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Hippocampal Neurogenesis and Neural Stem Cells in Temporal Lobe Epilepsy

Ramkumar Kuruba^{1,2}, Bharathi Hattiangady^{1,2}, and Ashok K. Shetty^{1,2,*}

¹Department of Surgery (Neurosurgery) Duke University Medical Center, Durham, NC 27710

²Medical Research and Surgery Services, Veterans Affairs Medical Center, Durham, NC 27705

Abstract

Virtually all mammals including humans exhibit neurogenesis throughout life in the hippocampus, a learning and memory center in the brain. Numerous studies in animal models imply that hippocampal neurogenesis is important for functions such as learning, memory and mood. Interestingly, hippocampal neurogenesis is very sensitive to physiological and pathological stimuli. Certain pathological stimuli such as seizures alter both amount and pattern of neurogenesis though the overall effect depends on the type of seizures. Acute seizures are classically associated with augmentation of neurogenesis and migration of newly born neurons into ectopic regions such as the hilus and the molecular layer of the dentate gyrus. Additional studies suggest that abnormally migrated newly born neurons play a role in the occurrence of epileptogenic hippocampal circuitry characteristically seen after acute seizures, status epilepticus or head injury. Recurrent spontaneous seizures such as those typically observed in chronic temporal lobe epilepsy are associated with substantially reduced neurogenesis, which interestingly co-exists with learning and memory impairments and depression. In this review, we discuss both extent and potential implications of abnormal hippocampal neurogenesis induced by acute seizures as well as recurrent spontaneous seizures. We also discuss the consequences of chronic spontaneous seizures on differentiation of neural stem cell progeny in the hippocampus and strategies that are potentially useful for normalizing neurogenesis in chronic temporal lobe epilepsy.

Keywords

adult neurogenesis; dentate neurogenesis; dentate gyrus; epilepsy; seizures; neural stem cells; neural progenitors; stem cell grafts; stem cell proliferation; stem cell differentiation

Introduction

Epilepsy, characterized by periodic and unpredictable occurrence of seizures, affects ~50 million people worldwide, and temporal lobe epilepsy (TLE) is among the most frequent types of intractable epilepsy [1-4]. While the precise cause of TLE is unknown in most cases, it is typically seen after an initial precipitating injury (IPI) such as status epilepticus (SE), brain injury, tumors, meningitis, encephalitis, and febrile seizures during childhood in other cases

*Correspondence should be addressed to: Ashok K. Shetty, M.Sc., Ph.D., Professor, Division of Neurosurgery, Box 3807, Duke University Medical Center, Durham NC 27710, Phone: 919-286-0411, Ext. 7096, E-mail: Ashok.Shetty@Duke.Edu.

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[5-9]. There is usually a latent period of several years between this injury and the emergence of chronic TLE characterized by spontaneous recurrent motor seizures (SRMS), learning and memory impairments, depression, substantial neurodegeneration in the dentate hilus (DH) and CA1-CA3 subfields, and aberrant synaptic reorganization [10-16].

Abnormal hippocampal neurogenesis has emerged as another important pathophysiology of TLE over the last decade [17-23]. Neurogenesis is a process of generation of new neurons in the central nervous system (CNS) through division of neural stem cells (NSCs) and neuronal differentiation of newly born cells. Although most of the neurogenesis occurs during the initial development, certain regions of the brain maintain neurogenesis throughout life. These include the dentate gyrus (DG) of the hippocampus and the subventricular zone lining the lateral ventricles [24-28]. Neurogenesis in the adult and aged hippocampus has received great attention [28-37] because of the importance of hippocampus in maintaining normal learning and memory function as well as its dysfunction in diseases such as TLE, Alzheimer's disease and major depressive disorders. Hippocampal NSCs reside in the subgranular zone (SGZ) of the DG, where they proliferate and produce new cells. A great fraction of these new cells differentiate into granule cells of the DG, which migrate up into the granule cell layer (GCL), extend dendrites into the dentate molecular layer, send axons into the dentate hilus and CA3 stratum lucidum. Over time, these newly added granule cells incorporate into the functional hippocampal circuitry through establishment of granule cell specific afferent and efferent synaptic contacts and participate in spatial memory formation [38-44].

