [6]. ROS also has a critical role in myelin phagocytosis and it has been observed that using ROS inhibitors like NADPH oxidase inhibitors, lipoic acid or catalase enzyme reduced myelin phagocytosis by macrophages [6]. Excitatory glutamate levels are increased in acute MS lesions and in normal-appearing white matter in MS patients [14]. In addition, oxidative stress contributes to the increase in glutamate concentrations in the extracellular space, as free radicals reduce the efficiency of GluTs [14]. TNF- $\alpha$  is found at high levels in multiple sclerosis (MS) plaques and induces both apoptotic and necrotic death of OLGs and inhibition of caspase-1 and

caspase-3 protects them against TNF- $\alpha$ -induced apoptosis [11]. Interferon gamma (IFN- $\gamma$ ) produced by lymphocytes in MS lesions plays a role in apoptosis of oligodendrocytes both *in vivo* and *in vitro* [11]. TNF- $\alpha$  increases the IFN- $\gamma$ -induced death of OPCs and this effect can be partially suppressed by caspase inhibition [11]. Interleukin-11 is expressed by reactive astrocytes in MS tissue samples along the myelinated border of both active and silent lesions [15].

### 2.2. Paraventricular Leukomalacia (PVL)

Paraventricular leukomalacia (PVL) is the leading cause of brain damage in preterm infants, prior to 32 weeks of gestation; resulting in cerebral palsy and cognitive impairment [16,17]; and occurs due to damage to OPCs and hypomyelination [18]. It involves death of small areas of brain tissue around ventricles, the fluid filled areas of brain; creating holes in the brain [19]. The pathogenesis of OPC injury relates to hypoxia-ischemia and systemic infection/inflammation, common occurrences in premature infants. Three downstream mechanisms have been identified, *i.e.*, microglial activation, excitotoxicity and free radical attack [20].

### 2.3. Stroke

Stroke, a leading cause of death occurs due to the interruption of blood supply to any part of the brain owing to the blockade or bursting of blood vessels, hence classified as ischemic and hemorrhagic stroke [21]. Immediately following interrupted blood supply to brain, the injury process initiates, if recovery of normal blood flow is not achieved within a short period of time, death of cells within the ischemic core begins [22]. Stroke disrupts the blood brain barrier (BBB) which in turn affects stroke progression and neuroregeneration [23]. Ischemia, in stroke, is known to cause cell death mainly through the oxidative stress and excitotoxicity. Energy deprivation in stroke leads to neuronal death, axonal dysfunction and loss of OLGs which are very sensitive to transient oxygen and glucose deprivation. It has been seen that OLGs in immature state are even more sensitive to ischemic injury in mature forms. These cells may release glutamate under ischemic conditions by reverse functioning of their glutamate transporter (GluTs) [14]. During ischemia/reperfusion of brain tissue, oxidative stress sets in with a rise in Hydrogen Peroxide (H<sub>2</sub>O<sub>2</sub>) levels for about 1hr reaching up to 175  $\mu$ M (approx.) [14]. Also, increased TNF-mRNA is seen 3 hr after stroke in transient Middle cerebral artery occlusion (MCAO) models in rats [23].

In humans, almost all cases of ischemic stroke involve white matter [24]. White matter ischemia may activate proteases like calpains which degrade neurofilament and cause phosphorylation of axonal microtubule proteins

like tau. Thereby, they weaken the structural integrity of axons and also impair axonal mechanisms for anterograde and retrograde transport [25].

