Epilepsy and Adult Neurogenesis

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Seizure activity in the hippocampal region strongly affects stem cell-associated plasticity in the adult dentate gyrus. Here, we describe how seizures in rodent models of mesial temporal lobe epilepsy (mTLE) affect multiple steps in the developmental course from the dividing neural stem cell to the migrating and integrating newborn neuron. Furthermore, we discuss recent evidence indicating either that seizure-induced aberrant neurogenesis may contribute to the epileptic disease process or that altered neurogenesis after seizures may represent an attempt of the injured brain to repair itself. Last, we describe how dysfunction of adult neurogenesis caused by chronic seizures may play an important role in the cognitive comorbidities associated with mTLE.

The epilepsies are a diverse group of neurological disorders that share the central feature of spontaneous recurrent seizures. Some epilepsies result from inherited mutations in single or multiple genes, termed idiopathic or primary epilepsies, whereas symptomatic or secondary epilepsies develop as a consequence of acquired brain abnormalities, such as from tumor, trauma, stroke, infection, or developmental malformation. Of acquired epilepsies, mesial temporal lobe epilepsy (mTLE) is a particularly common and often intractable form. In addition to pharmacoresistant seizures, the syndrome of mTLE almost always involves impairments in cognitive function (Helmstaedter 2002; Elger et al. 2004; von Lehe et al. 2006) that may progress even with adequate seizure control (Blume 2006).

Seizure activity in mTLE subjects typically arises from the hippocampus or other mesial

temporal lobe structures. Simple and complex partial seizures, the most common seizure types in this epilepsy syndrome, often become medically refractory and may respond only to surgical resection of the epileptogenic tissue. Patients usually also have secondarily generalized tonic-clonic seizures, although these are often controlled by anticonvulsants. Hippocampi in pharmacoresistant mTLE usually show substantial structural abnormalities that include pyramidal cell loss, astrogliosis, dentate granule cell axonal reorganization (mossy fiber sprouting), and dispersion of the granule cell layer (GCL) (Blumcke et al. 1999, 2012).

Humans with mTLE often have a history of an early “precipitating” insult, such as a prolonged or complicated febrile seizure, followed by a latent period and then the development of epilepsy in later childhood or adolescence.

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These historical findings have led to the development of what are currently the most common animal models, the status epilepticus (SE) models, used to study epileptogenic mechanisms in mTLE. In these models, a prolonged seizure induced by chemoconvulsant (typically kainic acid or pilocarpine) treatment or electrical stimulation leads to an initial brain injury, followed, after a latent period of days to weeks, by spontaneous recurrent seizures. These models recapitulate much of the pathology of human mTLE (reviewed in Buckmaster 2004). Experimental paradigms are necessary to investigate mechanisms underlying mTLE, as surgical specimens from mTLE cases are collected at late stages of the disease and, thus, are unlikely to reveal early features critical for the disease process. Studies of experimental mTLE indicate that excess neural activity in the course of seizures not only damages existing, mature structures of the hippocampal formation but also dramatically affects endogenous neural stem cells (NSCs) within the adult rodent dentate gyrus (Benzon et al. 1997; Parent et al. 1997; Scott et al. 1998). In the following, we will discuss the consequences of seizure activity on proliferation of NSCs, maturation and integration of newborn neurons, and the functional relevance of seizure-induced neurogenesis.

SEIZURE-INDUCED CELL PROLIFERATION

Prolonged seizure activity leads, after a latent period of several days, to a dramatic increase in cell proliferation (Fig. 1) judged by Ki67 ex-

