Injury of central white matter is a major cause of functional disability in cerebrovascular disease. White matter is a target of hypoxic-ischemic injury throughout life, in clinical settings ranging from periventricular leukomalacia in the neonatal period, stroke and cardiac arrest in adults, to vascular dementia in the aging brain. The traditional view from animal studies is that gray matter is more vulnerable than white matter to ischemia. In part, this view may be an artifact of how ischemic brain injury has been studied. Most experimental work has used rodents, in which white matter constitutes only about 14% of total brain volume; in man, white matter is about 50% of brain volume. In fact, the metabolic rate of white matter is only modestly lower than that of gray matter, and recent animal studies suggest that white matter can be damaged even by brief ischemia. Moreover, clinical experience teaches that human ischemic stroke is almost never confined to gray matter. White matter is damaged by infarction in the territory of small vessels which perfuse centrum semiovale and deeper fiber pathways, and it is also damaged by occlusion of the large intracranial arteries which supply superficial gray and white matter together. Disruption of central conduction pathways may cause disruption of motor and sensory function, neurobehavioral syndromes, and cognitive impairment. Lacking neuronal cell bodies, dendrites, or synapses, white matter is unlikely to be injured by many of the mechanisms defined specifically in gray matter. Along with growing recognition of the importance of white matter ischemia in clinical disease, there have been recent advances in white matter pathophysiology, pharmacology, and imaging.

Mechanisms of White Matter Injury

Major cellular components of white matter are axons, myelinated and unmyelinated, glial cells, and blood vessels. Successful impulse conduction requires that axons maintain structural integrity and electrical function. Extensive studies using rodent optic nerve preparations have shown that energy deprivation leads to axonal dysfunction by activation of voltage-dependent channels for sodium and calcium, causing intraxonial calcium accumulation and activation of calcium-dependent disruptive pathways.

New data suggest that white matter injury also involves an important contribution of brain macroglial cells, oligodendrocytes and astrocytes, which are abundant in white matter. Two separate stories have emerged.

White matter is injured by hypoglycemia, and studies have shown that glycogen plays an important role in protecting against this injury. Only astrocytes (not neurons or oligodendrocytes) contain glycogen. In the absence of glucose, astrocyte glycogen is converted to lactate and transferred via the extracellular space to neighboring axons. Within axons, lactate is converted back to pyruvate and fuels oxidative energy production to sustain axon function and stave off injury for periods up to 30 minutes. The period of protection from hypoglycemic injury is determined by astrocyte glycogen content; by increasing glycogen content the duration of protection is extended.

Oligodendrocytes, the myelin-forming cells of the central nervous system, are highly vulnerable to injury from energy deprivation or oxidative stress. Oligodendrocytes express functional glutamate receptors of non-NMDA types (AMPA and kainate-prefering receptors), and they can be killed by overactivation of these glutamate receptors. Blockade of AMPA/kainate receptors protects oligodendrocytes from hypoxic injury in cell culture and preserves white matter function in brain slice models. Oligodendrocyte injury likely impairs conduction through effects on myelin. An interesting question arising from these studies is whether excitotoxic damage to oligodendrocytes may trigger secondary injury in axons.

Protective effects of AMPA/kainate receptor blockade are also observed in vivo: AMPA/kainate antagonists reduce white matter injury in rodent models of spinal cord ischemia and transient focal cerebral ischemia. Recent studies suggest that AMPA/kainate receptor-mediated excitotoxicity may be a common pathway for white matter injury in several conditions, including perinatal ischemia, traumatic spinal cord injury, and experimental allergic encephalomyelitis. NMDA antagonist drugs have not improved outcome in several clinical trials of acute stroke. Inability to reduce white matter ischemia is one potential explanation for the failure of these drugs in human study. Because the NMDA class of glutamate receptors are not expressed in white matter, NMDA antagonists are not expected to have direct protective effects on white matter in focal ischemia. In contrast, antioxidant compounds, sodium channel blockers, and AMPA/kainate antagonists are among those predicted to reduce ischemic damage to both gray and white matter. Such agents are now entering late-phase clinical trials.

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would be extremely valuable to include analyses of white matter injury as separate clinical endpoints for such trials.

**Imaging White Matter**

Advances in understanding of white matter ischemia in clinical settings may be propelled by improvements in imaging techniques. Conventional CT and MRI methods can reliably distinguish white and gray matter. Indeed, a frequent observation from MRI studies is the presence of hyperintense T2-weighted signal in white matter areas. These white matter lesions have been associated with hypertension, and possibly cognitive impairment, and are hypothesized to represent regions of microvascular ischemic pathology. Although the precise significance of such signal changes remains to be determined, two recent trials provide intriguing data that the extent of white matter hyperintensities may be an independent prognostic measure of future stroke risk.

Diffusion-weighted imaging (DWI) is a valuable MRI technique for evaluation of clinical stroke because it is highly sensitive to early ischemic changes. DWI can provide early identification of subcortical infarcts and white matter injury after global cerebral hypoxia or ischemia. DWI is sensitive to the thermal movement of water molecules. Although such motion is random, it may be directionally sensitive, or anisotropic, according to the microscopic organization of the surrounding tissue. Diffusion tensor imaging (DTI) is a new imaging technique that allows measurement of the magnitude and direction of signal anisotropy. Because many white matter regions are organized in parallel fiber arrays with high anisotropy, DTI can distinguish gray and white matter and may provide unique information regarding brain white matter structure and development. In combination with functional MRI, DTI can be used to track functional fiber connections in the human brain. Current studies indicate that DTI is highly sensitive to white matter stroke. Therefore, DTI may prove especially valuable for characterizing early white matter vulnerability to cerebral ischemia.

New developments in magnetic resonance spectroscopy can provide supplemental information regarding axon integrity. Proton magnetic resonance spectroscopy allows in vivo measurement of N-acetyl aspartate (NAA), which is found only in neurons. Therefore, loss of NAA signal measured in white matter can suggest selective axon loss. This technique has been used to demonstrate axon loss in demyelinating multiple sclerosis plaques. Loss of NAA signal in the internal capsule correlated with functional impairment after clinical motor stroke. These and other imaging techniques offer the promise of improved understanding of the time course and pharmacology of white matter ischemia in clinical stroke.

**Future Directions**

Beyond protection, white matter may be a target for innovative therapies intended to improve functional recovery after injury. Two recent animal studies have examined novel approaches to stroke recovery. Chen and colleagues tested inosine, which promotes axon sprouting in vitro. Papadopoulos and others used the monoclonal antibody, IN-1, which blocks the myelin-associated neurite inhibitory factor, NOGO. In both cases, the experimental drugs enhanced axon sprouting and seemed to promote recovery of behavioral function after focal ischemia in rats.

Preclinical and clinical stroke studies should lead to treatment approaches that prevent white and gray matter injury or promote white matter recovery. These objectives can be accomplished only with an improved understanding of axonal and glial pathophysiology and only if animal and human trials include specific outcome measures to assess white matter pathology.

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