#### 2.4. Spinal Cord Injury (SCI)

Spinal cord injury (SCI) refers to the damage to the spinal cord resulting in permanent neurological deficit. It is caused by direct injury or indirectly from damage to the surrounding bones, tissues, or blood vessels resulting from auto accidents, falls, sports injuries and other accidents. It is a very tragic case with higher prevalence in young and otherwise healthy individuals, thus creating physical, emotional, and economic burdens on both sufferer and society [26]. The loss of axonal transmission of sensory and motor nerves occurs distal to point of SCI, leading to multiple health problems such as recurrent kidney stones, urinary tract infection, pressure sores, and cardiac and respiratory dysfunction [27]. Acute SCI involves mechanical primary and biochemical secondary mechanism of injury; primary due to blunt cord compression owing to dislocation of spinal cord or bone fragments; biochemical factors in hemorrhagic necrotic tissue causing secondary damage to spinal cord [28]. SCI causes strong up-regulation of genes involved in transcription, inflammation and cell death [29]. Excitotoxicity, oxidative stress, lipid peroxidation/free radical injury, inflammatory factors all seem to play parts worsening the homeostasis of the brain and causing cell death [28].

#### 2.5. Leukodystrophy

Leukodystrophies are rare diseases appearing during infancy or childhood and characterized by a progressive degeneration of the white matter due to imperfect growth or development of the myelin sheath [30]. Myelin is a complex framework made up of at least ten different chemicals. The leukodystrophies are a group of disorders caused by genetic defects in how myelin produces or metabolizes its chemicals components [4]. Each type of leukodystrophy results from the defect in the gene that controls one of the chemicals causing defects in enzymes such as arylsulphatase A (Metachromatic Leukodystrophy), aspartoacylase (Canavan disease), galactosylceramidase (Krabbe disease) or in enzymes responsible for breaking down phytanic acid (Refsum's disease), defects in a fatty acid transfer protein (Adrenoleukodystrophy), or defects in the myelin protein PLP1 (Pelizaeus-Merzbacher disease) [31].

#### 2.6. Alzheimer's Disease (AD)

AD is a neurodegenerative disease with stealth onset that progresses relatively rapidly with the parenchymal deposition of beta amyloid ( $A\beta$ ) in the form of senile/neuritic plaques and the neurofibrillary tangles (NFT) resulting

in the loss of neurons and synapses [32]. The white matter lesions and myelin abnormalities are common in the AD patients [33].  $A\beta$  is known to induce apoptosis of mature OLGs which can be attenuated by antioxidants.  $A\beta$  also causes oxidative stress by upregulation of inducible nitric oxide synthase (iNOS) in mature OLGs through a TNF- $\alpha$ -mediated ceramide pathway [32]. Some cases of AD are caused by mutation of presenilin-1 gene. It has been seen that glutamate-mediated excitotoxicity in OLGs is potentiated by presenilin-1 mutation [31]. OLGs that differentiate and myelinate later in life produce thinner myelin sheaths around axons and these neurons have been observed to be more susceptible to the damage in AD [32]. The transentorhinal region and nearby neocortical association areas are the late-myelinating regions known; these areas are also the seat for early  $A\beta$  deposits and myelin breakdown [5].

#### 2.7. Schizophrenia (SZ)

Schizophrenia is a complex mental disorder of unknown etiology, usually surfacing in the young adulthood, which carries a genetic link [34]. Neuroimaging and microarray studies have provided evidence for myelin and oligodendrocyte abnormalities in SZ. As evidenced from electron microscopy, OLGs are the most severely affected cells in SZ undergoing dystrophy, necrosis and apoptosis [35]. Decreased expression of myelin and oligodendrocyte-related genes is seen in postmortem samples obtained from prefrontal cortex regions of schizophrenic patients, suggesting OLG loss or disruption at functional levels [36]. Six myelin-related genes specific to OLGs have decreased expression levels in schizophrenia. OLGs are decreased in number in the superior frontal gyrus of schizophrenics. Absence of myelin associated glycoprotein (MAG) genes may be the link in schizophrenia since MAG-knockout mice develops as a mice model for the disease [37]. Abnormal glutamate homeostasis is considered one of the leading pathological mechanisms of schizophrenia and this also puts OLGs at increased risk for excitotoxic damage [38]. Abnormalities in the white matter have been observed; however, so far it is not clear whether it is a cause or a consequence of the disease [32].

