in neurons is likely an indispensable step for removing toxic substances and damaged organelles after brain ischemia. Autophagy in inflammatory cells, however, might be a double-edged sword; overactivation might make inflammatory cells capable of attacking repairable brain tissue especially at the early stage after ischemic stroke.

References


Mechanisms of Glial Death and Protection

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INTRODUCTION

Cerebrovascular diseases cause tissue damage to both gray and white matter, which contribute about half of the CNS volume and differ in structure and cellular composition. White matter exclusively contains axons and their glial cell partners including fibrous astrocytes, oligodendrocytes (myelinating and nonmyelinating), and microglia. Gray matter harbors neurons and is rich in protoplasmic astrocytes, which shape synaptic transmission as they partner with nerve endings and postsynaptic elements to form the tripartite synapse.

Pharmacological developments of potential treatments for stroke have failed in clinical trials because they typically aimed at protecting neurons from postischemic damage and neglected glial cells, especially
oligodendrocytes, which are highly vulnerable to shortage of oxygen and nutrients. Oligodendrocytes are most abundant in white matter whose damage is a major cause of functional disability in cerebrovascular disease and the majority of ischemic strokes.

Early animal studies indicated that oligodendrocytes can be damaged by even brief focal ischemia [1], preceding by several hours the appearance of necrotic neurons in ischemic regions. In addition, pathological changes after ischemic insults include segmental swelling of myelinated axons and the formation of spaces or vacuoles between the myelin sheath and axolemma [1,2]. These observations confirm that oligodendrocytes and myelin are vulnerable to ischemia and that their damage proceeds independently from neuronal injury.

Stroke, therefore, produces disability not only as a result of dysfunction of neurons and synapses, but also by primary or secondary damage to oligodendrocytes and other glial cells. This chapter summarizes current knowledge of the molecular mechanisms of ischemic injury to glia and discusses its translational implications for the treatment of stroke (Table 44.1).

**TABLE 44.1** Glial Cell Damage and Protection in Ischemia

<table>
<thead>
<tr>
<th>Glial Cell Type</th>
<th>Model and/or Preparation</th>
<th>Target</th>
<th>Protecting Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oligodendrocytes</td>
<td>OGD in dissociated cultures</td>
<td>AMPA/kainate receptors</td>
<td>CNQX</td>
</tr>
<tr>
<td>Oligodendrocytes</td>
<td>OGD in dissociated cultures</td>
<td>Glutamate uptake</td>
<td>Dihydrokainic acid</td>
</tr>
<tr>
<td>Oligodendrocytes</td>
<td>Chemical ischemia in slices and optic nerve</td>
<td>NMDA receptors</td>
<td>MK-801, 7-chlorokynurenic acid, D-AP5</td>
</tr>
<tr>
<td>Oligodendrocytes</td>
<td>OGD in optic nerve</td>
<td>AMPA/kainate receptors</td>
<td>NBQX</td>
</tr>
<tr>
<td>Perinatal ischemia</td>
<td></td>
<td>NMDA receptors</td>
<td>Memantine</td>
</tr>
<tr>
<td>Hypoxia-ischemia</td>
<td></td>
<td>P2X7 receptors</td>
<td>Brilliant Blue G</td>
</tr>
<tr>
<td>OGD in dissociated cultures</td>
<td></td>
<td>P2X7 receptors/pannexin-1</td>
<td>Brilliant Blue G/mefloquine</td>
</tr>
<tr>
<td>Myelin</td>
<td>Chemical ischemia in rat optic nerve</td>
<td>NMDA receptors</td>
<td>7-Chlorokynurenic acid</td>
</tr>
<tr>
<td>Myelin</td>
<td>Chemical ischemia in rat optic nerve</td>
<td>P2X7 receptors</td>
<td>Brilliant Blue G</td>
</tr>
<tr>
<td>Myelin</td>
<td>Perinatal ischemia</td>
<td>NMDA receptors</td>
<td>Memantine</td>
</tr>
<tr>
<td>Oligodendrocyte progenitors</td>
<td>Perinatal hypoxia-ischemia</td>
<td>Microglia</td>
<td>Minocycline</td>
</tr>
<tr>
<td>Oligodendrocytes and astrocytes</td>
<td>Optic nerve</td>
<td>Adrenoreceptors and nAChR</td>
<td>Propofol, mecamylamine</td>
</tr>
<tr>
<td>Astrocytes</td>
<td>Ligation of carotids</td>
<td>S-100 protein</td>
<td>Arundic acid</td>
</tr>
<tr>
<td>Astrocytes</td>
<td></td>
<td>Oxidative stress</td>
<td>Melatonin</td>
</tr>
<tr>
<td>Astrocytes</td>
<td></td>
<td>Blood supply</td>
<td>Adrenomedullin</td>
</tr>
</tbody>
</table>

