White matter (WM) exclusively contains axons and their glial cell partners including astrocytes, oligodendrocytes (myelinating and nonmyelinating), and microglia. WM comprises about half of the forebrain volume of humans, a 3- to 4-fold increase over rodents, the animals most used for neuroscience research.1,2 The low relative volume of WM in rodents led to neglect of this specialized brain area in studies of stroke pathophysiology and under-appreciation of the clinical importance of WM that has slowed progress to effective therapy.3 WM axons interconnect distant regions of the central nervous system and are metabolically independent of their cell bodies with regard to energy metabolism. Hence, proper propagation of electrical signals through WM axons demands a continuous supply of energy along their entire length and focal disruption of blood supply may compromise the viability of the whole axon. Yet, WM receives disproportionately less circulation than gray matter (GM) and is highly vulnerable to reduced blood supply exemplified by the frequency of pure WM strokes called lacunes or lacunar infarcts,4 which can accumulate, sometimes silently, and produce vascular dementia.5

Damage of WM is a major cause of functional disability in cerebrovascular disease and the majority of ischemic strokes involve both WM and GM.2,6 Early animal studies indicate that WM can be damaged by even brief focal ischemia.7 Thus, after 30 minutes of arterial occlusion massive swelling of oligodendrocytes and astrocytes occurs, and about 3 hours later most oligodendrocytes die. These changes precede by several hours the appearance of necrotic neurons in ischemic regions.7 Other pathological changes in ischemic WM include segmental swelling of myelinated axons and the formation of spaces or vacuoles between the myelin sheath and axolemma (Figure 1).8 These observations confirm that WM is vulnerable to ischemia and that this insult damages oligodendrocytes, myelin, and axons in a manner that can proceed independently from neuronal perikaryal injury. In fact, up to 25% of ischemic strokes in humans are of the lacunar variety and are confined to WM areas such as the internal capsule. The clinical importance of WM ischemic injury increases because the most susceptible population, the elderly, constitutes a larger and larger fraction of world population. Some types of dementia may actually represent a chronic and stealthy form of ischemia exclusive to WM.

Stroke, therefore, produces disability not only as a result of dysfunction of neurons and synapses, but also by primary or secondary damage to WM axons and glia. This review summarizes current knowledge of the molecular mechanisms of ischemic injury to WM and discusses its translational implications for the treatment of stroke (Table).9–16,17–30

White Matter Metabolism

Glucose is the primary energy source in the adult brain. Glucose transporter (GLUT) proteins on endothelial cells, glial cells, and axons are necessary for glucose uptake from the circulation and into cells. Astrocytes both in GM and WM express GLUT1, especially in their endfeet surrounding the capillaries, and these cells alone make and store glucose residues as glycogen.10 Oligodendrocytes express GLUT1 and GLUT2,11,12 and neurons and their axons express GLUT3, although the precise localization of GLUT3 on central nervous system axons has not been determined.13

In addition to glucose, lactate can also support WM energy metabolism and function.14 Lactate is produced constitutively, via glycolysis, and WM has a higher rate of aerobic glycolysis than GM under normal conditions.15 Although present at concentrations only a tenth of what is found in liver, astrocyte glycogen is quickly mobilized to produce lactate that can be delivered to axons ensuring function during high neuronal activity or when glucose supply is limited17 (for recent reviews, see refs. 38,39 [Figure 2]). Lactate is impermeable to the capillaries, and these cells alone make and store glucose residues as glycogen.10 Oligodendrocytes express GLUT1 and GLUT3, although the precise localization of GLUT3 on central nervous system axons has not been determined.13

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,24 and myelination is rescued during hypoglycemia
when exogenous lactate is supplied. Intriguingly, mature oligodendrocytes survive in the face of defective mitochondrial metabolism, probably because of enhanced glycolysis.36

During partial ischemia, when glucose would still be present although reduced, increased glycolysis in astrocytes, and possibly in oligodendrocytes,44 can contribute usable energy substrate to axons, although the mechanism(s) that signals axon metabolic need and mediates glial substrate production is still unknown.31,40,45 An attractive possibility is that neurotransmitters (ie, glutamate and ATP) released from discharging axons signal surrounding astrocytes, and possibly oligodendrocytes, to release fuel in the form of lactate that can be quickly used by the axons (Figure 2). This idea raises in turn the intriguing question of how energy substrates locally released by WM glial cells enter myelinated axons which have their surface mostly covered by the myelin. One design that would circumvent this potential problem would be to have lactate delivered via cytoplasmic compartments within the myelin sheath.36 Of course, in the case of complete ischemia, axons would not be able to use glial-derived lactate as a fuel because this requires at least low concentrations of O2.

