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Research Interest

Neonatal brain injury is an important cause of death and disability, with pathways of oxidant stress, inflammation, and excitotoxicity leading to damage that progress over a long period of time. Therapies have classically targeted individual pathways during early phases of injury, but more recent studies indicate that growth factors may also enhance cell proliferation, differentiation and migration of newly born neurons over time. Understanding how the cascade of injury responses occur and the key modulators during each phase will lead to more rational therapies. For example, we have shown that HIF is upregulated early after ischemic injury in neurons but some of its downstream target genes, like Epo, appear early in neurons but later in astrocytes. Using this information we designed a treatment protocol with Epo after neonatal stroke in rodent pups that showed that multi-dose Epo with prolonged therapy, drastically improved structural and functional outcomes and stimulated neurogenesis.

We are now investigating the role of the HIF 1a regulated downstream targets, VEGF and Epo, in protection and recovery from an ischemic insult to the newborn brain. VEGF has been reported to both enhance angiogenesis and blood brain barrier integrity . In the newborn brain, astrocyte derived VEGF has been reported to mediate stabilization of hypoxic brain microvascular endothelial cells. In addition to its effects on endothelial cells, VEGF has also been shown to stimulate neurite outgrowth and neurogenesis . It is well established that neural stem cells are concentrated around blood vessels that provide a ?niche? for proliferation. High levels of VEGF and its receptor, VEGFR2, are found in these regions, consistent with a role for VEGF in coupling angiogenesis with neurogenesis .Our hypothesis is that VEGF signaling plays a critical role in these processes after injury. A continuing search for factors that can increase neurogenesis show that erythropoietin (Epo) is a promising candidate capable of regulating the production of neuronal progenitors by neural stem cells. The upregulation of Epo in the brain after hypoxia supports a role for Epo in the brain's response to injury not only acutely after injury but in repopulating injured areas as well. The expression of the Epo receptor in the developing mouse and human central nervous system (CNS) also supports a role for Epo in CNS regeneration after injury during early development.

We propose that erythropoietin enhances ischemic brain repair through increased precursor cell proliferation and neural cell fate commitment, migration and integration in damaged areas.

Complete Publications [3]

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