**GLIA METABOLISM**

Glucose is the primary energy source in the adult brain. Glucose transporter proteins on endothelial cells, glial cells, neurons, and axons are necessary for glucose uptake from the circulation and into cells. Astrocytes take up glucose in their end feet surrounding the capillaries and store glucose residues as glycogen. In addition to glucose, lactate can also support brain energy metabolism and function. Thus astrocyte glycogen is quickly mobilized to produce lactate that can be delivered to neurons and axons ensuring function during high activity or when glucose supply is limited. Lactate is impermeable and is transported across cell membranes by monocarboxylate transporters present in neurons and glia. Lactate enters neurons and sustains their function by producing ATP via oxidative phosphorylation. Lactate is also taken up by oligodendrocytes and their myelin sheath via MCT1 transporters, and utilized for lipid metabolism and myelin synthesis. In vitro evidence suggests that oligodendrocytes consume lactate at a higher rate than neurons or astrocytes, apparently to support the
high lipid demand associated with myelin manufacture, and myelination is rescued during hypoglycemia when exogenous lactate is supplied.

During partial ischemia, when glucose would still be present, although reduced, increased glycolysis in astrocytes, and possibly in oligodendrocytes, can contribute usable energy substrate to neurons and axons, although the mechanism(s) that signals axon metabolic need and mediates glial substrate production is still unknown. An attractive possibility is that neurotransmitters (i.e., glutamate and ATP) released from discharging axons signal surrounding astrocytes, and possibly oligodendrocytes, to release fuel in the form of lactate, delivered via cytoplasmic compartments within the myelin sheath [3], which can be quickly used by the axons.

**Oligodendrocytes Are Vulnerable to Excitotoxicity Following Ischemia**

Cells of the oligodendroglial lineage express receptors to excitatory neurotransmitters including glutamate and ATP that are stimulated under physiological and pathological conditions.

Oligodendrocytes express functional α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), kainate, and N-methyl-d-aspartic acid (NMDA) receptors, which can be activated during ischemic injury. Glutamate signaling in oligodendrocytes is relevant to myelination since action potentials travelling along axons can release glutamate that promotes the local synthesis of major myelin proteins [4]. In turn, glutamate homeostasis is controlled by Na⁺-dependent glutamate transporters expressed mainly in astrocytes, and also in oligodendrocytes. Glutamate transporters are necessary to maintain very low basal levels of extracellular glutamate (the range is mid-nanomoles to low micromoles), and transporter blockade is sufficient to induce excitotoxic damage to oligodendrocytes. Under ischemic conditions, however, cells may depolarize and accumulate intracellular Na⁺ leading to reversal of Na⁺-dependent glutamate transport and toxic glutamate release. Thus collapse of ionic gradients during ischemia, especially the transmembrane Na⁺ gradient, causes glutamate efflux that can be blocked by glutamate transport inhibitors. Astrocytes may predominate in this process, or merely contribute along with oligodendrocytes and axons. On the other hand, microglia express the cystine/glutamate antiporter, which can release glutamate in response to oxidative stress, and thus constitute another source of toxic glutamate release.

