OLIGODENDROGENESIS AFTER CEREBRAL ISCHAEMIA AND TRAUMATIC BRAIN INJURY

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ABSTRACT

Stroke and traumatic brain injury (TBI) damage white and grey matter. Loss of oligodendrocytes and their myelin, impairs axonal function. Remyelination involves oligodendrogenesis during which new myelinating oligodendrocytes are generated by differentiated oligodendrocyte progenitor cells (OPCs). This article briefly reviews the processes of oligodendrogenesis in adult rodent brains, and promising experimental therapies targeting the neurovascular unit that reduce oligodendrocyte damage and amplify endogenous oligodendrogenesis after stroke and TBI.

Keywords: Cerebral ischaemia, traumatic brain injury, myelination, oligodendrocytes, oligodendrocyte progenitor cells.

INTRODUCTION

Stroke and traumatic brain injury (TBI) lead to white and grey matter damage and are leading causes of mortality and morbidity.1-5 White matter mainly contains axons and oligodendrocytes, myelin forming cells, in the central nervous system (CNS).1,3,5 Acute axonal injury is one of the most common pathological features of closed head injury.3 Oligodendrocytes are vulnerable to ischaemic stroke.6 Loss of oligodendrocytes and their myelin, impairs axonal function.7 However, compared to investigations conducted in the area of neuroprotection, studies to reduce oligodendrocyte damage and to regenerate myelinating oligodendrocytes are few after stroke and TBI, which has impeded development of effective therapy for stroke and TBI.8

Emerging data indicate that in the adult rodent brain, new oligodendrocytes are generated to myelinate the previously unmyelinated axons in the cortical grey matter and subcortical white matter.8-11 In addition to ensheathment of axons, which facilitates electrical conduction, oligodendrocytes in the adult brain contribute to neural plasticity and circuitry function.8-11 New oligodendrocytes derived from non-myelinating oligodendrocyte progenitor cells (OPCs) are required to form myelin sheaths for sprouting axons during brain repair processes after brain injury, because mature oligodendrocytes do not proliferate in the adult brain and injured oligodendrocytes no longer form new myelin sheets.7,12-16 Brain injury induces OPC proliferation, leading to a substantial increase in the number of OPCs. However, in the injured brain, OPCs do not effectively differentiate into myelinating oligodendrocytes.8 Thus, it is imperative to elucidate the pathophysiology of white matter damage after stroke and TBI in order to develop therapies designed specifically to reduce oligodendrocyte damage and to enhance remyelination.

In light of the failures of neuroprotective therapies in clinical trials, promising new concepts suggest that therapies for brain injury should target the neurovascular unit.17
The neurovascular unit comprises of cerebral endothelial cells, astrocytes, neurons, and oligodendrocytes. In this article, we will briefly review the processes of oligodendrogenesis in the adult rodent brain under normal and injured conditions, and experimental therapies targeting the neurovascular unit that reduce oligodendrocyte damage and amplify endogenous oligodendrogenesis after stroke and TBI.

**AFTER STROKE AND TBI**

**Acute Oligodendrocyte Damage**

OPCs comprise 3–9% of the total cell number in the adult CNS and are the majority of proliferating cells. OPCs are locally present in the corpus callosum, the striatum, and the cortex, and are derived from neural progenitor cells in the subventricular zone (SVZ) of the lateral ventricle. In the adult brain, OPCs continuously differentiate into mature oligodendrocytes to myelinate the previously unmyelinated axons throughout the grey and white matter. Recent studies show that in addition to facilitating salutatory conduction, myelination in the adult brain contributes to maintaining axonal integrity, neural plasticity, and circuitry function. For example, myelinating oligodendrocytes offset metabolic stress on neurons by providing trophic support to axons.

Mature oligodendrocytes are acutely vulnerable to stroke, and damage of mature oligodendrocytes leads to the loss of myelin and axons. However, there is a paucity of studies which characterise acute oligodendrocyte damage after TBI, although traumatic axonal injury has been intensively investigated. Loss of myelinating oligodendrocytes exacerbates traumatic axonal injury, because myelinated axons are less vulnerable to damage compared to non-myelinated axons, following fluid percussion injury in the rat. Injured oligodendrocytes no longer form new myelin sheets, and remyelination requires generation of new oligodendrocytes. Thus, in addition to the neuroprotection, therapeutic approaches designed to reduce acute white matter damage may also require minimising mature oligodendrocyte injury. Mechanisms of oligodendrocyte injury include oxidative stress, excitotoxicity, proinflammatory cytokines, among others. Clinical trials show that none of the neuroprotective drugs achieve clinical benefit for treatment of acute stroke and TBI, although neuroprotection has been demonstrated in experimental stroke and TBI.