#### 2.8. Other Diseases

Oligodendrocytes are also injured in a variety of other diseases like Progressive Multifocal Leukoencephalopathy [7], Post-Infectious Encephalitis [39], and also following radiation injury [40], etc.

### 3. Different Mechanisms of Injury to Oligodendrocytes

Oligodendrocytes known to be the most vulnerable cells

in the brain undergo injury in different disease states by various mechanisms like oxidative stress, excitotoxicity, and inflammatory cytokines. Developing therapeutic approaches to OLG injuries and related diseases needs better understanding of the underlying mechanism by which damage occurs to these cells. The mechanism of injury in neurons which has been researched for long may not fit in case of OLGs and hence should be considered separately. The injury mechanism and mediators causing the injury in disease states are often intertwined with one type eliciting the other in response. Various mechanisms of injury to OLGs has been summed up and presented below in **Figure 1**.

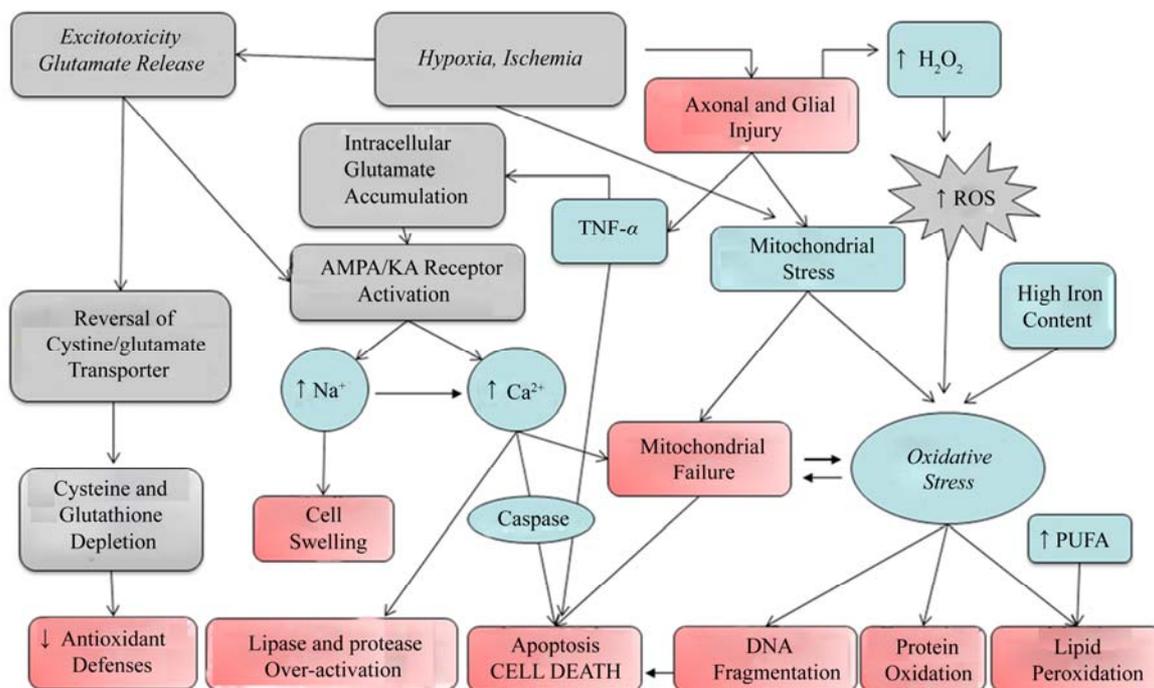
### 3.1. Oxidative Stress

OLGs on exposure to reactive oxygen species (ROS) causes formation of lipid peroxides which further react with proteins leading to oxidative modifications of amino acid residue. Also the protein aggregates are formed and protein fragmentation occurs [41], and also leads to DNA fragmentation and finally apoptosis of cells.  $H_2O_2$ , a ma-

ior ROS, is normally produced in the brain in small amounts. Its toxicity is due to its reaction with transition metals (iron-mediated Fenton reaction) to form hydroxyl radicals, which can further react with amino acids, nucleic acids, phospholipids and sugars, eventually causing cell death [42].