However, the extent of hippocampal neurogenesis in the adult brain is not static, as it responds to both physiological and pathological stimuli though the net result of a particular stimulus varies depending on the activation of positive or negative regulators of neurogenesis. For instance, physical exercise or exposure to enriched environment positively enhances the amount of hippocampal neurogenesis through up-regulation of multiple positive regulators of neurogenesis. On the other hand, pathological stimuli such as seizures induce abnormalities in hippocampal neurogenesis though the overall effect depends on the type of seizures. Acute seizures or status epilepticus abnormally increase the amount of hippocampal neurogenesis and induce aberrant migration of a significant fraction of newly born neurons into the dentate hilus and the dentate molecular layer. Spontaneous recurrent motor seizures that occur in chronic temporal lobe epilepsy lead to a radically waned neurogenesis. In the following sections, we review current knowledge on the extent and implications of abnormal hippocampal neurogenesis induced by acute seizures as well as recurrent spontaneous seizures. Additionally, the outcome of recurrent spontaneous seizures on hippocampal NSC activity, neuronal differentiation of the progeny of NSCs, and strategies that are potentially useful for stimulating NSCs and normalizing neurogenesis in chronic TLE are also discussed.

Response of Hippocampal Neurogenesis to Acute Seizures

Pioneering studies on neurogenesis in animal models of TLE by Parent et al [17] and Bengzon et al [45] gave the initial evidence for increased hippocampal neurogenesis following acute seizures. In these studies, a dramatic increase in the production of new cells/neurons was observed in the SGZ-GCL of the DG following pilocarpine induced SE [17] or kindling stimulations [45]. However, by 3-4 weeks after SE, neurogenesis returned to baseline levels [17]. A subsequent study showed that administration of chemoconvulsant kainic acid under anesthesia also increases neurogenesis in the hippocampus [46]. Figure 1 illustrates a schematic of different changes (including increases in DG neurogenesis) that occur following acute seizures. Investigations in a variety of epilepsy models have confirmed the above plasticity of hippocampal neurogenesis to acute seizures [22,47-54]. This raised a question whether or not a similar phenomenon occurs in humans after acute seizures. While evaluation of hippocampal neurogenesis shortly after acute seizures is yet to be performed in humans, examination of the

hippocampus from young TLE patients (<2 years old) suggested increased cell proliferation [55]. Furthermore, epileptic hippocampus from young children (<4 years) also exhibited significant numbers of neural precursor cells [55]. Thus, there is some evidence for increased hippocampal neurogenesis in the early phase of TLE in pediatric patients, which is consistent with studies in animal models of TLE described above.

Potential mechanisms of increased neurogenesis after acute seizures

A proliferative surge occurs in NSCs of the SGZ shortly after SE leading to an increased production of new neurons during the first few weeks after the seizure episode [17,54,56,57]. The precise mechanisms underlying the seizure-induced increase in hippocampal neurogenesis are unclear. However, several potential mechanisms have been proposed. First, it is believed that the release of mitogenic factors from dying neurons, deafferented granule cells and reactive glia likely increase the proliferation of NSCs and the survival of newly formed neurons. This is because, multiple studies demonstrate that several factors that are known to promote NSC proliferation and neuron survival (such as nerve growth factor [NGF], brain-derived neurotrophic factor [BDNF], fibroblast growth factor-2 [FGF-2], vascular endothelial growth factor [VEGF] and sonic hedgehog (Shh) are up-regulated in the hippocampus after acute seizures [58-66]. Second, it is plausible that increased levels of GABA in the DG during the early post-seizure period positively influences neurogenesis, as studies show that GABA has crucial roles in regulating different steps of adult neurogenesis, including proliferation of neural progenitors, migration and differentiation of neuroblasts, and synaptic integration of newborn neurons [67]. Third, it is possible that increased levels of neuropeptide Y (NPY) found typically after acute seizures enhances the proliferation of NSCs in the DG, as studies demonstrate that NSCs increase neurogenesis in the presence of NPY [68-72]. Fourth, modulation of neuron-restrictive silencing factor (NRSF) activity has been suggested to be one of the factors responsible for increased neurogenesis after acute seizures because blocking of NRSF activity through administration of Valproic acid diminishes seizure-induced increases in hippocampal neurogenesis [73]. Fifth, it is likely that augmented neuronal activity during and after seizures promotes an increased proliferation of NSCs, as increased excitatory stimuli can act directly on NSCs and influence the production of new neurons [74]. Thus, it appears that multiple mechanisms underlie increased hippocampal neurogenesis observed after acute seizures.

