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Hold that thought: Induction of erythropoietin to protect the ischemic brain

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Ischemic brain injury inflicted by stroke and cardiac arrest ranks among the leading causes of death and long-term disability in the United States. The brain is exquisitely sensitive to interruptions in its blood supply, and suffers irreversible damage within 10-15 minutes of severe ischemia. The complexities of the injury cascades ignited by ischemia and reperfusion have thwarted development of effective neuroprotective interventions. Although recombinant tissue plasminogen activator and therapeutic hypothermia have been found efficacious for stroke and cardiac arrest, respectively, these treatments are constrained by narrow therapeutic windows, potentially detrimental side effects and the limited availability of hypothermia equipment. Mounting evidence demonstrates the cytokine hormone erythropoietin (EPO) to be a powerful neuroprotective agent and a potential adjuvant to established therapies. Moreover, the brain parenchyma can produce EPO internally, and EPO's membrane receptors and signaling components also are expressed in neurons and astrocytes. EPO activates signaling cascades that increase the brain's resistance to ischemia-reperfusion stress by stabilizing mitochondrial membranes, limiting formation of reactive oxygen and nitrogen intermediates, and suppressing pro-inflammatory cytokine production and neutrophil infiltration. Collectively, these mechanisms preserve functional brain tissue, thereby improving post-ischemic neurocognitive recovery. Research conducted in this laboratory has demonstrated that pyruvate, a blood brain barrier-permeable energy substrate and antioxidant, induces EPO synthesis in the brain by stabilizing transcription of the hypoxia-inducible EPO gene, raising the possibility of therapeutic induction of EPO to preserve brain threatened by severe ischemia.

Biography

Robert Mallet, Ph.D., Regents Professor of Integrative Physiology at University of North Texas Health Science Center, Fort Worth, TX has devoted his research career to harnessing the complex intermediary metabolism of the heart and brain to foster recovery of these organs from ischemic insults. His research, funded by the National Institute of Neurological Disorders and Stroke, is deciphering the mechanisms by which pyruvate-enhanced cardiopulmonary resuscitation prevents irreversible damage to the brain and fosters neurobehavioral recovery from cardiac arrest. He earned his Ph.D. degree in 1986 from George Washington University and from 1986-1990 completed a Postdoctoral Fellowship at Uniformed Services University of the Health Sciences. In 2013, he was named a Distinguished Scientist of the Society for Experimental Biology and Medicine.

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