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2005 Program
New Investigator (3-year project)

Project Title: Ischemic Axon Injury: Role of Neurotrophic Factors and Electrical Activity

Project Summary: Both current and prior tobacco use is a major risk factor for stroke, likely contributing to >50% of strokes in the U.S. annually. However, it is not known why neurons in the central nervous system (CNS) die after these ischemic injuries. Even in cases where CNS neurons survive, they fail to regenerate their axons appropriately; thus deficits after stroke are frequently permanent.

Most stroke models study the effects of large scale global or focal ischemia and reperfusion, in which grey matter, where neuronal cell bodies are located, is subjected to the ischemic insult. Most strokes in humans, however, occur in CNS white matter, where neuronal axons are located, either exclusively or in part, but models of white matter ischemia are much less well studied. White matter ischemia leads to axon injury and then in most cases to retrograde cell death of CNS neurons. Thus effort must be directed towards modeling and studying white matter strokes directly.

Here we will examine the mechanisms of neuronal cell death using the rat retina and optic nerve in a novel model of white matter ischemia. Retinal ganglion cells (RGCs), which die after ischemic axon injury in the optic nerve, are critical to carrying visual information from the eye to the brain, and blindness is a major consequence of stroke; in addition, the optic nerve is easily accessible in vivo and contains all of the normal components of CNS white matter, making it an ideal model system for white matter injury. We will use a laser-induced thrombosis model to induce a local ischemic lesion to the rat optic nerve, and address the following 3 major hypotheses, any of which may prove critical to our understanding of the mechanisms of neuronal cell death after stroke. First, is retrograde cell death developmentally regulated, analogous to the developmental regulation of axon regenerative ability? Here we will compare the time course of RGC cell death between developing and adult optic nerve strokes. Second, are adult RGCs less able to activate survival pathways after ischemic axon injury? Here we will use immunostaining and microscopy of retinal explants to study RGCs' ability to activate intracellular signaling pathways critical for survival after ischemic axon injury. Finally, can adult RGCs be stimulated to survive and regenerate after ischemic axon injury with exogenous addition of neurotrophic factors, plus drugs that enhance their responsiveness to such signals? Here we will test whether specific combinations of neurotrophic factors and pharmacologic agents that enhance neurotrophic responsiveness are able to prevent RGC death after ischemic axon injury.

These experiments will for the first time examine the molecular basis for RGC death after ischemic axon injury. Our goal is to discover new pathways to prevent neuronal death, then to see how these pathways interact with co-morbid disease (such as smoking) and ultimately to develop new treatments to maintain CNS neuronal survival after white matter stroke.