Adverse effects of increased DG neurogenesis after acute seizures

Numerous studies suggest that increased DG neurogenesis after acute seizures is associated with anomalous migration of a fraction of newly born granule cells into the dentate hilus and/or the dentate molecular layer [11,17-21,72,75-81]. Further investigations demonstrate that aberrantly migrated newly born granule cells exhibit deviant integration with the CA3 network [19], get activated when epileptic rats exhibit spontaneous seizures [73,82] and respond to perforant path stimulation with a longer latency to onset of evoked responses [21]. Additional studies imply that displaced granule cells in the dentate hilus establish afferent connectivity with mossy fiber terminals [83], exhibit spontaneous bursts of action potentials [19], and contribute to spontaneous seizures in chronically epileptic animals [76,84]. Similarly displaced granule cells have also been observed in hippocampal tissues obtained from patients with TLE [11,18,85,86]. Thus, it appears that acute seizure induced abnormal DG neurogenesis promotes aberrant circuitry development, which likely contributes to the evolution of initial seizure-induced hippocampal injury into chronic epilepsy.

Likely reasons for anomalous migration of newly born granule cells after acute seizures

The precise reasons for anomalous migration of newly born granule cells are still being examined. However, indirect evidences propose the following. A study by Jessberger et al [54] demonstrates that acute seizures do not significantly influence the proliferation of nestin-

expressing NSCs (type 1 cells) but rather stimulate the division of doublecortin (DCX) expressing cells (transit amplifying cells [type 2 cells] and immature neurons [type 3 cells]). Based on this, it is presumed that delayed proliferation during the process of neurogenesis interferes with migration, leading to a significant dispersion of DCX-positive early post-mitotic neurons away from the GCL into the dentate hilus and the molecular layer. However, a recent study suggests that loss of reelin (a secreted migration guidance cue) expression after acute seizures largely contributes to the chain migration and aberrant integration of newly born dentate granule cells into ectopic locations [77]. This study demonstrates that subclasses of interneurons that are typically lost in TLE express reelin and dentate granule cell progenitors express the downstream reelin signaling molecule Disabled 1 (Dab1). This arrangement in normal conditions is believed to promote appropriate migration of newly born neurons into the GCL. However, prolonged seizures decrease reelin (likely due to the loss of reelin expressing interneurons) but increase Dab1 expression in hilar-ectopic neuroblasts. Because exogenous reelin increases detachment of chain-migrating neuroblasts and blockade of reelin signaling increases chain migration in DG explants, it has been suggested that reelin deficiency after acute seizures contributes to ectopic chain migration and aberrant integration of newborn dentate granule cells into the dentate hilus.