pression or short-pulse bromodeoxyuridine (BrdU) labeling in the dentate gyrus (Parent et al. 1997; Gray and Sundstrom 1998; Jessberger et al. 2005) and rostral subventricular zone (SVZ) (Parent et al. 2002). In the dentate, the immediate proliferative response appears to be mediated by radial glia-like type-1 cells, whereas at the peak of cell proliferation increased activation of doublecortin (DCX)-expressing neuroblasts occurs (Huttmann et al. 2003; Jessberger et al. 2005; Lugert et al. 2010). BrdU labeling before SE has shown that most of the proliferating cells that respond to seizure activity are mitotically active even before the insult (Parent et al. 1999, 2006a). The severity and duration of seizure activity does not seem to be a major factor as even single, seizure-like discharges induce cell proliferation (Benzon et al. 1997). However, the survival of seizure-generated granule cells, at least in certain SE models, appears to decrease with increased seizure severity (Mohapel et al. 2004)—an effect that is potentially mediated by subsequent inflammation (Ekdahl et al. 2003). Cell proliferation returns to baseline levels approximately 3 to 4 wk following the initial SE episode (Parent et al. 1997; Bonde et al. 2006). Recent evidence suggests that, at later stages following SE, the potential for adult neurogenesis might even be reduced (Hattiangady et al. 2004; Kralic et al. 2005). The reasons for reduced neurogenesis late after seizures might either be “exhaustion” of the NSC pool or alterations in the neurogenic niche preventing support and proper function of NSCs.

Figure 1. Pilocarpine-induced status epilepticus (SE) increases dentate gyrus cell proliferation. Dentate gyrus bromodeoxyuridine (BrdU) labeling in adult rats 35 d after pilocarpine-induced SE (*right*) or saline treatment in a control (*left*). BrdU immunoreactivity is increased markedly in the inner granule cell layer (GCL), hilus (h), and molecular layer (ML) of the animal that experienced 2 h of continuous seizure activity (*right*). BrdU was given on days 7–21 after pilocarpine or saline treatment. Scale bar, 100 μ m.

A critical question that remains to be answered is how seizure activity translates into increased cell proliferation. It seems that NSCs are capable of “sensing” electrical activity (Deisseroth et al. 2004), and recent data suggest that many genes/pathways that regulate neurogenesis during embryonic development are also important in the context of adult NSC proliferation (Faigle and Song 2013). Direct mechanisms may involve signaling pathways, such as Notch, Sonic hedgehog, and Wnt signaling (Banerjee et al. 2005; Sibbe et al. 2012; Jang et al. 2013). Further, activation of glutamate and γ -aminobutyric acid (GABA) receptors expressed by dentate NSCs (Gould et al. 1994; Tozuka et al. 2005; Song et al. 2012) or changes in histone acetylation induced by seizures (Huang et al. 2002; Jessberger et al. 2007b) can alter dentate NSC proliferation in the adult. Alternatively, seizure-induced expression of trophic factors, such as brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF), and others by surrounding tissue, could indirectly induce NSC proliferation (Isackson et al. 1991; Gall 1993; Newton et al. 2003). A combination of mechanisms seems most probable, although defining them precisely is very challenging given the substantial alteration in gene expression that occurs following SE (Elliott and Lowenstein 2004).

MATURATION AND INTEGRATION OF SEIZURE-GENERATED GRANULE CELLS

The accelerated NSC proliferation likewise is reflected by a marked increase in net neurogenesis (which is the number of new neurons that is actually generated). Similar to normal conditions, ~75%–90% of all newly generated cells express markers characteristic of dentate granule cells 4 wk after labeling dividing cells with BrdU or retroviral reporter vectors (Parent et al. 1997; Jessberger et al. 2005, 2007a). Interestingly, seizure activity appears to accelerate the functional maturation and integration of adult-born granule cells, although the consequences of these effects on hippocampal network function are unknown (Overstreet-Wadiche et al. 2006). Some populations of seizure-generated

granule cells in most temporal lobe epilepsy (TLE) models studied, however, show severe morphological abnormalities that might critically affect dentate connectivity. Basically, two features are altered in the course of seizure-induced neurogenesis: the formation of hilar basal dendrites and the ectopic migration of newborn granule cells into the polymorphic cell layer.