Stroke and TBI injure all brain cells, and a new integrative approach for treatment of stroke and TBI is emerging to restore the normal function of the neurovascular unit. Treatment of acute stroke requires rapid restitution of cerebral blood flow (CBF) in the ischaemic cerebral microvascular bed, to preserve blood brain barrier (BBB) integrity, and to minimise ischaemic cell death. Preclinical data support the concept of new therapies to target the neurovascular unit. For example, tissue plasminogen activator (tPA) is the only Food and Drug Administration (FDA) approved treatment for acute stroke (within 4.5 hours). In addition to clot lysis, tPA induces brain haemorrhage and neurotoxicity, which limit its usage to a small minority of patients with acute stroke. Experimental studies indicate that combination of tPA with neuroprotective agents or matrix metalloproteinase (MMP) inhibitors, substantially reduce the deleterious effects of tPA on disruption of the BBB and ischaemic cell damage. Neuroprotective agents, or other agents that are to be used for the adjuvant treatment with thrombolysis, need to be safe without exacerbating brain injury, especially, brain haemorrhage.

Clinical data are emerging to examine the safety and efficacy of neuroprotective agents in conjunction with thrombolysis. Cerebrolysin®, a mixture of neurotrophic peptides, had a favourable outcome trend in patients with severe stroke when it was administered within 12 hours of the onset of stroke. A recently published pilot clinical trial of combined treatment with tPA and Cerebrolysin® in acute ischaemic stroke including 119 patients with acute hemispheric stroke, has shown that this combination therapy is safe when tPA was administered within 3 hours of the onset of stroke, and Cerebrolysin® was given 1 hour after tPA treatment and subsequently daily for 10 consecutive days. [Combined Treatment With Alteplase (Rt-PA) and Cerebrolysin® in Acute Ischaemic Hemispheric Stroke (CERE-LYSE-1), www.clinicaltrials.gov, NCT00840671]. In addition, a clinical Phase III trial, Efficacy Study of Combined Treatment With Uric Acid and rtPA in Acute Ischaemic Stroke (Urico-Ictus, www.clinicaltrials.gov, NCT00860366), is currently underway to determine whether a combination therapy of uric acid and tPA is superior to a monotherapy of tPA.
in patients with acute ischaemic stroke within 4.5 hours of symptom onset.41,42 Uric acid is an endogenous product derived from the metabolism of purines and exerts neuroprotection by its antioxidant capacity.41

Another drug, a postsynaptic density-95 (PSD-95) protein inhibitor (NA-1), has marked potential for the combination therapy for patients with acute ischaemic stroke.42 NA-1 substantially reduces ischaemic neuronal damage in rodent and primate models of stroke.43,44 A published Phase II, randomised, double-blind, placebo-controlled trial showed that treatment of patients who underwent endovascular brain aneurysm repair, with NA-1 at the completion of aneurysm repair procedures, sustained fewer ischaemic infarcts than patients in the placebo group, as measured by diffusion-weighted MRI and fluid-attenuated inversion recovery MRI of the ischaemic lesion (Evaluating Neuroprotection in Aneurysm Coiling Therapy [ENACT] trial, www.clinicaltrials.gov, NCT00728182).42,45 Although the effect of these combination therapies on oligodendrocyte injury has not been reported, one may expect that the integrative approach for treatment of acute brain injury may reduce oligodendrocyte damage.

Oligodendrogenesis During Brain Repair

Stroke and TBI are associated with chronically progressive cognitive impairment.1,46-49 Myelination is essential for maintenance of the axon.50,52 Failure of remyelination of axons after stroke and TBI could lead to axonal degeneration, and consequently, to cognitive impairment.3,10,52,53 Remyelination involves oligodendrogenesis, during which new myelinating oligodendrocytes are generated by differentiated OPCs localised to the corpus callosum or derived from SVZ neural stem cells.7,8,12-16 Loss of mature oligodendrocytes provokes remyelination.50,54 Studies in the rodent indicated that stroke and TBI trigger a substantial increase in OPCs generated by actively proliferating OPCs not only in young but also in aged animals.55-57 These OPCs are recruited to the injured tissue region and later some OPCs differentiate into myelinating oligodendrocytes, where sprouting axons are present.52,55,56,58 However, endogenous oligodendrogenesis in response to stroke and TBI is limited.