### 3.2. Excitotoxicity

Oligodendrocytes injury and death occurs on exposure to excitotoxic agents like glutamate and extracellular ATP [14]. Mature OLGs undergo necrosis on exposure to kainite through the Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and kainite (KA) receptors; recently N-methyl-D-aspartate (NMDA) have also been known to play role in OLG pathology [43,44]. Oka *et al.* was the first to provide evidence that OLGs are highly vulnerable to glutamate using the primary cultures. The oligodendroglial toxicity is mediated by a transporter-related mechanism involving the inhibition of cystine uptake, which results in glutathione depletion and cellular vulnerability to toxic-free radicals. Glutamate



**Figure 1. Oligodendrocyte injury mechanisms.** Schematic representation portrays different mechanisms of injury to oligodendrocytes. Hypoxia/ischemia, excitotoxicity, oxidative stress and cytokines are considered to be important players exerting cytotoxic effects to the oligodendrocytes. Glutamate mediated excitotoxicity occurs directly through activation of AMPA and KA receptors, and indirectly by causing intracellular depletion of cysteine and glutathione, thereby making them more prone to oxidative injury. Hypoxia/ischemia causes a direct injury to axons and glia causing  $TNF-\alpha$  release (inflammatory cytokine) and indirectly increases excitotoxicity; increases mitochondrial stress.  $TNF-\alpha$  causes apoptosis and necrosis in oligodendrocyte by caspase related pathways and indirectly by increasing intracellular glutamate concentration by interrupting astrocytes uptake.  $H_2O_2$  produced in higher levels from injured microglia increases ROS production which proceeds to cause oxidative stress and aftermath features like DNA fragmentation, protein oxidation, lipid peroxidation, apoptosis. High iron stores and high level of PUFA in OLGs make them prone to oxidative stress and lipid peroxidation respectively.

can also cause glial death indirectly by inducing the release of toxic agents like TNF- $\alpha$  from microglia [14].

### 3.3. Inflammatory Cytokines

Cytokines, a family of proteins related to immune system, are known to cause oligodendrocyte injury accompanying autoimmunological pathology; studies have mainly focused on TNF- $\alpha$ , IFN- $\gamma$  and Interleukin-1 $\beta$  (IL- $\beta$ ). TNF- $\alpha$  produced by immune system cells and by neurons, astrocytes and microglia. It induces both apoptotic and necrotic death of OLGs and inhibition of caspase-1 and caspase-3 protects them against TNF- $\alpha$ -induced apoptosis [11]. Mutations or breakages in mitochondrial DNA, damage to oligodendrocyte mitochondria or inhibition of oxidative metabolism could also deplete the supply of energy for biosynthesis of the components of mature membrane sheets and/or trigger oligodendroglial degeneration [45]. TNF- $\alpha$  regulates glutamate transport capacity in astrocytes, which leads to the accumulation of glutamate, increasing excitotoxic damage to OLGs and neuron [46]. TNF- $\alpha$  pro-apoptotic actions on OLGs are attributed to decreased IGF-1 expression and activity which can be rescued for external application of IGF-1 both *in vivo* and *in vitro* [11]. TNF- $\alpha$  may directly damage OLGs by forming peroxides of the long-chain fatty acids in lipids or via generation of ceramide which is cytotoxic to OLGs [47]. IFN- $\gamma$  produced by lymphocytes in MS lesions plays a role in apoptosis of oligodendrocytes both *in vivo* and *in vitro*. TNF- $\alpha$  increases the IFN- $\gamma$  induced death of OPCs and caspase inhibition partially suppresses it [11]. IL-1 $\beta$ , a prominent microglial pro-inflammatory cytokine adversely affects oligodendrocyte survival. It is a potent regulator of the production of various matrix metalloproteinase (MMP) members which are implicated in demyelination and axonal loss in CNS diseases [48].

