CURRENT LITERATURE

FUNCTIONAL REPAIR OF THE HIPPOCAMPUS BY NEURAL PROGENITORS

Regeneration of Hippocampal Pyramidal Neurons after Ischemic Brain Injury by Recruitment of Endogenous Neural Progenitors

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The adult brain is extremely vulnerable to various insults. The recent discovery of neural progenitors in adult mammals, however, raises the possibility of repairing damaged tissue by recruiting the latent regenerative potential. Here we show that activation of endogenous progenitors leads to massive regeneration of hippocampal pyramidal neurons after ischemic brain injury. Endogenous progenitors proliferate in response to ischemia and subsequently migrate into the hippocampus to regenerate new neurons. Intraventricular infusion of growth factors markedly augments these responses, thereby increasing the number of newborn neurons. Our studies suggest that regenerated neurons are integrated into the existing brain circuitry and contribute to ameliorating neurologic deficits. These results expand the possibility of novel neuronal cell-regeneration therapies for stroke and other neurologic disorders.

COMMENTARY

Seizures cause neuronal injury in animal models and in humans. Specific neuronal populations appear selectively vulnerable to seizure-induced injury, including hilar neurons and pyramidal cells in the hippocampus. Selective injury to hippocampus and other limbic structures likely underlies progressive memory dysfunction in patients who have recurrent seizures or status epilepticus. Considerable recent attention has focused on the concept of *neuroprotection* and the testing of agents for their neuroprotective potential, especially in animal models. In part because of disappointing results, some investigators have turned to consider strategies for *repair* of seizure-induced injury such as neuronal transplantation and stimulation of neurogenesis.

Neuronal injury and selective neuronal vulnerability are characteristic of many neurologic disorders, including degenerative conditions such as Parkinson's, Huntington's, and Alzheimer's diseases; metabolic disease such as hypoglycemia; and cerebrovascular disease. Although important differences between these diseases exist, it is likely that they share at least some similar mechanisms of injury and may respond to similar strategies for repair. Nakatomi et al. conducted elegant experiments to examine regeneration of hippocampal pyramidal neurons after ischemic brain injury and to characterize regenerated neurons and their relation to the local environment. Their results are at once surprising, exciting, and likely to be relevant to epilepsy.

With a transient forebrain ischemia model in rats, the authors noted not only the expected delayed death of CA1 pyramidal neurons beginning 2–4 days after ischemia (DAI2-4), but a small increase in NeuN+ cells at DAI28. These cells had morphologic characteristics highly reminiscent of pyramidal neurons, including a large nucleus and soma, and they displayed markers of immaturity including Hu and β-tubulin type III. They were able to increase the number of regenerating neurons successfully by treating animals with intraventricular infusions of a cocktail of fibroblast growth factor-2 (FGF-2) and epidermal growth factor (EGF). Growth factors did not significantly affect cell counts on DAI17, arguing against a protective effect. Instead, cell counts were increased later after ischemia, on DAI28, indicating delayed regeneration. Some of these cells were persistent up to 6 months after the initial insult.

With 5-bromo-2'-deoxyuridine (BrdU), they convincingly demonstrated that the observed neurons are new rather than rescued. Treatment with the antimitotic drug Ara-C significantly decreased cell counts in CA1, further supporting the notion that many apparent pyramidal cells in this model are the result of proliferation. DiI and GFP experiments indicate that proliferating cells originate in both periventricular regions and in the hippocampal parenchyma itself, whereas immunohistochemical experiments using synaptophysin, electron microscopy, and tracing studies with FluoroGold indicate that proliferating cells develop synaptic connections and are integrated into existing neural circuitry. Moreover, by using hippocampal slices, the authors demonstrated increased field excitatory postsynaptic potentials (EPSPs) and apparent partial rescue of the late phase of LTP (although not the early phase).

Finally, the authors demonstrated modest improvement in performance in the Morris water maze in growth factor–treated animals late after injury, suggesting that this treatment strategy may have meaningful functional consequences in the whole animal.

Why is this study relevant to the epilepsy research community? First, there are likely to be mechanisms of injury and repair that are shared in brain after seizures and ischemia. Second, the notion of facilitating endogenous repair mechanisms such as normal neuronal proliferation is vastly more straightforward than attempting to initiate repair de novo. Third, previous studies of neurogenesis in epilepsy have concentrated mainly on hippocampal granule cells. Whereas granule cells are clearly injured by recurrent seizures, it is likely that pyramidal cell injury is paramount in mediating the cognitive disturbances that accompany recurrent seizures and status epilepticus. This study indicates that pyramidal cells can be induced to regenerate. Fourth, epilepsy is a network disorder, and this study demonstrates that regenerating cells can integrate into existing networks both anatomically and functionally. It will be an important challenge to tune the gain of the restored system to achieve a normal physiologic response. For example, the choice of trophic factors, the dose, and the timing of delivery might all be critical in determining whether a "normal" network will result, or whether the restored network will be hyper- or hypoexcitable. In summary, this study indicates that endogenous capacity for repair can be modified by manipulation of the local biochemical milieu. In other words, as in life, the best outcome may arise when a supportive family exists in a nurturing environment.

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