**Animal Models of WM Damage**

There are few experimental preparations that specifically produce WM stroke damage (for a recent extensive review, see ref. 46). The most common in vitro preparations are cultured oligodendrocytes, acutely isolated rodent optic nerve, and acutely isolated spinal cord dorsal column.12,15,47

Oxygen-glucose deprivation can be conveniently applied to these preparations and they have been invaluable in helping to define mechanisms of ischemic/reperfusion damage in WM, including the ionic mechanism of intracellular Ca2+ overload and WM excitotoxicity. However, insights from these in vitro models have significant limitations. Surviving oligodendroglial cells in vitro may represent a subpopulation of oligodendroglia adapted to nonphysiological culture conditions possibly causing them to respond differently to simulated ischemic insults. The acutely isolated optic nerve or spinal cord dorsal column preparations no longer receive O2 and glucose from blood vessels but by diffusion from bath solution. Consequently, it is likely that there is excess O2 and glucose at the tissue surface and too little at the midpoint. It is also possible that these preparations behave differently as a result of acute transection. The greatest shortcoming, however, is the fact that they are strictly models of acute injury and do not permit assessment of the later stages of stroke injury that are likely to involve inflammatory cells and signals derived from blood. Some of these shortcomings may be partially overcome using a rodent photoembolic stroke model of anterior ischemic optic neuropathy which reproduces the reactive responses in the retina and optic nerve observed in humans.48

An animal model with local infarct location in WM has been developed using stereotaxic injection of vasoconstrictive agents in rats49 (reviewed in ref. 46). In this model, endothelin-1 is commonly used to reduce blood flow in subcortical WM and striatum. Endothelin-1-induced lesions disrupt myelin and cause axonal injury, 2 major features of WM damage, and the peri-infarct zone evolves, which can be exploited to test for the efficacy of potentially protective drugs. Limitations of this model include a different inflammatory response to that observed in humans, the fact that WM and GM are both damaged and the confounding activity of endothelin-1 in neurons and glia as well as in the repair of stroke damage.

An alternative model of WM damage is based on chronic cerebral hypoperfusion after bilateral common carotid artery stenosis using fine external microcoils.50 WM lesions in this model occur in corpus callosum, anterior commissure, and striatum. Endothelin-1-induced lesions disrupt myelin and cause axonal injury, 2 major features of WM damage, and the peri-infarct zone evolves, which can be exploited to test for the efficacy of potentially protective drugs. Limitations of this model include a different inflammatory response to that observed in humans, the fact that WM and GM are both damaged and the confounding activity of endothelin-1 in neurons and glia as well as in the repair of stroke damage.

A recently developed model addresses the study of neuroinflammation in WM damage in spontaneously hypertensive stroke-prone rats with permanent unilateral carotid artery occlusion.51 Although damage in this model is not restricted to WM, it causes lesions with a marked loss of myelin, oligodendrocyte death, astrocytosis, and activated microglia along with blood-brain-barrier disruption and tissue infiltration of blood-borne cells. Together with these structural alterations, this animal model shows evidence of cognitive impairment, thus exhibiting unique similarities to the small vessel form of vascular cognitive impairment seen in elderly patients.51 The model’s full value for studying chronic WM ischemia will depend on proving that the WM changes are...
not secondary to GM changes and showing that the cognitive changes are not because of hippocampal dysfunction, which is also injured. These concerns notwithstanding, this model may prove useful to assess agents to block inflammation in stroke.