## 4. Oligoprotectants and White Matter Protecting Agents

Research on oligoprotectants has been going on for a long time, since oligopathy has long been noted in demyelinating diseases like multiple sclerosis, periventricular leukomalacia (PVL), acute disseminated encephalomyelitis (ADEM). Later on, with the focus on protecting neurovascular unit in stroke and other neurological diseases more researches have been carried out aimed at protecting oligodendrocytes. Hereby, a few drugs and factors that have proved useful in protecting OLGs and white matter as a whole using different models are discussed, a summary of which can be seen in **Table 1**.

### 4.1. Antibacterial Agent—Minocycline

Minocycline, a second-generation tetracycline, has shown

beneficial effects in a wide range of acute neurological injuries. In rodent brain ischemic models, it showed anti-inflammatory effects by inhibiting immune mediators such as microglia. It has shown to attenuate hypoxia/ischemia-induced white matter injury in the neonatal rat though report of directly protecting OLGs against ischemic stress in adult rodent stroke model is missing. It has also been seen that delayed minocycline treatment reduced long-term functional deficits as well as white matter injury in ET-1-induced rat ischemia model. Despite reports from animal models clinical trial using minocycline in Amyotrophic lateral sclerosis (ALS) patients, failed to show efficacy, this could be attributed to the long term use of minocycline, a powerful metalloproteinase inhibitor. It has been suggested that long-term suppression of metalloproteinases may be detrimental for neurovascular homeostasis [49].

### 4.2. Antioxidants and Free Radical Scavengers

Antioxidants and free radical scavengers have proved beneficial to OLGs which show a great vulnerability to oxidative stress. Body's endogenous component and various synthetic drugs have been tried for use in preventing damage to OLGs and a few of them which proved beneficial have been listed below.

#### 4.2.1. Endogenous Component-CoenzymeQ10 (CoQ10)

CoQ10 an endogenous component of the mitochondrial electron transport chain is known to attenuate the peroxidation of lipids and protect neurons against free radical in both *in vitro* primary cell culture and experimental animals. It was shown that it can protect OLGs against TNF- $\alpha$  using primary culture of rat glial cells. In the same study, CoQ10 restored the numbers of mature myelin basic protein-positive cells and the ability of the OLGs to form membrane sheets [47]. However, there is published case of an *in vivo* model of focal and global ischemia in rats where CoQ10 failed to protect brain [50].

#### 4.2.2. Synthetic Drugs

Various synthetic drugs in the market possessing antioxidant activity are being screened for their effectiveness in protecting the OLGs in different injury models. Here, we have listed some drugs that have proved to be useful in the researches aimed at protecting OLGs and white matter injury.

##### 4.2.2.1. Ebselen

Ebselen is a synthetic seleno-organic drug with glutathione peroxidase like activity [51]. Imai *et al.* using rat transient ischemia models showed that ebselen reduced axonal damage and oligodendrocyte pathology [24].

