

task of physicians — listening to our patients — we ought to hang on to our stethoscopes a bit longer than practical usefulness dictates.

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FOCUS ON RESEARCH

Stroke and Neurovascular Protection

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Neurons are extremely sensitive cells, whose function, like that of all cells, can be influenced by changes in their environment. Using pumps to regulate the internal and external electrolyte milieu, neurons keep toxic calcium ions outside the cell but allow the cell membrane to transmit signals electrically. If changes in the environment damage the membranes or if the energy-driven pumps fail, calcium ions can enter the neuron and permanently disable it. Local oxygen deprivation, such as that which occurs during ischemic stroke, can lead rapidly to transient or permanent injury of neurons by affecting the cells' energy requirements, pump function, membrane integrity, or immediate environment.

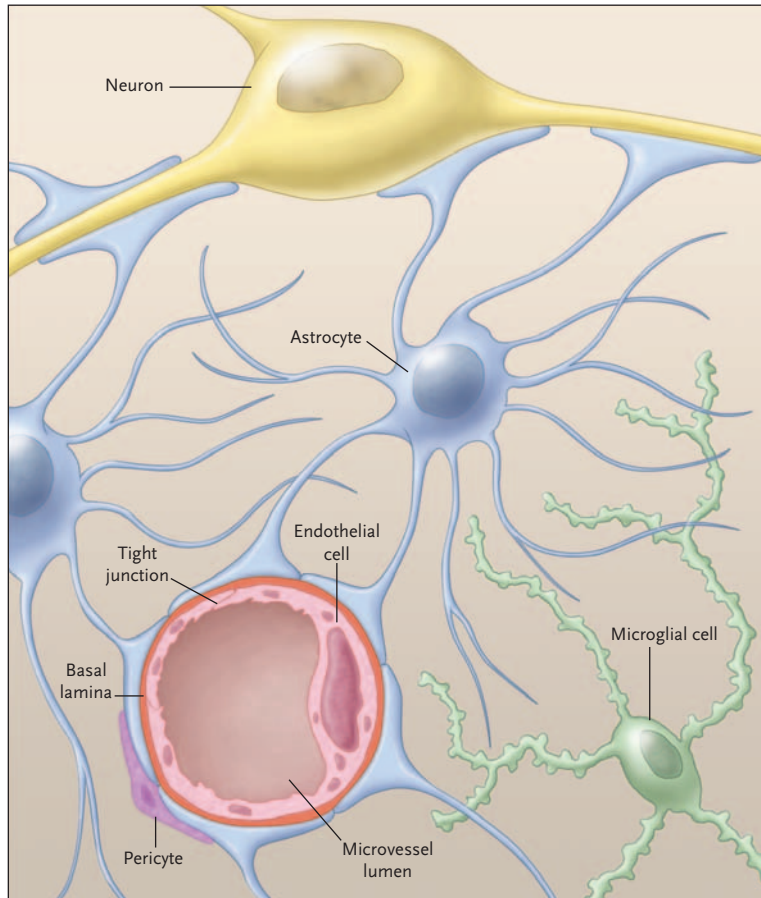
For many years, biomedical researchers have hoped that agents could be developed for the treatment of stroke that would prevent the influx of calcium by blocking the regulated pores and ion channels, preserving membrane integrity, or inhibiting the cell pathways that lead to cell injury or death. Many such agents have been shown to decrease injury to cultured neurons or par-

ticularly sensitive neurons from the hippocampus of rodents in experimental models of ischemic stroke. Many of these "neuroprotectant" agents have been further tested in prospective clinical trials involving patients with ischemic stroke. The notion has been that giving patients such agents within hours after the onset of symptoms could preserve the function of neurons and reduce the extent of injury to the brain tissue or allow time for reperfusion strategies, such as the use of recombinant tissue plasminogen activator, to work. Most such agents, however, have failed to show any beneficial activity in patients with stroke.

The disappointing results of this line of research reflect our still insufficient understanding of the evolution of ischemic injury in the brain. They are also partially attributable to unforeseen limitations in how the modulation of channel properties in ischemic neurons might translate into tissue protection; problems with the design or conduct of clinical trials, including delay in treatment; and the complexity of cerebral ischemia in both experimental models and humans.