Dendritic abnormalities in granule cells that are born after acute seizures

A study by Shapiro et al [53] showed that a significant fraction of new dentate granule cells that are born after acute seizures exhibit abnormal morphological features in the form of basal dendrites. As these basal dendrites seem to run along the GFAP-labeled astrocytic processes in the hilus, involvement of an ectopic glial scaffold in the hilus has been proposed for the formation of hilar basal dendrites after acute seizures. Further studies demonstrate that these basal dendrites persist for prolonged periods and exhibit immature synapses [87], suggesting their involvement in the formation of epileptogenic circuitry. A recent study by Walter and colleagues [88] has elegantly demonstrated that ~50% of immature granule cells exposed to pilocarpine-induced seizures (i.e. new neurons that were born shortly before the induction of seizures) and ~40% of new granule cells that are born after the induction of seizures exhibit aberrant hilar basal dendrites. These results suggest the existence of a critical period after the birth of adult-generated neurons during which they are vulnerable to being recruited into epileptogenic neuronal circuits. Furthermore, seizures seem to accelerate the morphological development of newly born granule cells, causing their dendrites to extend swiftly through the molecular layer leading to a rapid functional integration of adult-generated granule cells [89]. Interestingly, neurons born one month after acute seizures also exhibit alterations in dendrite morphology, suggesting persistent effects of seizures on granule cell maturation [89]. A recent study by Arisi and Garcia-Cairasco [90] reports that apical dendrites of newly born neurons born shortly after the SE exhibit more bifurcations inside the granular cell layer and more terminations in the inner molecular layer, implying that a concentration of apical dendrites occurs in the inner molecular layer where mossy fibers typically sprout after SE. This dendritic arrangement likely facilitates formation of greater number of synapses between aberrantly sprouted mossy fibers and the dendrites of newly born granule cells and contributes to increased epileptogenesis. Thus, the overall dendritic properties of newly born neurons that are born shortly after SE are predisposed for epileptogenesis.

Will suppression of abnormal neurogenesis after acute seizures reduce epileptogenesis and prevent cognitive impairment?

As acute seizure induced abnormal DG neurogenesis promotes aberrant circuitry development and likely contributes to the evolution of initial seizure-induced hippocampal injury into chronic epilepsy, an important question emerges. Will prevention or suppression of acute seizure-induced abnormal neurogenesis reduce the frequency and intensity of spontaneous seizures in the chronic phase of epilepsy? Jung and associates [84] reduced SE-induced

hippocampal neurogenesis through administration of an antimitotic agent cytosine-b-D-arabinofuranoside (Ara-C) into the lateral ventricle in an animal model and evaluated the frequency of spontaneous seizures. They reported reduction in both frequency and duration of spontaneous seizures in animals that received Ara-C following SE, in comparison to animals that received vehicle after SE. These results are supportive of the notion that seizure-induced abnormal neurogenesis contributes to the development of chronic epilepsy. However, there are some caveats that need to be addressed in future studies. First, it remains to be addressed whether the beneficial effects of Ara-C would persist for prolonged periods after SE, as spontaneous seizures were quantified only during the early phase (28-34 days) after SE. Second, it will be necessary to resolve whether the positive effects of Ara-C treatment after SE is a result of decreased number of ectopic granule cells or decreased proliferation of glia. Third, it is critical to determine whether Ara-C treatment blocks other epileptogenic changes that promote chronic epilepsy. It is interesting to note that, studies by Raedt et al. [91] and Pekcec et al. [92,93] report contrasting results. Exposure of rats to whole brain low-dose (8 Gy) γ -radiation one day before the initiation of rapid hippocampal kindling significantly suppressed the generation of new granule cells but had no effect on the final establishment of the permanent fully kindled state [91]. Based on these results authors argue that seizure-induced neurogenesis does not play a prominent role in epileptogenesis. Pekcec et al [92,93] examined the effects of reducing the proliferation rate of hippocampal NSCs and the fate of newborn neurons via transient enzymatic depolysialylation of neural cell adhesion molecule (NCAM) in two different models of epilepsy. They found no changes in the generation of a hyperexcitable kindled network in the kindling model of epilepsy or development of spontaneous seizures in the SE model of epilepsy following the above suppression of neurogenesis. Because both radiation exposure and enzymatic depolysialylation of NCAM might lead to multiple side effects [94-99], additional studies that selectively ablate neurogenesis are however required to confirm these findings. Thus, it remains to be seen whether complete elimination of aberrant neurogenesis after the SE would prevent the evolution of SE into chronic epilepsy.