**WM Signaling by Neurotransmitters**

WM cells and axons communicate using most if not all classical neurotransmitters (for a recent review, see ref. 52). Glutamate and ATP, the two major excitatory neurotransmitters, have been extensively studied and shown to be relevant to the pathophysiology of stroke. WM axons communicate with oligodendrocyte progenitors by glutamatergic and GABAergic synapses (reviewed in ref. 52). This signaling has some similarities with classical synaptic transmission but there are many structural and functional differences. Synapses account for the major proportion of energy use in GM,53,54 so it comes as no surprise that WM, with no classical synaptic transmission, has only a third of the energy needs of GM.34

Glutamate activates ionotropic and metabotropic receptors that are expressed in WM (for recent reviews, see refs. 55,56). Oligodendrocytes express functional α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), kainate, and N-methyl-D-aspartate (NMDA) receptors, which can be activated during ischemic injury, as detailed in the next section.11 Glutamate signaling in oligodendrocytes is relevant to myelination because action potentials travelling along axons can release glutamate that promotes the local synthesis of major myelin proteins.57 Dorsal column axons are also endowed with internodal AMPA and kainate receptors that are coupled to endoplasmic reticulum release of intracellular Ca2+ via ryanodine or inositol trisphosphate receptors 58,59 (Figure 2). Proof of principle exists that local activation of axonal AMPA/kainate receptors by glutamate released from periaxonal astrocytes may increase the width of action potentials while they travel down axons and facilitate synaptic transmission to postsynaptic neurons.60 These mechanisms, however, should be considered with some caution because they mainly apply to the

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**Table. White Matter Damage and Protection in Ischemia**

<table>
<thead>
<tr>
<th>WM Compartment</th>
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<th>Protecting Agent</th>
<th>References</th>
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<tr>
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<td>AMPA/Kainate receptors</td>
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<td></td>
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<td></td>
<td>OGD in young optic nerve</td>
<td>Na+/Ca2+ exchanger</td>
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<td>Chemical ischemia in rat optic nerve</td>
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<td>Perinatal ischemia</td>
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<td>S-100 protein</td>
<td>Arundic acid</td>
<td>30</td>
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</table>

7-CKA indicates 7-chlorokynurenic acid; CNQX, 6-cyano-7-nitroquinoxaline-2,3-dione; D-AP5, D(-)-2-amino-5-phosphonovaleric acid; GABA, γ-aminobutyric acid; KB-R 7943 mesylate, 2:2-[4(4-nitrobenzoyl)phenyl]ethylisothiourea mesylate; LPS, lipopolysaccharide; MCAO, middle cerebral artery occlusion; nAChR, nicotinic acetylcholine receptor; NBQX, threo-beta-benzyloxyaspartate; TBOA, threo-beta-benzyloxyaspartate; and WM, white matter.
largest myelinated axons (these are most amenable to experimental manipulation), have been tested in only a few brain areas and have been evaluated primarily in young animals.

Cellular glutamate uptake in WM, as in GM, is mediated by Na+-dependent glutamate transporters. In GM, 90% or more of glutamate uptake is provided by astrocytes. WM astrocytes in situ robustly express the glutamate transporter GLT-1, and GLT1 expression increases with advanced age. It is premature to say, however, that astrocytes are the major provider of that function in WM as oligodendrocytes and nodal membrane of mature axons can also express glutamate transporters. Glutamate transporters in WM are necessary to maintain very low basal levels of extracellular glutamate (the range is mid nmol/L to low µmol/L), and transporter blockade is sufficient to induce excitotoxic damage to oligodendrocytes. Under pathological 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 WM ischemia, especially the transmembrane Na+ gradient, causes glutamate efflux which can be blocked by glutamate transport inhibitors. Astrocytes may predominate in this process, or merely contribute along with oligodendrocytes and axons. More work is needed to settle this interesting question. Microglia are another possible source of toxic glutamate release. Microglia express the cystine/glutamate antiporter which can release glutamate in response to oxidative stress.