Granule cells that are born under normal conditions in the adult dentate gyrus are highly polarized neurons (Zhao et al. 2006; Toni et al. 2007). They have a single dendrite arising from the apical portion of the cell body branching in the distal GCL or proximal molecular layer (ML). Within the ML, excitatory synapses are formed onto granule cell dendrites by perforant path axons that connect neurons from the entorhinal cortex with dentate granule cells (van Praag et al. 2002; Schmidt-Hieber et al. 2004; Ge et al. 2006; Zhao et al. 2006). In striking contrast to cells born under normal conditions, a portion of seizure-generated granule cells extends an additional basal dendrite toward the hilus (Fig. 2) (Ribak et al. 2000; Dashtipour et al. 2003; Shapiro et al. 2005). During the immature, DCX-expressing stage of neuronal development, hilar basal dendrites form non-spiny immature synapses with mossy fiber axons (Shapiro and Ribak 2006). At later stages of granule cell development (>4 wk postmitotic), hilar basal dendrites are covered with numerous spiny processes, among them mature mushroom spines (Jessberger et al. 2007a; Walter et al. 2007; Kron et al. 2010). Despite the abnormal integration that might result in the establishment of recurrent excitatory networks (Overstreet-Wadiche et al. 2006), granule cells that extend hilar basal dendrites become stably integrated into the dentate circuitry (Jessberger et al. 2007a; Walter et al. 2007; Kron et al. 2010), thus leading to lasting changes in dentate connectivity. The molecular mechanisms responsible for the extension of hilar basal dendrites are unknown but may involve an alteration in the glial scaffold and/or growth factor expression (Shapiro et al. 2005; Waterhouse et al. 2012). In contrast to hilar basal dendrites, sprouting of mossy fibers following seizures does not de-

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Figure 2. Neurogenesis following kainic acid (KA)-induced seizures is largely aberrant. Retroviral labeling reveals the highly polarized morphology with a single apical dendrite (arrow) and an axon (arrowhead) extending from newborn granule cells that were born under normal conditions (*left* panel). KA-induced seizures lead to the formation of a basal dendrite (blue arrow) in addition to the apical dendritic (arrow) and axonal processes (arrowhead, *middle* panel). Another portion of seizure-generated granule cells ectopically migrates into the hilus (*right* panel). Surprisingly, some ectopic granule cells morphologically appear very normal despite the aberrant localization. Scale bar, 15 μ m. GCL, granule cell layer; h, hilus; ML, molecular layer.

pend to a large extent on granule cells born after the epileptic insult (Parent et al. 1999), even though retroviral approaches showed that cells born after seizures also extend aberrant mossy fibers (Kron et al. 2010).

In addition to aberrant dendritic growth, SE alters the migration of adult-born neurons. Neuroblasts generated in the SVZ migrate more rapidly to the olfactory bulb, and a portion exits the migratory stream prematurely to enter nonolfactory forebrain regions (Parent et al. 2002). Few, if any, of the neuroblasts that reach the cortex appear to survive. In the dentate gyrus of adult rats, a substantial fraction of seizure-generated granule cells ectopically migrates into the hilus and toward the hilar/CA3 border, where they survive and integrate (Figs. 2 and 3) (Parent et al. 1997; Scharfman et al. 2000). Despite their abnormal localization, the intrinsic electrophysiological features of ectopic

granule cells are remarkably similar to cells born under control conditions. However, ectopic granule cells burst in synchrony with CA3 pyramidal cells indicating aberrant integration into the dentate circuitry after SE (Scharfman et al. 2000). Remarkably, ectopic cells still receive normal synaptic input from the perforant path (Scharfman et al. 2002, 2003).

Why some seizure-generated granule cells migrate into the hilus remains unclear. Recent work suggests that SE induces abnormal chain migration of granule cell progenitors toward the hilus (Parent et al. 2006b), and this aberrant migratory behavior may be initiated by loss of reelin signaling (Gong et al. 2007; Teixeira et al. 2012). In addition, it has been shown recently that mTOR signaling is involved in the migratory behavior of newborn granule cells and that excessive (transgenic) activation of the mTOR pathways leads to aberrant migration of newborn cells in the hilus, phenocopying some of the effects of seizures on dentate neurogenesis (Pun et al. 2012). Future experiments are required to understand in more detail the cellular and molecular mechanisms that underlie cell-autonomous and non-cell-autonomous effects leading to aberrant migration and dendritic integration of adult-born granule cells in models of mTLE.

