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Glucose, Acid, and Aspartate: Friends and Foes of the Axon

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Myelinated axons comprise the physical "connectome" that integrates functional activity across brain regions. These white matter tracts occupy >50% of human brain, but only 10 to 15% of rodent brain. Rodent models of human central nervous system (CNS) disorders are thus relatively insensitive to white matter injury, and for this same reason the mechanisms contributing to white matter injury have been more difficult to unravel. Hypoglycemic white matter injury is a case in point; it remained essentially unrecognized over 3 decades of research using rodent models, and its pathophysiology has been obscure. In this issue of the *Annals of Neurology*, Yang et al characterize the mechanism by which hypoglycemia leads to axonal injury, with intriguing implications for other disorders.[1]

Acute hypoglycemic brain injury occurs almost exclusively in diabetic patients using insulin or other hypoglycemic agents; however, this group includes >12 million people in the United States alone, and consequently hypoglycemic brain injury is not uncommon.[2] Animal models and clinical experience suggest that widespread acute neuronal death occurs after profound and prolonged reductions in blood glucose. It remains an open question whether lesser degrees of hypoglycemia, repeated over time, may cause a more chronic, cumulative brain injury.[3] Fear of hypoglycemia is a major factor limiting tight glucose control, a factor that may indirectly also contribute to morbidity in diabetes.

A puzzling aspect of hypoglycemic injury is that it affects the CNS almost exclusively, with other tissues, including the heart, essentially unaffected. The standard explanation attributes this to energy failure; neurons are uniquely vulnerable because they have a uniquely high energy demand. Although intuitively appealing, this explanation turns out to be wrong - hypoglycemic neuronal death is attributable foremost to glutamate excitotoxicity. Hypoglycemia-induced elevations in extracellular glutamate produce sustained activation of N-methyl-D-aspartate (NMDA)-type glutamate receptors with resultant Ca^{2+} influx and triggering of cell death cascades. In animal models, hypoglycemic neuronal death can be prevented by blocking NMDA receptor activation or by blocking various downstream events in these cell death cascades.[4,5] The occurrence of white matter injury in hypoglycemia further weighs against the energy failure explanation. Magnetic resonance imaging studies of patients with hypoglycemic brain injury show white matter structures to be affected as frequently and severely as gray matter,[6,7] despite energy demand in white matter being much less than in gray matter neurons.

To determine how white matter is damaged by hypoglycemia, Yang et al employed the acutely isolated mouse optic nerve as a model white matter structure. Like other CNS white matter tracts, the optic nerve contains myelin-producing oligodendrocytes, scattered astrocytes, and neuronal axons, but no neuronal soma or dendrites. Studies have previously used this preparation (and others) to evaluate mechanisms of ischemic axonal injury, and found that antagonists of non-NMDA glutamate receptors preserved axonal function, whereas antagonists of NMDA receptors did not, despite expression of NMDA receptors on myelin processes.[8,9] By contrast, Yang et al show that in hypoglycemia, loss of axonal function is unaffected by non-NMDA receptor blockers, but strikingly preserved by NMDA receptor blockers. The result is significant both in demonstrating fundamental differences in hypoglycemic

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axonal injury and in suggesting new approaches for treating profoundly hypoglycemic patients.

What explains the differing effects of NMDA receptors in ischemic and hypoglycemic white matter injury? One factor identified by Yang et al is aspartate. Whereas ischemia causes glutamate levels to increase in axonal extracellular space, Yang et al show that hypoglycemia reduces glutamate levels, and instead increases extracellular aspartate. These reciprocal changes in glutamate and aspartate likely stem from accumulation of the aspartate precursor oxaloacetate when glucose-derived acetyl-CoA limits Krebs cycle flux.[10] Importantly, aspartate is a potent and relatively selective agonist at NMDA receptors, and unlike glutamate it has little effect on non-NMDA glutamate receptors.

A second factor identified by Yang et al is the contrasting effects of ischemia and hypoglycemia on tissue pH. Ischemia produces acidosis, which attenuates NMDA receptor–mediated neuronal injury,[11,12] whereas hypoglycemia produces alkalinization. Yang et al confirmed that glucose deprivation produces alkalosis in the isolated optic nerve, and further showed that axonal function is improved when this pH change is negated. The authors attribute this pH effect to H^+-regulated Ca^{2+} flux through NMDA receptors, but other mechanisms are also possible.[11] Nevertheless, the finding plausibly explains the more dominant role of NMDA receptor activation in hypoglycemic than ischemic axonal injury, and also highlights the role of pH in excitotoxic injury more broadly. The role of pH has been largely overlooked in recent years, but it may also be significant in other conditions, such as postischemic reperfusion and iatrogenic hyperventilation, that produce brain alkalinization.

There are caveats to this study, as is usually the case with model systems. Mouse optic nerve may not necessarily mimic other central white matter tracts in this pathophysiology, and the optic nerve itself is not a structure known to be injured by hypoglycemia. A second consideration is the severity of hypoglycemia used in the studies; it is difficult to know how the glucose concentration in the optic nerve preparation compares to that producing clinical hypoglycemic brain injury. Last, the outcome measures employed are short-term functional measures that may not necessarily predict structural or irreversible injury in situ. These caveats aside, the findings identify fundamental differences in the mechanisms of hypoglycemic and ischemic axonal injury. These differences likely stem from the differing effects of these insults on both aspartate metabolism and tissue pH, factors that may by extension also be important in other disorders affecting axon function and viability.

Potential Conflicts of Interest

Nothing to report.

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