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EPILEPSY AND THE PLASTIC MIND

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Seizures are linked to many neuroplastic changes within hippocampal circuits, including alterations in neurogenesis and dendritic growth in the dentate gyrus. How do brief seizures cause the long-term plastic changes in the hippocampus that are associated with recurrent epilepsy? Recent experiments by Ma and colleagues provide insights. They demonstrate an epigenetic mechanism for long-lasting neuroplastic changes that is both activity-dependent and brain region-specific. Focusing on Gadd45b, a DNA excision repair gene, they show it is up-regulated after electroconvulsive seizures or glutamate dependent activation of NMDA receptors. Gadd45b demethylates DNA regulatory elements in promoters of genes encoding fibroblast growth factor 1 and brain-derived neurotrophic factor, increasing the expression of these genes within granule neurons of the dentate gyrus. These changes in growth factor expression promote neurogenesis in the subgranular zone and dendritic growth in the granule cell layer of the dentate gyrus. Further regional and temporal differences in the proliferation of astrocytes and microglia after seizures were demonstrated by two additional studies. Together this work highlights how activity-dependent epigenetic modifications to DNA can alter gene expression with remarkable regional and cell type specificity.

In the 1967 film *The Graduate*, Dustin Hoffman received memorable and succinct career advice: “plastics.” Now, more than 40 years later, budding neuroscientists might consider that advice as well. From the Greek “plastikos,” plastic refers to a substance that is malleable and capable of assuming a variety of shapes. Structural brain plasticity is based on neural activity, including adult neurogenesis and other morphological changes at the level of individual dendritic spines and synapses. Propelled by the discovery that very few aspects of the adult brain

are fixed and immutable, current thinking in the field of neuroplasticity is undergoing seismic upheavals. Research has shown that a host of external phenomena, including environmental stimuli, exercise, and hormones, enable organisms to adapt to a changing environment by forming new memories and altering behaviors. Conversely, conditions that do not promote adaptive structural plasticity, such as seizures, stress, and depression, can trigger maladaptive plasticity and result in hyperexcitability, cognitive impairment, or both. Moreover, forms of psychiatric illness, such as depression and schizophrenia, have been linked to defective adult neuroplasticity.

The scientific upheavals in this field even have caught the public's attention. Bestselling self-help books, including *The Plastic Mind* by Sharon Begley and *The Brain That Changes Itself* by Norman Doidge, describe case studies in which patients overcome neurological impairments through focused attention and sensory feedback exercises (1,2). In addition, the computer software company Posit Science is profitably selling interactive computer programs that promise to tune-up auditory or visual perception in the elderly through a series of discrimination exercises—a sort of Pilates class for sensory processing and memory. Other software, based on findings in rodents and monkeys, claims to help learning disabled children and rehabilitate cognitive deficits in stroke patients (3).

So, how much of this new neuroscience is hype, and does any of it help to understand the neurological basis for epileptogenesis and chronic epilepsy? Will effective new therapies based on brain plasticity findings be able to alleviate depression or cognitive deficits in patients with chronic temporal lobe epilepsy (4)? It appears this is a field that bears watching. Several noteworthy papers published this year have examined, mechanistically, how neuronal activity or seizures regulate neurogenesis in the adult hippocampus. These studies identify various molecules and signaling pathways through which neural activity regulates adult neurogenesis, suggesting potential targets for ameliorating maladaptive plastic changes that occur in the hippocampus of patients with temporal lobe epilepsy.