FUNCTIONAL RELEVANCE OF SEIZURE-INDUCED NEUROGENESIS

Seizure-associated neurogenesis may play a role in two features of mTLE that are poorly understood from a mechanistic point of view. The first one is the progression from a brain insult to the clinical syndrome of epilepsy, a process called epileptogenesis (Dalby and Mody 2001; Magloczky and Freund 2005). What is the evidence that altered neurogenesis might be involved in epileptogenesis? Unquestionably, SE leads to heightened excitability and recurrent excitatory networks within the hippocampal circuitry. One reason for this might be the excitotoxic loss of inhibitory, GABAergic neurons, although debate is ongoing regarding the relevance of cell death or interneuronal disconnection in the establishment of an epileptic circuitry (Bernard

Figure 3. Ectopic granule cells in experimental and human mesial temporal lobe epilepsy (mTLE). (*Top panels*) Prox1 immunoreactivity in adult rat dentate gyrus 35 d after saline treatment (A) or pilocarpine-induced status epilepticus (SE) (B) shows many ectopic granule neurons in the epileptic rat (B) but not in the control (A). (*Bottom panels*) NeuN immunoreactivity in control human (C; temporal lobe tumor) and human mTLE (D) dentate gyrus shows granule cell layer (GCL) dispersion and ectopic granule-like neurons in the hilus (h) and molecular layer (ML) only in the patient with mTLE who had mesial temporal sclerosis (D). Arrowheads (C) point to larger, NeuN-immunoreactive hilar neurons in the control tissue that are not seen in the mTLE subject (D) caused by hilar cell loss, or in either rat (A,B) because Prox1 is expressed specifically in dentate granule cells. Scale bars, 100 μ m (A,B); 50 μ m (C,D).

et al. 1998; Dalby and Mody 2001; Sloviter et al. 2003; Ratzliff et al. 2004). Seizure-generated granule cells show two features that might indicate an epileptogenic role. Seizure-generated granule cells with hilar basal dendrites receive excitatory input from mossy fibers and could, thus, form a recurrent excitatory circuit (Fig. 4) (Shapiro and Ribak 2006). Similarly, ectopic granule cells appear to be abnormally synchronized with spontaneous, rhythmic bursts of CA3 pyramidal neurons (Scharfman et al. 2000). Compatible with those data is the finding that the reduction of seizure-generated neurons impairs epileptogenesis and reduces the frequency of spontaneous recurrent seizures (Jung et al. 2004, 2006). Abnormal network formation that results from altered neurogenesis after brain injury may also support seizure propagation or adversely influence seizure termination mechanisms. Even stronger support comes from the recent finding that aberrant neurogenesis is

sufficient to induce spontaneous seizures in an otherwise intact animal (Pun et al. 2012). Strikingly, as few as 9% of “wrongly” connected newborn granule cells, induced by mTOR activation (see above), are sufficient to induce spontaneous seizures (Pun et al. 2012). These data strongly suggest a proepileptogenic role for new neurons. However, there is also evidence that seizure-induced neurogenesis may play a compensatory role in SE models using electrical stimulation to induce SE (Jakubs et al. 2006). In this model, seizure-generated granule cells have less excitatory but increased inhibitory input resulting in overall decreased excitability compared with newborn cells generated in running rats (Jakubs et al. 2006). Given this finding, the heightened excitability within the epileptic hippocampal circuitry might be compensated through more inhibited newborn granule cells. This hypothesis is supported by other studies that showed no detrimental or rather positive