ATP signaling in oligodendrocytes occurs through P2X and P2Y receptors. P2X receptors are highly Ca²⁺ permeable, and P2Y receptors mobilize Ca²⁺ from intracellular stores. In particular, the low-affinity P2X7 receptor is expressed at relatively high levels in oligodendrocytes and myelin and could be activated by ATP release in pathological states. In contrast, P2X receptors with higher affinity might be activated by ATP released during axonal electrical activity and/or from astrocytes. Microglia express several P2X and P2Y receptors that act as sensors of damage and trigger a potent microglial inflammatory reaction. Postischemic anoxic depolarization triggers the release of ATP, in addition to glutamate. The mechanisms underlying ATP release include opening of pancxen channels, activation of calcium homeostasis modulator channels (CalMH), and exit of the transmitter through pore-forming P2X7 receptor itself. Regardless of the source, excess of extracellular ATP causes oligodendrocyte excitotoxicity and demyelination.
perinatal ischemia, by glutamate receptor antagonists and glutamate uptake inhibitors (Table 44.1). Ischemia induces an inward current in “young” oligodendrocytes that is mediated, in part, by NMDA and AMPA/kainate receptors, and increases Ca$^{2+}$ levels in myelin itself (an effect that is abolished by NMDA receptor antagonists) causing ultrastructural damage to myelin, and perhaps secondarily to axon cylinders as well [6].

However, oligodendrocytes in adult or old rodents behave very differently during ischemia. Although oligodendrocytes express NMDA receptors throughout life, these receptors do not participate in ischemic injury in fully mature tissue; blocking these receptors actually worsens ischemic damage [7]. In adult and old animals, dysregulation of intracellular [Ca$^{2+}$] remains a crucial feature of irreversible ischemic injury, but the dramatic benefit of Ca$^{2+}$-free extracellular fluid is lost for unclear reasons. It is possible that Ca$^{2+}$ release from intracellular Ca$^{2+}$ stores becomes more critical during ischemia in oligodendrocytes from older animals. Although NMDA receptors are not involved in ischemic injury in older animals, glutamate excitotoxicity is enhanced, at least partly due to increased glutamate release during ischemia. These age differences in the pathophysiology of oligodendrocyte ischemic damage highlight the need for age-specific stroke therapies.

Intracellular levels of ATP decline and extracellular ATP is elevated during cerebral ischemia, coincident with secondary anoxic depolarization. The rise in extracellular ATP during ischemia is sufficient to activate P2X$_7$ receptors and kill neurons and oligodendrocytes; blocking P2X$_7$ receptors is protective. Ischemia causes ATP release by opening of oligodendrocyte pannexin channels, which leads to mitochondrial depolarization and oxidative stress culminating in oligodendrocyte death and myelin destruction. These pathological events are attenuated by P2X$_7$ receptor antagonists, by the ATP-degrading enzyme apyrase, and by blockers of pannexin hemichannels [8].

Antioxidants may attenuate poststroke glial cell damage. Oligodendrocytes are very susceptible to oxidative stress for two reasons: they lack a high-potency antioxidant system and they have high iron content. When exposed to hypoxia or ischemia, these cells exhibit robust production of superoxide radical, lipid peroxidation, and conversion of iron stores to the oxidizing agent, ferrous ion [2]. The antioxidant ebselen significantly reduces axonal and oligodendrocyte damage as well as the neurological deficit associated with transient ischemia when administered 2 h after the onset of stroke (Table 44.1). More antioxidants should be tested in models of ischemia to gain deeper insight into the therapeutic potential of this class of compounds in attenuating oligodendrocyte death.

Other agents that may ameliorate oligodendrocyte ischemic damage include minocycline, citicoline, and arundic acid (Table 44.1). Minocycline is a potent inhibitor of microglia and a neuroprotective agent of oligodendrocyte damage after hypoxia-ischemia in neonatal animal models. Daily postinsult treatment with minocycline abolished neuroinflammation and attenuated damage of oligodendrocyte precursors. Its efficacy in adults is untested.