Seizure-Dependent Disruption of Adult Neurogenesis Is Associated with Migration Errors and Miswired Connections

While most neurons are born during fetal development in humans and rodents, persistent neurogenesis occurs in the hippocampus throughout life. Seizures have a marked effect on cell genesis in this brain structure, but the effect is age-dependent. In the more mature brain, a brief period of seizures causes a marked increase neurogenesis (5), but in neonates, multiple seizures

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suppress neurogenesis (6–8). In adult rodents with spontaneous recurrent seizures, neurogenesis may be further augmented (9). One consequence of seizure-induced increases in neurogenesis in the adult hippocampus is that many new cells born in the subgranular zone of the dentate gyrus do not integrate into their normal destination in the granule cell layer; instead, they move toward ectopic sites in the hilus (10). Seizure-induced alterations in the dentate gyrus have been viewed as a maladaptive regenerative response of the brain that causes hippocampal connections to rewire, leading to hyperexcitability and epileptogenesis (5,11). Abnormal electrical discharges are associated with most, if not all, experimental models of epilepsy. Models that induce seizures by injections of pilocarpine or kainate as well as by kindling (5,12) or electroconvulsive treatment (13,14) are all associated with elevated dentate granule cell neurogenesis. Despite certainty that seizures alter adult neurogenesis and migration, it has not been easy to pinpoint which cellular mechanisms are responsible for these actions, although comparisons across the different models have provided insight. While each model has certain advantages and disadvantages, one distinguishing feature of electroconvulsive treatment and kindling models is that they upregulate neurogenesis, without concomitant cell death. A number of cytokines and growth factors have been identified as critical regulators of seizure-induced neurogenesis (15,16). Now, emerging evidence from several new studies shows that even a brief seizure episode can have long-lasting effects on neurogenesis in a region-specific manner. Moreover, the new work demonstrates that there is a shift from neurogenesis to gliogenesis in chronic epilepsy, stemming from changes in cell fate determination (16–18).

How Do Seizures Produce Long-Lasting Neuroplasticity?

One puzzling issue involves how brief periods of seizures can have long-lasting effects on neural plasticity and neurogenesis. About 10 years ago, Holiday proposed that DNA modifications might provide a stable, but reversible mechanism for long-term memory (19), and recent studies have finally provided convincing evidence for experience-dependent modifications to histones and DNA (17). Ma and colleagues employed electroconvulsive treatment to study epigenetic modifications to DNA that might provide a mechanism for seizure-induced upregulation of adult neurogenesis (see commentary on Ma et al. by Parent in this issue) (20). Focusing on *Gadd45b*, a gene involved in DNA repair and DNA 5-methylcytosine excision in cells, they demonstrated strong activity-dependent induction of *Gadd45b* in the granule neurons of the dentate gyrus of adult mice after they explored a novel environment or were subjected to a single episode of electroconvulsive treatment. These findings showed that both normal physiological stim-

ulation and brief seizures can induce expression of *Gadd45b*. The investigators next asked whether the induction of *Gadd45b* by physiological activity was dependent upon NMDA-receptor signaling. Cultured hippocampal neurons depolarized by elevated K^+ or by glutamate-dependent activation of NMDA receptors show strong induction of *Gadd45b*. However, when NMDA receptors are blocked, *Gadd45b* expression is reduced, while *Gadd45b* expression is increased by the GABA_A receptor antagonist bicuculline, which increases neuronal excitability. Increased *Gadd45b* expression is linked to increases in intracellular Ca^{2+} and signaling, via the calcium/calmodulin-dependent protein kinase pathway.

Two approaches by Ma and coworkers have helped to determine whether electroconvulsive treatment-induced adult neurogenesis requires *Gadd45b*. First, they compared the proliferation of neural progenitors after electroconvulsive treatment in *Gadd45b* knockout mice and wild-type littermate controls. Electroconvulsive treatment-induced neurogenesis is significantly diminished in the knockout mice. Second, the investigators showed that *Gadd45b* knockdown, mediated by RNA interference in the dentate gyrus, eliminates neurogenesis induced by electroconvulsive treatment. Stimulation of dendritic branching in newborn granule neurons is a second effect of electroconvulsive treatment, and *Gadd45b* is apparently essential for this process as well.