##### 4.2.2.2. Edaravone

Edaravone, a radical scavenger of hydroxyl radicals, has

**Table 1. Oligoprotectants and white matter protecting agents.**

Oligoprotectants	Effects Berved-Mechanism	Experimental Model	References
CNTF	Inhibits TNF- $\alpha$ -induced apoptotic death of oligodendrocyte precursor cell	<i>In vitro</i> systems of oligodendrocyte precursor cell line	[54]
C enzyme Q10	Protects oligodendrocytes against TNF-injury	Primary cultures of rat glial cells	[47]
Cord blood	Protects striatal white matter tracts <i>in vivo</i> ; protects mature oligodendrocytes in culture	<i>In vivo</i> model; primary oligodendrocyte cultures oxygen and glucose deprivation model	[55]
Ebselen	Reduces axonal damage and oligodendrocyte pathology	Rat transient ischemia models	[24]
Edaravone	Decreases oligodendrocyte loss and attenuates white matter lesions	Rat chronic hypoperfusion model	[52]
Erythropoietin	Increases oligodendrogenesis, recovery of injured white matter and improved neurological function recovery	Neonatal hypoxic-ischemic injury in rats	[56]
HSP90 inhibitors	Protects OPCs and adult oligodendrocytes against HSP90 autoantibodies in MS	<i>In vitro</i> OPC cultures	[57]
IGF-1	Decreases the pro-apoptotic actions of TNF- $\alpha$	<i>In vitro</i> and <i>in vivo</i> systems	[11]
IL-11	Potentiates oligodendrocyte survival and maturation; myelin formation	<i>In vitro</i> human cell cultures; rodent co-culture studies	[15]
Linomide	Prevents oligodendrocytes damage by suppressing nitric oxide production in microglia and astrocytes	Primary cultures of rat glial cells	[58]
Melatonin	Reduces oxidative damage in neurons and oligodendrocytes	Mouse MCAO model	[59]
Memantine	Attenuated white matter injury, reduced ischemic damage to mature and precursor oligodendrocytes in brain slices	Rat model of periventricular malacia and ischemia; patch clamp system	[60]
Methylprednisolone	Selectively inhibits oligodendrocyte but not neuronal death	Staurosporine or AMPA model of injury through glucocorticoid receptor	[53]
Minocycline	Attenuates white matter injury	In neonatal hypoxia/ ischemia induced	[49]
NAC	Restores the number of MBP positive cells; restores ability of oligodendrocytes to form membranous sheets	<i>In vitro</i> primary rat cell culture; neuroblastoma cultures	[47]
NBQX	Reduces white matter injury and improve locomotor function	Rat ischemic spinal cord model	[24]
NGF	Protects oligodendrocytes from TNF- $\alpha$ -mediated cytotoxicity	Primary cultures of rat oligodendrocytes	[61]
PBN	Protects both oligodendrocytes and axons from ischemic insults	Rat MCAO model	[60]
Ramipril	Attenuates white matter injury	Chronic hypoperfusion ishemia	[62]
Sodium channel blockers	Offers protection to white matter against anoxia-induced injury	<i>In vitro</i> rat optic nerve preparation	[63]

List of different drugs that showed promise in protecting the Oligodendrocytes or white matter as a whole, the mechanism of their protection, experimental models they were tested in along with the appropriate references.

shown to decrease the loss of OLGs and attenuate white matter lesions through endothelial protection and free radical scavenging effects in a chronic hypoperfusion model in rats. Randomized clinical trial setting has also shown significant functional improvement in acute ischemic stroke patients [52].

#### 4.2.2.3. N-Acetyl Cysteine (NAC)

NAC is a free radical scavenger and an antioxidant that can modulate gene transcription and apoptosis. Cammer using *in vitro* primary rat cell culture showed that NAC was able to restore the numbers of mature myelin basic protein-positive cells and the ability of the OLGs to form

membrane sheets following studies that it protected neuroblastoma cultures against oxidative stress and cytotoxicity [47].

#### 4.2.2.4. Methylprednisolone

Methylprednisolone, an anti-inflammatory and antioxidant drug, is used to treat a variety of neurological disorders involving white matter injury like MS, acute disseminated encephalomyelitis, and SCI. It selectively inhibits oligodendrocyte but not neuronal cell death via a receptor-mediated action and may be a mechanism for its limited protective effect after SCI. It was shown to attenuate oligodendrocyte death in a dose-dependent man-

ner in staurosporine or AMPA model of injury through glucocorticoid receptor dependent mechanism; however, same dose failed to prevent the neurons [53].

#### 4.2.2.5. Phenyl-N-tert-butyl-nitron (PBN)

PBN a free radical scavenger has proved to be useful in preventing oligodendrocyte damage in various models. Using rat MCAO model, Irving *et al.* demonstrated that a free radical scavenger PBN reduced injury to the OLGs through the reduced number of tau-positive OLGs in the sub-cortical white matter of the ischemic hemisphere in PBN treated rats. Lin *et al.* using hypoxia-ischemia model in the neonatal rat brain displayed PBN treatment protected both OLGs and axons from ischemic insults. In the same model, it was seen that PBN also inhibits up-regulation of inflammatory cytokines such as IL-1 $\beta$ , TNF- $\alpha$  and inducible NOS mRNA expression [60].