Suppression of abnormal hippocampal neurogenesis after acute seizures might also be important for reducing behavioral abnormalities such as learning and memory impairments. Indeed, a study demonstrated that blockage of seizure-induced neurogenesis through an antiepileptic drug Valproic acid (VPA) protected animals from seizure-induced cognitive impairment in a hippocampus-dependent learning task [73]. These results imply that seizure-generated granule cells have the potential to interfere with hippocampal function and contribute to cognitive impairment caused by epileptic activity within the hippocampal circuitry. Similarly, Pekcec et al [93] demonstrated that blockage of seizure-induced neurogenesis through enzymatic depolysialylation of NCAM during SE and in the early phase of epileptogenesis resulted in a cognition sparing effect as revealed by the water maze test. Thus, blocking of seizure-induced abnormal neurogenesis appears useful for minimizing cognitive impairments associated with acute seizures. Hence, rigorous studies on early interventions that thwart seizure-induced abnormal neurogenesis are needed in the future to develop this strategy for diminishing both chronic epilepsy development and cognitive impairments.

Response of Hippocampal Neurogenesis to Chronic Spontaneous Seizures

Changes in the extent of neurogenesis in animal models of chronic epilepsy

Increased neurogenesis observed shortly after acute seizures returns to baseline by about 2 months after the initial seizure episode in rats [73]. However, the extent of neurogenesis declines radically in the chronic phase of epilepsy when significant numbers of spontaneous seizures manifest [22]. By employing DCX as a marker of newly born neurons in two distinct rat models of TLE, Hattiangady et al. [22] reported 64-81% decrease in neurogenesis. Furthermore, an inverse relationship was evident between the frequency of spontaneous

seizures and the extent of neurogenesis, as the overall decrease in neurogenesis was considerably greater in rats exhibiting increased number of spontaneous seizures. Additional evaluation using pulsed injections of 5'-bromodeoxyuridine (BrdU) at 5 months post-SE demonstrated that the overall addition of new cells to the SGZ-GCL and the extent of long-term survival in chronic epilepsy are analogous to that observed in the age-matched intact hippocampus [100]. However, phenotypical characterization revealed that only ~4% of newly generated cells differentiated into mature neurons in chronic epileptic conditions, in contrast to 80% of newly born cells exhibiting neuronal differentiation in the age-matched intact hippocampus. A subsequent study using a mouse model of TLE also reported similar changes in neuronal differentiation of newly born cells in chronic epilepsy where reduced neurogenesis was associated with increased production of new astrocytes [52]. Another study by Heinrich et al [101] reported a gradual fall in neurogenesis at one week and virtual loss of all neurogenesis by 4-6 weeks after the initial seizure episode, which interestingly paralleled granule cell dispersion and widening of GCL. In contrast to the above findings, Bonde et al [102], using an electrically evoked SE model, reported no changes in neurogenesis within the dorsal hippocampus at 6 months post-SE. Similarly, in a lithium-pilocarpine model of epilepsy using postnatal day 20 rats, a modest increase in neurogenesis was observed even at 2 months post-SE [103]. From the above findings, it emerges that decreased levels of hippocampal neurogenesis in chronic epilepsy depends on the model and age of the animal at the time of the initial seizure episode. Adult animals seem to be vulnerable for an almost complete loss of neurogenesis in the chronic phase after the initial seizure episode.