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Figure 4. Aberrant integration of adult-born neurons after SE alters dentate gyrus circuitry. *Top* panel shows a schematic of the normal dentate gyrus with radial glia-like neural stem cells (NSCs) (green) that generate more proliferative type-2 cells (blue) that give rise to immature neurons that extend dendrites toward molecular layer (ML) and their axons (mossy fibers) toward the hilus (orange). Mature newborn neurons functionally integrate with their dendrites in the ML and send their axons to area CA3 and hilar regions (red). In experimental mesial temporal lobe epilepsy (mTLE) (*bottom* panel), status epilepticus (SE) increases neurogenesis and also alters the integration of differentiating neurons. Proliferation of radial glia-like cells (green) and also type-2 cells is strongly enhanced (blue). Cells born after SE extend aberrant dendrites into the hilar region (orange). Aberrant dendrites remain also on fully mature newborn granule cells (red) that may be implicated in disturbing dentate connectivity. Furthermore, mossy fiber sprouting occurs from seizure-generated (red) but also preexisting mature granule cells (not shown in this scheme). In addition to aberrant neurite extension and integration, some seizure-generated neurons migrate ectopically to reside in hilus (figure prepared by Simon Braun, University of Zurich).

effects of SE-induced neurogenesis on hippocampal network function (Raedt et al. 2007; Pekcec et al. 2011).

Without a doubt, the question of whether seizure-generated granule cells are part of the disease or an attempt of the injured brain to repair itself is far from conclusively answered. Given the heterogeneous nature of DGCs generated after SE in the adult hippocampus (Murphy et al. 2011), populations of normally and aberrantly integrated adult-born DGCs likely arise after SE that may exert opposing influences on excitability. However, future studies that reproduce consequences of seizure activity on adult neurogenesis in otherwise intact animals likely will help answer this critical question.

Another consequence of mTLE is the common occurrence of cognitive dysfunction that often leads to substantial morbidity (Helmstaedter et al. 2003; Elger et al. 2004). There is growing evidence that adult neurogenesis is involved in certain forms of hippocampus-dependent learning and memory under normal conditions (Shors et al. 2001, 2002; Santarelli et al. 2003; Snyder et al. 2005; Meshi et al. 2006; Saxe et al. 2006; Winocur et al. 2006). Seizure-generated neurons might contribute to cognitive impairment associated with TLE in three respects. First, the “normal” function of adult-generated neurons that might depend on specific plasticity of immature neurons (Schmidt-Hieber et al. 2004) might be disrupted because of an altered integration pattern (Overstreet-Wadiche et al. 2006; Jessberger et al. 2007b). Second, the well-documented aberrant integration (hilar basal dendrites and ectopic granule cells) in most rodent models of mTLE could critically interfere with synaptic transmission and information processing (Fig. 4). A third potential influence is that chronic suppression of neurogenesis in the epileptic brain (Hattiangady et al. 2004) could interfere with hippocampus-dependent learning and memory (Clelland et al. 2009; Deng et al. 2010; Sahay et al. 2011). As is the case for adult neurogenesis under normal conditions, however, the functional role of seizure-generated neurons in epileptogenesis or cognitive impairment will only be satisfyingly answered if ablation strategies with a higher spe-

cificity and selectivity than the ones that are currently available are developed.

SUMMARY

The finding that adult neurogenesis is altered dramatically during epileptogenesis challenges the conceptual understanding of the cause and consequences of mTLE. Most rodent models of mTLE are associated with severe alterations in morphology and connectivity of adult-born neurons, such as the extension of hilar basal dendrites and the ectopic migration into the hilus of granule cell progenitors. To date, however, the role new neurons actually play in the epileptic disease process remains unclear. Simply put, are they good or bad? In the end, both descriptions may prove valid in that some aspects of seizure-induced neurogenesis might be beneficial and others harmful for the epileptic brain. In any case, the characterization and identification of cellular and molecular mechanisms underlying seizure-induced neurogenesis will bring us one step further toward understanding ongoing plasticity in the adult brain. Without a doubt, seizure-induced neurogenesis represents a promising target for intervention in the treatment of human epilepsy and its comorbidities.

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Cold Spring Harb Perspect Biol 2015; doi: 10.1101/cshperspect.a020677 originally published online November 9, 2015

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