#### 4.2.2.6. Ramipril

Ramipril, an angiotensin converting enzyme inhibitor, has shown to attenuate white matter lesions against chronic hypoperfusion ischemia owing to its free radical scavenging effect in rat models [62].

### 4.3. Cord Blood

It has been shown that infusion of human umbilical cord blood cells protects striatal white matter tracts *in vivo* and directly protects mature primary oligodendrocyte cultures from oxygen glucose deprivation (OGD) [55].

### 4.4. Endogenous Factors

Different endogenous factors secreted in animals have positive influences in OLGs. The PDGF, basic-fibroblast growth factor (b-FGF), and IGF-1 are known to influence oligodendrocyte lineage cell proliferation and survival [64]. A few of these endogenous factors have shown to afford protection to the OLGs against different stress conditions. The promising results from endogenous factors have been listed below.

#### 4.4.1. Ciliary Neurotrophic Factor (CNTF)

CNTF, a trophic factor found in astrocytes, has shown to inhibit TNF- $\alpha$  apoptotic death of oligodendrocytes in an *in vitro* model. It plays a role in survival of OLGs during development and may help in developing treatment strategies aimed at demyelinating diseases [54].

#### 4.4.2. Insulin-Like Growth Factor-1 (IGF-1)

IGF-1 is known for its neuroprotective effects and is taken as a promising candidate for neuromuscular diseases [65]. It plays an immense role in OLGs right from the developmental stage, enhancing OPC survival to maturation and stimulating myelination [64,66,67]. IGF-1 also known as the survival factor for OLGs [68], when applied externally has shown to decrease the pro-apoptotic actions of TNF- $\alpha$  [11].

#### 4.4.3. Interleukin-11 (IL-11)

IL-11, an astrocyte-derived which is localized in the active and silent lesions of MS, is linked with increase in OLG number and remyelination in the early stages. It potentiates oligodendrocyte survival and maturation, and myelin formation. *In vitro* human cell cultures have shown that immature OLGs express IL-11R $\alpha$  receptors and IL-11 has been linked with enhanced oligodendrocyte survival and maturation. Rodent CNS co-culture studies have linked it to increased myelination, thus implicating IL-11 in oligodendrocyte viability, maturation, and myelination [15].

#### 4.4.4. Nerve Growth Factor (NGF)

NGF has long been known for causing neurite outgrowth and hence the name nerve growth factor. It protects OLGs from TNF- $\alpha$  mediated cytotoxicity. Nerve growth factor also prevented the tumor necrosis factor-induced loss of mitochondrial membrane potential [61].

### 4.5. Glutamate Receptor Antagonist

Glutamate excitotoxicity related death of oligodendrocyte is seen in many disease states and thus exploiting the receptor antagonists have proved to be beneficial in different experiments. The antagonists of AMPA/KA and NMDA receptor types associated with glutamate signaling have shown significant reduction of OLG death in hypoxia/ischemia models. Hence, they may prove beneficial targets for prevention of ischemic stroke and related OLG deaths.

#### 4.5.1. AMPA/KA Antagonist—NBQX

The AMPA/kainate receptor mechanism has recently been implicated in white matter injury following white matter ischemia. NBQX, an AMPA/kainate receptor antagonist, has shown to reduce ischemia-induced white matter injury and improve locomotor function in a rat ischemic spinal cord model [24].

#### 4.5.2. NMDA Antagonist—Memantine

Memantine, an uncompetitive NMDA receptor antagonist, is a licensed drug for moderate-to-severe Alzheimer's disease in US and EU. Memantine attenuated white matter injury in a rat model of periventricular leukomalacia and may also be protective to white matter in ischemia. It has been reported that memantine reduced ischemic damage to mature and precursor OLGs in brain slices following assessment by patch-clamp system [60].