Characteristics of hippocampal neurogenesis in human TLE

Only a few studies have so far examined neurogenesis in hippocampal tissues of TLE patients. Accurate interpretation of results from these specimens has been difficult because of several constraints, which include non-availability of hippocampal tissues at different stages of epilepsy and apt age-matched control samples, and lack of apt markers that detect neurogenesis. Mathern et al [104] demonstrated decreased density of cells positive for PSA-NCAM (a putative marker of newly born neurons) in the DG from children exhibiting frequent spontaneous seizures than the DG from age-matched autopsy samples, implying that severe seizures during early childhood are associated with decreased hippocampal neurogenesis. Examination of hippocampal tissues from adult patients with chronic TLE in subsequent studies also revealed reduced density of PSA-NCAM+ cells [23,105]. Another study by Crespel et al [106] also found minimal numbers of DCX+ cells in the SGZ of hippocampal tissues from patients with mesial TLE, despite an evidence for increased proliferation of cells immunopositive for Musashi-1 (a putative marker of NSCs) in these samples. Furthermore, a study by Fahrner et al [107] demonstrated both decreased synthesis of mRNA for DCX and absence of cells positive for Ki-67 (an endogenous marker of proliferative cells) in hippocampal tissues from chronic TLE patients. Thus, available reports are supportive of the finding in animal models that chronic epilepsy is associated with declined hippocampal neurogenesis. Considering the potential functions of hippocampal neurogenesis, it is likely that hippocampal-dependent learning and memory deficits and depressive behavior observed in TLE are at least partially linked to decreased hippocampal neurogenesis.

Potential mechanisms underlying decreased neurogenesis in chronic TLE

While the precise mechanisms underlying decreased neurogenesis in chronic TLE are unknown, several potential reasons have been proposed. Although a role for chronic inflammation in this decline is an attractive hypothesis, a study on activated microglial cells has almost ruled out this possibility as only minimal density of such cells was found in the hippocampus during chronic epilepsy [22]. Another potential reason underlying decreased neurogenesis includes the presence of adverse hippocampal milieu for neurogenesis from NSCs and decreased numbers of NSCs. While unfavorable NSC milieu can be gleaned from

decreased levels of NSC mitogenic factors such as FGF-2, IGF-1 and BDNF in chronic epilepsy [22,63], numbers of NSCs do not appear to change drastically in chronic epilepsy. In fact, a human study suggests an increased number of putative NSCs positive for Musashi-1 in chronic TLE [106]. Furthermore, a recent study reports only moderate decreases in numbers of putative NSCs positive for Sox-2 or vimentin in the SGZ of chronically epileptic animals [108]. Thus, significant numbers of NSCs persist during chronic epilepsy. However, neuronal differentiation of the progeny of NSCs is impaired in chronic epilepsy [100,52], likely due to an unfavorable hippocampal milieu discussed above. Increased concentration of Wnt protein inhibitor Dickkopf-1 in chronic epilepsy [109] further supports the unfavorable milieu hypothesis. This is because blockade of Wnt signaling abolishes DG neurogenesis [110].

Is diminished neurogenesis linked to persistence of spontaneous seizures, cognitive impairments and depressive behavior in chronic TLE?

Diminished hippocampal neurogenesis might contribute to the persistence of spontaneous seizures, learning and memory impairments and depression prevailing in chronic TLE. First, it is plausible that decreased addition of new neurons to the GCL interferes with the possible spontaneous repair of hyperexcitability in the DG. This is because, a study using an electrical stimulation model of SE implies that granule cells that are born and integrated into the GCL at extended time-points after the SE receive reduced excitatory synaptic input and display an enhanced inhibitory synaptic drive [111]. Second, in view of findings that newly formed neurons get incorporated into the hippocampal circuitry and actively participate in learning and memory function [40,42,112-114], decreased addition of new functional granule cells into the GCL in chronic epilepsy likely contributes to impairments in hippocampal-dependent learning and memory functions observed in TLE. This notion is also supported by the finding that the overall granule cell density is the most significant predictor accounting for the total memory capacity in an individual TLE patient [115,116]. Third, from the perspective of findings that increased production of new neurons in the hippocampus is essential for effective action of antidepressants [117-121], diminished addition of new granule cells into the GCL perhaps plays a role in depressive like behavior prevailing in chronic epilepsy. Thus, available evidence is supportive of the perception that diminished hippocampal neurogenesis plays a role in maintaining spontaneous seizures, learning and memory impairments and depression in chronic TLE. It remains to be determined however whether strategies that have the potential to increase neurogenesis in chronic epileptic conditions would be capable of easing any of these impairments.