Oligodendrocyte precursor cells (OPCs) in the adult brain contribute to replenish the mature oligodendrocyte population. After damage to the later caused by prolonged cerebral hypoperfusion, OPCs compensate for oligodendrocyte loss by differentiating into mature oligodendrocytes via mechanisms that are only partially understood. Thus astrocytes support the maturation of OPCs by secreting brain-derived neurotrophic factor (BDNF) [9]. As hypoperfusion may damage oligodendroglia in stroke and in vascular dementia, regulating astrocytic BDNF expression may provide a broad therapeutic approach for cerebrovascular disorders.

### MECHANISMS OF ASTROCYTE DAMAGE AND PROTECTION IN STROKE

Astrocytes are the most abundant cell type within the central nervous system. They play essential roles in maintaining normal brain function, as they are a critical structural and functional part of the tripartite synapses and the neurovascular unit, and communicate with neurons, oligodendrocytes, and endothelial cells. After an ischemic stroke, astrocytes perform multiple functions both detrimental and beneficial, for neuronal survival during the acute phase [10]. At later stages after injury, astrocytes also contribute to angiogenesis, neurogenesis, synaptogenesis, and axonal remodeling, and thereby promote neurological recovery. Thus the pivotal involvement of astrocytes in normal brain function and responses to an ischemic lesion designates them as excellent therapeutic targets to improve functional outcome following stroke.

Astrocytes are generally more resistant than neurons and oligodendrocytes to ischemia [10]. Thus astrocytes are better preserved in the penumbra of the infarct, and a subpopulation of them within the ischemic core remains viable and metabolically active after the onset of reperfusion. Oxidative stress is a major mechanism leading to astrocyte demise in ischemia and, accordingly, melatonin enhances astrocyte survival during reperfusion. In addition, vasodilation with adrenomedullin gene delivery also improves the outcome of the astrocyte population following ischemic insults.

On the other hand, arundic acid interferes with astrocyte activation during injury and controls the expression of S100 Ca$^{2+}$-binding protein that is primarily expressed in astrocytes. The levels of S100 correlate with the
volume of the cerebral infarct and treatment with arundic acid before and after ischemia greatly reduced the levels of S100 in astrocytes (Table 44.1). The mechanism of protection by arundic acid may be downregulation in astrocytes of inducible nitric oxide synthase, with decreased nitric oxide production and, consequently, less toxicity to neighboring cells including oligodendrocytes. Finally, citicoline has neuroprotective effects in a model of chronic hypoperfusion, although the mechanism of action is not clear. It also promotes neurogenesis, which may contribute to repair after ischemic damage.

Astrocytes play an essential role in the induction of brain ischemic tolerance without producing any noticeable brain damage [11]. Astrocytic activation correlates with ischemic tolerance and is accompanied by P2X7 receptor upregulation in activated astrocytes. Importantly, induction of ischemic tolerance with a sublethal ischemic insult (preconditioning) is abolished in P2X7 receptor knockout mice. Thus astrocytes play indispensable roles in inducing ischemic tolerance, and upregulation of P2X7 receptors in astrocytes is essential. In contrast, P2X7 receptors play a deleterious role after ischemia in the absence of preconditioning, as they mediate damage to neurons and oligodendrocytes and P2X7 receptor antagonists are strongly protective [6].

**CONCLUSION**

Astrocytes and oligodendrocytes are highly vulnerable to stroke. Ischemia causes these glial cells to lose ion homeostasis, due to loss of ATP, which results in Ca\(^{2+}\) overload. This process is accelerated by glutamate- and ATP-mediated overactivation of ionotropic receptors. Based on recent experimental work, several strategies for therapeutic intervention in glial cells after stroke seem promising.

**References**

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