### 4.6. Hormones

Even the hormones like erythropoietin and melatonin have proved beneficial in improving recovery of injured white matter through increased oligodendrogenesis and through reduction of oxidative stress. Also thyroxine is

considered to be vital for survival of OLGs and it is known to trigger the maturation process of OLGs [69].

#### 4.6.1. Erythropoietin

The hormone erythropoietin made by the kidney cells under hypoxic conditions acts on stem cells in the bone marrow to increase the production of red blood cells. Erythropoietin mediated neuroprotection against neonatal hypoxic-ischemic brain injury has been known since 2003. It promotes differentiation and maturation of OLGs and is also expected to affect the ability of OLGs to promote myelin repair in normal and damaged CNS [70]. Increased oligodendrogenesis, recovery of injured white matter and improved neurological function recovery by delayed and repeated administration of erythropoietin was seen after neonatal hypoxic-ischemic brain injury in rats although the delayed administration of erythropoietin did not decrease infarct volume [56].

#### 4.6.2. Melatonin

Melatonin, a naturally occurring hormone, has been in use for the treating sleep related disorders. It has been found to reduce oxidative damage in neurons and OLGs through antioxidant and radical scavenging activity as seen in an experiment using mouse middle cerebral artery occlusion (MCAO) model using amyloid precursor protein (APP) and microtubule associated protein Tau-1 as markers for evaluating post-ischemic disrupted axonal flow and oligodendrocyte pathology respectively through immunohistochemical studies. It is known to reduce infarct volumes and enhance neurobehavioral and electrophysiological recoveries [59].

#### 4.7. HSP90 Inhibitors

Heat shock protein 90 (HSP90) present in OPCs surface has been known to form autoantibodies in Multiple Sclerosis. HSP90 inhibitors radicicol and 17-allylamino-17-demethoxygeldanamycin (17-AAG) at non-cytotoxic doses target cell-surface HSP90 in OPCs and through competitive inhibition of receptors prevent HSP90-antibody-induced OPC death thus protecting them against antibody attack. They also have shown protective effect on adult OLGs [57].

#### 4.8. Immunomodulator (Synthetic)-Linomide

Bao *et al.* using primary cultures of rat glial cells showed that a synthetic immunomodulator linomide prevents OLGs damage by suppressing nitric oxide production in microglia and astrocytes [58].

#### 4.9. Sodium Channel Blockers

Ischemic injury in the gray matter is associated with excitatory amino acid neurotransmitters release, and in the white matter is associated with intracellular sodium ac-

cumulation. The effect of sodium channel blocking drugs phenytoin, carbamazepine and diazepam on anoxia-induced injury in CNS white matter *in vitro* rat optic nerve preparation has shown to offer protection against anoxic injury at concentrations much lower than that required for treating epilepsy [63]. Sodium channel blockers represent an attractive therapeutic target because of their ability to simultaneously interfere indirectly with several calcium sourcing pathways [71].

### 5. Conclusions

Oligodendrocytes are most vulnerable cells of the brain with highest energy requirement, high iron stores, and low glutathione content; implicated primarily in demyelinating diseases and secondarily in neuropathies. The maintenance of OLGs at functional level is necessary for proper functioning of neuronal pathways, the loss of which may lead to multiple functional loss, axonal degeneration and/or neuronal death. Therefore, the neurocentric view of neuroprotection has widened to embrace the glial cells. In order to get along with neuroprotection, which has been the central focus for long, much work needs to be done on finding ways of protecting the glial cells. For this, a better understanding of the mechanisms by which glial cells death ensues in various disease states is utmost important. A better understanding of the injury mechanisms of OLGs should be beneficial as we move along the path of protecting the long shadowed glial cells hand in hand with neuroprotection as the concept of the neurogliovascular unit flourishes.

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