Potential strategies for augmenting dentate neurogenesis in chronic TLE

Based on studies in animal models of brain disease and injury, the following strategies appear promising for increasing neurogenesis in chronic epilepsy: administration of distinct neurotrophic factors, physical exercise, exposure to an enriched environment, antidepressant therapy and grafting of NSCs. Figure 2 illustrates various time-points after acute seizures at which interventional strategies may be applied to alleviate the acute seizure induced chronic epilepsy, learning and memory impairments, and depression. Administration of neurotrophic factors is relevant because many factors that promote neurogenesis (such as FGF-2, IGF-1 and BDNF) exhibit decreased levels in chronic epilepsy [22,63]. While no studies are currently available on the effects of administration of these factors into the chronically epileptic hippocampus, this approach has promise based on their ability to enhance neurogenesis in both intact and injured aged hippocampus [122-126]. Performing physical exercise and exposure to enriched environment for increasing neurogenesis in chronic epilepsy are very appealing because these approaches are non-invasive and have many beneficial effects [127-129] other than increasing neurogenesis [130-132]. Pertaining to physical exercise, studies imply that physical exercise decreases the incidence and severity of seizures in epileptic patients as well as in animal models of epilepsy [133-137]. Furthermore, physical exercise enhances the

concentration of several factors (such as BDNF, NGF, VEGF) and phosphorylated cAMP response element binding protein (pCREB) that promote neurogenesis and cognitive function [102,138-141]. Regarding exposure to enrichment, studies demonstrate that environmental enrichment of rats prior to KA administration increases the seizure threshold, decreases hippocampal neurodegeneration, improves learning and memory abilities and alleviates depressive-like behavior [142-146].

Antidepressant therapy in chronic epilepsy is another interesting approach for increasing neurogenesis and cognitive impairments, as antidepressant treatments enhance DG neurogenesis [117-121] likely via increases in the concentrations of serotonin, norepinephrine, CREB and multiple neurotrophic factors [147-150]. Because decreased neurogenesis, cognitive impairments and depression co-exist in chronic epilepsy, prolonged antidepressant therapy appears to be a useful approach for easing these problems.

Grafting of NSCs or glial progenitors into the chronically epileptic hippocampus might also increase neurogenesis, as a study showed that dramatically diminished neurogenesis in aging hippocampus could be reversed considerably with this approach [151]. Grafting of NSCs into the chronically epileptic hippocampus might also induce other beneficial effects such as seizure control through generation of new GABA-ergic interneurons [79,152] and improved cognitive function through the release of useful neurotrophic factors by the grafted NSCs. Thus, several approaches appear promising for improving neurogenesis, cognitive function, and mood in chronic epilepsy. However, rigorous long-term studies in chronic epilepsy models are clearly needed in the future to validate these approaches.

Potential consequences of increasing neurogenesis in chronic TLE

Although increasing hippocampal neurogenesis in chronic epilepsy using a variety of strategies proposed above is attractive considering the possible involvement of neurogenesis in hippocampal-dependent learning and memory function and mood, it is difficult to predict the overall impact of increased neurogenesis in chronic epilepsy on the frequency and intensity of spontaneous seizures. This uncertainty stems from the suggested role of aberrant DG neurogenesis occurring at early time-points after SE towards the evolution of SE into chronic epilepsy [18,19,21,72,78]. Beneficial effects such as restrained spontaneous seizures, reduced learning and memory impairments and better mood are expected, if the majority of newly generated granule cells migrates into the GCL and integrate into the hippocampal circuitry with apt connectivity or with a pattern of connectivity described by Jakubs et al [111]. However, exacerbation of the epileptogenic circuitry in the hippocampus might occur if a greater fraction of newly born neurons exhibit aberrant migration and incorporate inappropriately into the dentate hilus or the molecular layer. Therefore, detailed studies examining these issues are critical in future.