A general assessment of the causes of the failure of neuroprotectants to realize their promise in the clinic points to the complexity of postischemic brain injuries. Ischemia initiates inflammation, increases microvascular permeability (which produces tissue edema), and causes local hemorrhage, in addition to having direct effects on cells. Ischemic stroke has such effects because it is really a vascular disorder affecting neuronal function. Because neurons constitute less than 5 percent of the cells in cerebral gray matter, ischemia affects not only neurons but also astrocytes and other glial cells that support the neurons, the axons of neurons that relay their signals to other cells, and the microvessels that supply oxygen and nutrients to them. Neurons and microvessels respond equally rapidly to the ischemic insult.¹

These observations have led recently to a shift in perspective from a focus on the neurons alone to a focus on the complex of neurons, the microvessels that supply them, and the supportive cells (astrocytes, other glial cells, and resident inflammatory cells). This



The Neurovascular Unit.

A conceptual framework, the neurovascular unit comprises neurons, the microvessels that supply them, and their supporting cells. Cerebral microvessels consist of the endothelium (which forms the blood–brain barrier), the basal lamina matrix, and the end-feet of astrocytes. Microglial cells and pericytes may also participate in the unit. Communication has been shown to occur between neurons and microvessels through astrocytes.

“neurovascular unit,” which may vary in composition and function from site to site within the brain, may be a more realistic target of ischemic injury (see diagram). Injury to any part of the unit could affect the other components.

The ability of neurons to direct microvascular responses has been recognized for more than a century.² Microvessels permit the entry of vascular inflammatory cells and proteins that are toxic

to neurons, when the blood–brain barrier, formed by endothelial cells with the help of astrocytes, is disrupted by ischemia. Injury to the microvasculature can lead to injury to neurons in the same territory.

In experimental models of cerebral ischemia, strategies that prevent or reduce microvascular thrombosis and inflammation substantially reduce brain injury. In fact, in patients with ischemic stroke, antithrombotic strategies

that reduce vascular causes of injury to the brain tissue have been the most successful therapeutic approaches to limiting the extent of injury from ischemic stroke. These findings suggest that during ischemic stroke, the microvascular component of the “unit” contributes to neuronal injury. It may also explain why the use of agents that specifically reduce injury to neurons has not led to apparent reductions in brain injury in ischemic stroke.

During ischemic stroke, free radicals are generated from oxygen and can injure brain tissue. These reactive molecules disturb neurons in culture, causing them to die. Indeed, mice from which the gene for one type of natural free-radical scavenger, superoxide dismutase (SOD1), has been removed have larger areas of brain injury when a major brain-supplying artery is occluded than do mice in which the gene functions normally. Similarly, an excess of the enzyme SOD1 in other small-animal models can reduce neuronal and brain-tissue injury. Such studies suggest that compounds that appear to limit the injurious effects of free radicals on neurons could be beneficial in ischemic stroke. Similar benefits have been observed with the free-radical-quenching agent NXY-059 and have led to its characterization as a potential “neuroprotectant.”

The trial reported by Lees et al. in this issue of the *Journal* (pages 588–600) indicates that some small reduction in cerebral injury and some small improvement in neurologic outcome can occur in patients who are treated with NXY-059 within six hours after the onset of stroke. The hint of benefit seen in this trial is in-

triguing. Could this be the first neuroprotectant to be successfully translated from animal models and neuron culture to humans? Perhaps. But the observations of Kontos et al. more than 10 years ago suggest that the benefits may not result from the selective protection of neurons (neuroprotection).³ Those authors showed that very early after the onset of ischemia in animal models, oxygen free radicals were generated at the interface between the microvessels and the brain tissues, not restricted to neurons, in the regions of ischemic injury.³ It may be that NXY-059 traps free radicals that are generated rapidly

in response to ischemia by the microvascular portion of the neurovascular unit and that this effect reduces neuronal injury and tissue damage. The microvasculature generates free radicals early during focal ischemia, and other cells that appear later — including inflammatory cells — can do so as well. An agent that acts by reducing neuronal injury alone would be expected to be less successful.

Thus, effective therapies for ischemic stroke may need to provide protection to the entire neurovascular unit. Discovering how such “neurovascular protection” can salvage neurons may well lead

us to the next frontier in the treatment of stroke.

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