Hippocampal neurogenesis and neural stem cells in temporal lobe epilepsy

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1. Introduction

Epilepsy, characterized by periodic and unpredictable occurrences 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 such as status epilepticus (SE), brain injury, tumors, meningitis, encephalitis, and febrile seizures during childhood in other cases [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, learning and memory impairments, depression, substantial neurodegeneration in the dentate hilus and CA1–CA3 subfields, and aberrant synaptic reorganization [10–16].

Abnormal hippocampal neurogenesis has emerged as another important pathophysiology of TLE over the past decade [17–23]. Neurogenesis is a process of generation of new neurons in the central nervous system through division of neural stem cells (NSCs) and neuronal differentiation of newly born cells. Although most neurogenesis occurs during 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 the hippocampus in maintaining normal learning and memory function as well as its dysfunction in diseases such as TLE, Alzheimer 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, and 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 an 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.

2. 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]. Fig. 1 illustrates a schematic of various 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 the question whether 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 of age) suggested increased cell proliferation [55]. Furthermore, epileptic hippocampus from young children (<4 years of age) 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.

2.1. 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 probably 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 postseizure period positively influence neurogenesis, as studies show that GABA has crucial roles in regulating various 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 enhance 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.
2.2. 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 and demonstrate that aberrantly migrated newly born granule cells extend molecular layer [11,17–21,72,75–81]. Further investigations of newly born granule cells into 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 circuity development, which likely contributes to the evolution of initial-seizure-induced hippocampal injury into chronic epilepsy.

2.3. 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 evidence proposes 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 postmitotic 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 (probably owing 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.

2.4. 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 circuity. A recent study by Waller 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 1 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 probably facilitates formation of a 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.

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

As acute-seizure-induced abnormal DG neurogenesis promotes aberrant circuity development and probably 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-β-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 are 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 1 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 the 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 depolylysialation 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 depoly sacylation 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, 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 depoly sacylation 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.

3. Response of hippocampal neurogenesis to chronic spontaneous seizures

3.1. 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 an increased number of spontaneous seizures. Additional evaluation using pulsed injections of 5'-bromodeoxyuridine 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 those 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 in which 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 1 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 the 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 these findings, it emerges that decreased levels of hippocampal neurogenesis in chronic epilepsy depend on the model and the age of the animal at the time of the initial seizure episode. Adult animals seem to be vulnerable to an almost complete loss of neurogenesis in the chronic phase after the initial seizure episode.

3.2. 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 nonavailability of hippocampal tissues at different stages of epilepsy and apt age-matched control samples and a lack of apt markers that detect neurogenesis. Mathern et al. [104] demonstrated a decreased density of cells positive for PSA–NCAM (a putative marker of newly born neurons) in the DG of children exhibiting frequent spontaneous seizures compared to 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 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.

3.3. 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 an adverse hippocampal milieu for neurogenesis from NSCs and decreased numbers of NSCs. While an 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 study on humans suggests an increased number of putative NSCs positive for Musashi-1 in chronic TLE [106]. Furthermore, a recent study reports only moderate decreases in the 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], probably owing to an unfavorable hippocampal milieu as discussed above. Increased concentration of
the 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].

3.4. 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 prevalent 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 is likely to contribute to impairments in hippocampal-dependent learning and memory functions observed in TLE. This notion is also supported by the finding that 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 the effective action of antidepressants [117–121], diminished addition of new granule cells into the GCL perhaps plays a role in depressive-like behavior prevalent 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.

3.5. 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. Fig. 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 an enriched environment for increasing neurogenesis in chronic epilepsy are very appealing because these approaches are noninvasive 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 patients with epilepsy 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 (CREB), that promote neurogenesis and reducing cognitive function [102,138–141]. Regarding exposure to enrichment, studies demonstrate that environmental enrichment of rats prior to kainic acid 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 reducing cognitive impairments, as antidepressant treatments enhance DG neurogenesis [117–121] probably via increases in the concentrations of serotonin, norepinephrine, CREB, and multiple neurotrophic factors [147–150]. Because decreased neurogenesis, cognitive impairments, and depression coexist 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.

3.6. 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 toward 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 migrate 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 for the future.

4. 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 occur. Studies on hippocampal tissues from pediatric patients in the early phase of TLE support these findings. However, the relative contribution of this aberrant circuitry to 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-in-
duced 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 of 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 the persistence of seizures, learning and memory dysfunction, and depression observed in chronic epilepsy. Considering these, the development of strategies that enhance hippocampal neurogenesis, such as administration of distinct neurotrophic factors, physical exercise, exposure to an enriched environment, antidepressant therapy, and grafting of NSCs, is 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.

Conflict of Interest

The author has no conflict of interests to report that would influence the content of this paper.

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