Figure 2. Neurotransmitter-metabolic coupling in white matter (WM) and its contribution to axonal damage during ischemia. In physiological conditions, astrocytes, oligodendrocytes, and axons take up glucose from capillaries through glucose transporters (GLUTs). Glucose uptake is coupled to metabolic demand (related to neural activity) through adjustments in cerebral blood flow mediated, in part, by astrocyte endfeet. Higher activity in axons increases extracellular glutamate, by the reversal functioning of transporters, which is then removed from the extracellular space via Na+-dependent glutamate transporters located in astrocyte perinodal processes. The resulting increase in [Na+]i activates Na+/K+ ATPase, and that determines an increase in ATP consumption, in glucose uptake, glycolysis and, eventually, glycogenolysis in astrocytes. Lactate produced by astrocytes from glycolysis and, eventually, glycogenolysis is predominantly released in the extracellular space by monocarboxylate transporter 4 (MCT4) whereby is taken up as an energy substrate by axons and oligodendrocytes via MCT2 and MCT1, respectively. This pathway is further activated during ischemia. In turn, glutamate extracellular elevation by ischemia causes excessive activation of glutamate receptors (formed by GluR4-6 subunits) located in myelinated axons, and subsequent axoplasmic Ca2+ overload arising from Ca2+ influx through the receptors themselves, Ca2+ voltage-gated channels, Na+/Ca2+ exchanger as well as from intraxonal Ca2+ stores, which may compromise axonal function (see text for details). The use of astrocyte glycolgen stores may transiently support axon energy needs and thus partially compensate for the functional loss of axons caused by ischemia. In parallel, glutamate excess can damage oligodendrocytes and myelin by excitotoxicity mediated by AMPA, kainite, NMDA receptors, as depicted in Figure 3. EAAT indicates excitatory amino acid transporter.
electrical activity and from astrocytes. Microglia express several P2X and P2Y receptors that act as sensors of damage and trigger a potent microglial inflammatory reaction, the significance of which remains unstudied in WM.

Mechanisms of WM Protection in Stroke

Table summarizes the best-established molecular pathways of WM damage and promising agents that act on these pathways in a protective fashion.

Energy failure during ischemia results in failure of ion pumps, most importantly the Na⁺ pump, leading to axon Na⁺ accumulation, depolarization, and loss of excitability. In axons, Na⁺ accumulation is mediated primarily by Na⁺ channels, especially the subset of these channels that do not inactivate with depolarization. This setting promotes the destructive accumulation of intracellular Ca²⁺, primarily as a result of reverse Na⁺/Ca²⁺ exchange, abetted by L-type Ca²⁺ channel activation. The loss of transmembrane Na⁺ gradients also causes slowed or reversed Na⁺-dependent glutamate uptake, and glutamate slowly accumulates in the extracellular space. High extracellular glutamate activates a complex sequence of pathological events in WM that are reminiscent of GM excitotoxicity, but with at least a notable difference: the activation of NMDA receptors is not toxic in adult WM (see further on). Depolarization leading to Ca²⁺ channel activation and ryanodine signaling and glutamate activation of axonal glutamate receptors can cause release of Ca²⁺ from intracellular stores in spinal cord axons. With these pathways in mind, it is not surprising that blockers of axon Na⁺ channels, reverse Na⁺-Ca²⁺ exchange, Na⁺-dependent glutamate transport, and intracellular Ca²⁺ release diminish ischemic WM damage. However, adenosine acting through A₁ receptors on oligodendrocytes could also have deleterious effects. Paradoxically, both agonists and antagonists of α2 noradrenergic receptors improve WM recovery after ischemic/reperfusion injury, apparently by reducing axonal Na⁺ and Ca²⁺ accumulation. Complex, but plausible, actions of these agents might explain these strange results.