The presence of inhibitory molecules predominantly blocks OPC differentiation into mature myelinating oligodendrocytes, which limits remyelination processes.5,52 Treatment of stroke or TBI with mesenchymal stromal cells (MSCs) suppressed the expression of Nogo, an endogenous inhibitor of myelination, and was associated with substantial increases in mature oligodendrocytes in the peri-infarct striatum and corpus callosum, and with improvement of neurological outcome in the rodent 4 months after stroke.54,59-65 These data suggest that the blockage of inhibitory molecules may enhance remyelination in the injured brain. Currently, there is a clinical Phase I safety trial to block a potent oligodendrocyte differentiation inhibitor, the LRR and Ig domain-containing Nogo receptor-interacting protein (LINGO-1), in multiple sclerosis (Safety Study of BIIB033 in Subjects With Multiple Sclerosis, www.clinicaltrials.gov, NCT01244139).66,67 However, the relevance of LINGO-1 antagonist to enhance remyelination in the setting of stroke and TBI remains to be determined.

In addition to targeting oligodendrocyte differentiation inhibitors, preclinical studies show that therapies targeting the neurovascular unit increase endogenous oligodendrogenesis and axonal outgrowth after stroke and TBI.3,4,5,62,66-68 Oligodendrogenesis couples with angiogenesis in the injured brain during the brain repair process.3,4,69 In vitro studies show that cerebral endothelial cells may promote the proliferation of OPCs through the release of trophic factors, such as brain derived neurotrophic factor (BDNF) and basic fibroblast growth factor (bFGF).69 Compounds that induce angiogenesis enhance the generation of oligodendrocytes. For example, EPO, in addition to regulating angiogenesis, promotes OPC differentiation into mature oligodendrocytes through interaction with its receptor EPOR.70-74 Treatment of stroke with recombinant human EPO (rhEPO) induced sustained OPC proliferation and substantially amplified myelinating oligodendrocytes and increased myelinated axons in peri-infarct white matter, which was associated with improvement of neurological outcome.66,75 Aging reduces oligodendrocytes in rodent and human brains.54,76-78 Sildenafil, a potent phosphodiesterase type 5 (PDE5) inhibitor, induced cerebral angiogenesis after ischaemic stroke.79,80 Moreover, the treatment of aged ischaemic mice with sildenafil markedly augmented new oligodendrocytes in peri-infarct corpus callosum and striatum.55 These data suggest that even in aged animals, oligodendrogenic
potential is present in response to stroke and the treatment.

The Sonic hedgehog (Shh) signalling pathway regulates oligodendrogenesis and mediates OPC differentiation in the adult rodent brain. Blocking of the Shh signalling pathway leads to a decrease of OPC proliferation and differentiation in a model of focal demyelination induced by lyssolecithin in the corpus callosum of adult mice. Stroke upregulates the Shh signal that is associated with the generation of new oligodendrocytes. For example, treatment of stroke with Cerebrolysin® amplified the generation of OPCs and mature oligodendrocytes in white matter of the peri-infarct region. Inhibition of the Shh signalling pathway abolished the therapeutic effect of Cerebrolysin® on brain remodelling, including oligodendrogenesis. In vitro studies show that Cerebrolysin® induced upregulation of Shh expression in cerebral endothelial cells. In addition to its action on oligodendrogenesis, the Shh pathway plays an important role in maintenance of BBB integrity. Inactivation of the Shh pathway led to exacerbation of BBB leakage and demyelination in experimental autoimmune encephalomyelitis, a model of multiple sclerosis. Collectively, these data suggest that amplification of the Shh signalling pathway has therapeutic potential for the enhancement of myelination after stroke and TBI.

CONCLUSION

Stroke and TBI induce demyelination which comprises of the functional unit of axon and oligodendrocyte. Remyelination involves oligodendrogenesis. Promising data, mainly derived from animal models of stroke and TBI, call for an integrative approach for minimising oligodendrocyte damage and amplifying oligodendrogenesis. Although the relevance of this approach in patients remains to be established, pilot clinical trials suggest that an integrative approach is achievable.

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