These findings have been extended by investigations showing that *Gadd45b* induction produces changes in adult neurogenesis and dendritic growth that persist for weeks after an initial electroconvulsive treatment episode. *Gadd45b* is responsible for demethylating regulatory promoter regions in the genes encoding two secreted molecules, fibroblast growth factor 1 (*Fgf1*) and brain-derived neurotrophic factor (*Bdnf*). By showing that electroconvulsive treatment-induced seizures trigger *Gadd45b*-dependent demethylation of DNA regulatory elements in the promoters of the *Fgf1* and *Bdnf* genes, Ma and colleagues have demonstrated an additional epigenetic mechanism for creating long-lasting neuroplasticity that is activity- and brain-region specific.

What Signals Create Regional Differences in Neuroplasticity and Cell Fates?

Two additional recent studies have explored regional differences in neuroplasticity during epileptogenesis and chronic temporal lobe epilepsy. Jung et al. compared cell proliferation and microglial activation within the hippocampus and in extrahippocampal areas, including the amygdala, thalamus, piriform cortex, entorhinal cortex, striatum, and globus pallidus after inducing status epilepticus with lithium-pilocarpine (16). In addition to hippocampal degeneration in the hilus and CA1 regions, 2 weeks after status epilepticus, they found marked

neurodegeneration in the piriform and entorhinal cortices, with less severe degenerative changes in the amygdala and thalamus. An increase in microglial activation in each of these areas indicates that inflammation is associated with neurodegeneration.

Jung and colleagues used birth-dating studies combined with immunostaining for cell-type specific markers for astrocytes, oligodendrocytes, microglia, and neurons to examine regional differences in the proliferative response to the seizures. Nestin-positive neural stem cells were initially found within the subgranular zone of the dentate gyrus and subventricular zone lining the walls of the lateral ventricle—two recognized stem cell niches within the adult brain. As expected from prior studies, status epilepticus increases neurogenesis in the subgranular zone. In regions outside of the hippocampal dentate gyrus, including the amygdala, and the piriform and entorhinal cortices, status epilepticus causes gliogenesis from nestin-positive progenitors, resulting in production of new astrocytes and oligodendrocytes. Cell tracking studies using lipophilic tracers showed that stem cells in the extrahippocampal regions were separate populations from those in the subgranular zone or the subventricular zone. These regional differences in neural stem cell populations and cell fates also were associated with regional increases in astrocyte and granule neuron production of the chemokine stromal cell-derived factor-1 α (SDF-1 α), which is required for new cells to integrate into the adult brain.

In a closely related study, Hattiangady and Shetty determined that chronic temporal lobe epilepsy in rats is not associated with upregulated neurogenesis in the dentate gyrus; in fact, hippocampal neurogenesis becomes markedly suppressed (18). The suppression occurred within the neurogenic niche of the subgranular zone in the dentate gyrus and was due to alterations in cell fate choices, corresponding to a shift away from neuronal differentiation and toward glia production. Based on the findings of Ma and colleagues, it is tempting to speculate that spatial and temporal differences in neurogenesis and gliogenesis after status epilepticus or in chronic epilepsy might be a consequence of differential demethylation and remethylation of the promoters for the gene families responsible for regulating proliferation of adult neural stem cell populations.

Conclusions

The novel finding that a DNA excision repair mechanism may be responsible for neural circuitry reorganization during epileptogenesis will undoubtedly stimulate further work to determine whether *Gadd45b* is a common target in other experimental models of epilepsy and if so, whether preventing seizure-induced upregulation of *Gadd45b* also prevents epileptogenesis. Neural activity has been linked to structural plasticity in the brain through multiple regulatory networks, including changes in transcription factor expression, modifications of histones,

demethylation of chromatin regions controlling growth factor expression, and regional-specific differences in neural stem cells as well as the fates of their daughter cells. The potential to systematically manipulate each of the neuroplastic regulatory networks in experimental models of epilepsy, raises hope for reducing maladaptive plastic changes in patients with severe temporal lobe epilepsy.

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