Oligodendrocytes, not axons, are the primary victims of WM excitotoxicity. Overactivation of oligodendrocyte glutamate receptors causes Ca²⁺ overload of the cytosol leading to endoplasmic reticulum stress, mitochondrial depolarization, oxidative stress, Bax-mediated, caspase-dependent and -independent cell death, and myelin destruction. Thus, oligodendrocytes can be partially protected from irreversible ischemic injury, including perinatal ischemia, by glutamate receptor antagonists and glutamate uptake inhibitors. In models of developing WM, simulated ischemia induces an inward current in oligodendrocytes that is mediated, in part, by NMDA and AMPA/kainate receptors, and increases Ca²⁺ 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.\textsuperscript{18,20}

However, WM in adult or old rodents behaves 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.\textsuperscript{11} In adult and old animals, dysregulation of intracellular [Ca\textsuperscript{2+}] remains a crucial feature of irreversible WM ischemic injury, but the dramatic benefit of Ca\textsuperscript{2+}-free extracellular fluid is lost for unclear reasons.\textsuperscript{11} It is possible that Ca\textsuperscript{2+} release from intracellular Ca\textsuperscript{2+} stores becomes more critical during ischemia in WM from older animals.\textsuperscript{31} Although NMDA receptors are not involved in ischemic injury in older animals, glutamate excitotoxicity is enhanced, at least partly because of increased glutamate release during ischemia.\textsuperscript{11} These age differences in the toxicity is enhanced, at least partly because of increased glutamate release during ischemia.\textsuperscript{11}

Intracellular levels of ATP decline and extracellular ATP is elevated during cerebral ischemia, coincident with secondary anoxic depolarization in GM.\textsuperscript{78} The rise in extracellular ATP during ischemia is sufficient to activate P2X\textsubscript{2} receptors and kill neurons and oligodendrocytes; blocking P2X\textsubscript{2} receptors is protective.\textsuperscript{15,79} 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\textsubscript{2} receptor antagonists, by the ATP-degrading enzyme apyrase, and by blockers of pannexin hemichannels\textsuperscript{2} (Figure 3).

Antioxidants may attenuate WM stroke damage. Oligodendrocytes are very susceptible to oxidative stress for 2 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.\textsuperscript{8} The antioxidant ebselen significantly reduces axonal and oligodendrocyte damage as well as the neurological deficit associated with transient ischemia when administered 2 hours after the onset of stroke.\textsuperscript{27} More antioxidants should be tested in models of pure WM ischemia to gain deeper insight into the therapeutic potential of this class of compounds.

Other agents that may ameliorate WM ischemic damage include minocycline, citicoline, and arundic acid. Minocycline is a potent inhibitor of microglia and a neuroprotective agent of WM damage after hypoxia-ischemia in neonatal animal models.\textsuperscript{23} Daily postinsult treatment with minocycline abolished neuroinflammation and attenuated damage of oligodendrocyte precursors. Its efficacy in adults is untested. Arundic acid interferes with astrocyte activation during injury and controls the expression of S100 Ca\textsuperscript{2+}-binding protein that is primarily expressed in astrocytes. The levels of S100 correlate with the volume of the cerebral infarct\textsuperscript{80} and treatment with arundic acid before and after ischemia greatly reduced the levels of S100 in WM astrocytes.\textsuperscript{30} 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.\textsuperscript{41} Finally, citicoline has neuroprotective effects in a model of chronic hypoperfusion,\textsuperscript{28} although the mechanism of action is not clear. It also promotes neurogenesis which may contribute to repair after ischemic damage.\textsuperscript{29}

**Conclusions**

Axons, astrocytes, and oligodendrocytes, the main components of central nervous system WM, are highly vulnerable to stroke. In humans, more than half of the cerebral is WM. Ischemic stroke affects WM exclusively in about 25% of patients, and the majority of strokes involve both WM and GM. Moreover, the clinical deficits seen with stroke are often because of WM damage. Despite the many structural and functional differences between WM and GM, some of the mechanisms of damage are common to both regions. Ischemia causes cells in both areas to lose ion homeostasis, because of loss of ATP, which results in Ca\textsuperscript{2+} overload of axons and glia. This process is accelerated by glutamate-mediated overactivation of ionotropic receptors. Major distinctions between WM and GM stroke pathophysiology are the greater importance of oligodendrocytes in the functional deficits in WM, compared with GM, and that NMDA-type glutamate receptors are prominently involved in causing GM, but not WM, stroke injury in adults. Based on recent experimental work, several strategies for therapeutic intervention in WM stroke seem promising.

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None.

**References**


Protecting White Matter From Stroke Injury
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