Overall Conclusions

Studies in animal models clearly reveal that, at early time-points after an initial precipitating injury such as acute seizures or SE, increased hippocampal neurogenesis and abnormal recruitment of newly born neurons into the hippocampal circuitry occurs. Studies on hippocampal tissues from pediatric patients with early phase of TLE support these findings. However, the relative contribution of this aberrant circuitry for the evolution of initial seizure-induced hippocampal injury into chronic epilepsy remains to be determined. Approaches that selectively ablate aberrant neurogenesis need to be developed for determining the full impact of blocking the initial seizure-induced abnormal neurogenesis on spontaneous seizures, cognitive function and mood. Studies in both animal models and hippocampal tissues from patients with TLE reveal that the chronic phase of epilepsy is associated with substantially decreased hippocampal neurogenesis. Available analyses suggest that decreased neurogenesis

is a consequence of dramatic decreases in the neuronal differentiation of newly born cells rather than decreased production of new cells or substantial decreases in numbers of NSCs. Impaired neuronal differentiation of newly generated cells in chronic epilepsy appears to be related to the presence of an unfavorable hippocampal microenvironment, typified by depletion in the concentration of several factors that promote neurogenesis. Based on the suggested functions of DG neurogenesis, it is possible that dramatically waned DG neurogenesis contributes to persistence of seizures, learning and memory dysfunction and depression observed in chronic epilepsy. Considering these, development of strategies that enhance hippocampal neurogenesis such as administration of distinct neurotrophic factors, physical exercise, exposure to enriched environment, antidepressant therapy, grafting of NSCs are proposed for easing various impairments associated with chronic epilepsy. However, the outcome of increased DG neurogenesis during chronic epilepsy will largely depend upon the behavior and connectivity of newly born neurons. Therefore, studies that examine the effects of increased DG neurogenesis in chronic epilepsy on spontaneous seizures, learning and memory function, and mood are critically needed to make further progress in this field.

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Figure 1.

Schematic of different changes that occur following acute seizures. Acute seizures or status epilepticus typically occur following head trauma, stroke, brain injury or brain infections. Acute seizures induce multiple structural alterations in the brain particularly the hippocampus. The major hippocampal changes include degeneration of fractions of dentate hilar neurons and CA1-CA3 pyramidal neurons, aberrant sprouting of mossy fibers into the dentate supragranular layer and substantial loss of inhibitory interneurons. Acute seizures also transiently up-regulate multiple neurotrophic factors and other proteins in the hippocampus. These include nerve growth factor (NGF), brain derived neurotrophic factor (BDNF), fibroblast growth factor-2 (FGF-2), vascular endothelial growth factor (VEGF), neuropeptide Y (NPY), sonic hedgehog (Shh) and Cystatin C. Additional cellular changes in the hippocampus following acute seizures

comprise increased neurogenesis, abnormal migration of newly born neurons into the dentate hilus and dentate molecular layer, and occurrence of hilar basal dendrites in newly added granule cells. All of the above changes are believed to contribute to the formation of aberrant circuitry and epileptogenesis in the hippocampus, and learning and memory impairments.

Figure 2.

Schematic showing various time-points after acute seizures at which interventional strategies may be applied to alleviate the acute seizure induced chronic epilepsy, learning and memory impairments, and depression. Acute seizures induce multiple structural, neurochemical and cellular changes in the hippocampus, which are believed to contribute to the development of chronic epilepsy characterized by spontaneous seizures. Chronic epilepsy leads to a substantial decline in hippocampal neurogenesis which is believed to contribute towards learning and memory impairments and depression. Interventional strategies such as administration of neurotrophic factors, antidepressant therapy, physical exercise, exposure to enriched environment, and grafting of neural stem cells (NSCs) and glial progenitors, may be useful when applied during the latent period (or silent phase after acute seizures), at the commencement of spontaneous seizures or after the establishment of chronic epilepsy. Interventional strategies such as antiepileptic drug therapy are likely useful at all of the above time-time points as well as immediately after the onset of acute seizures.