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Relevance of Seizure-Induced Neurogenesis in Animal Models of Epilepsy to the Etiology of Temporal Lobe Epilepsy

Helen E. Scharfman[*,†] and **William P. Gray**[‡]

[*]*Center for Neural Recovery and Rehabilitation Research, Helen Hayes Hospital, New York State Department of Health, West Haverstraw, New York, U.S.A.*

†*Departments of Pharmacology and Neurology, Columbia University, New York, New York, U.S.A.*

‡*Division of Clinical Neurosciences, University of Southampton, Southampton, United Kingdom*

Summary

Seizure induction in laboratory animals is followed by many changes in structure and function, and one of these is an increase in neurogenesis—the birth of new neurons. This phenomenon may be relevant to temporal lobe epilepsy (TLE), because one of the regions of the brain where seizure-induced neurogenesis is most robust is the dentate gyrus—an area of the brain that has been implicated in the pathophysiology of TLE. Although initial studies predicted that neurogenesis in the dentate gyrus would be important to normal functions, such as learning and memory, the new neurons that are born after seizures may not necessarily promote normal function. There appears to be a complex functional and structural relationship between the new dentate gyrus neurons and preexisting cells, both in the animal models of TLE and in tissue resected from patients with intractable TLE. These studies provide new insights into the mechanisms of TLE, and suggest novel strategies for intervention that could be used to prevent or treat TLE.

Keywords

Dentate gyrus; Granule cell; Hilus; Status epilepticus; Ectopic; Epileptogenesis

Although there has been experimental evidence that neurogenesis occurs in the adult mammalian brain for many decades (Altman 1962; Altman and Das, 1965), the concept has become widely accepted only after more recent studies were conducted using the thymidine analog bromodeoxyuridine BrdU; (Christie and Cameron, 2006; Gage 2002). BrdU is incorporated into DNA during synthesis in the S-phase of the cell cycle, allowing the identification of cells within the cell cycle or their postmitotic progeny, depending on the elapsed time between BrdU administration and cell fixation for immunohistochemical detection. These studies, which were mostly conducted in laboratory rats or mice, appear to also apply to man, because in humans that had been administered BrdU, there was evidence of ongoing neurogenesis, even at age 72 (Eriksson et al., 1998). As a result, a great deal of interest developed in the possible use of neurogenesis from a clinical perspective. For example, it was suggested that neurogenesis might be able to “repair” neuronal loss that occurs slowly during the natural aging process. In addition, there has been considerable interest in treatments that might increase the rate of neurogenesis to compensate for the loss of neurons after traumatic brain injury (Kozorovitskiy and Gould, 2003; Lie et al., 2004). In the context of epilepsy, new

Address correspondence and reprint requests to Helen E. Scharfman, Center for Neural Recovery and Rehabilitation Research, Helen Hayes Hospital, New York State Department of Health, West Haverstraw, New York 10993–1195, U.S.A. E-mail: scharfmanh@helenhayeshopsp.org.

neurons could conceivably reverse neuronal loss due to seizure-related neuronal death. However, as will become clear below, the concept that newly born neurons in the adult brain may reverse the pathology in temporal lobe epilepsy (TLE) appears to be much more complicated than initially anticipated (Parent and Lowenstein, 2002; Scharfman 2004; Shapiro and Ribak, 2005).

In this review, we will initially provide a brief discussion of some of the fundamental aspects of neurogenesis in the adult brain, and then discuss seizure-induced neurogenesis. Next, the ability of these studies to help explain the etiology of TLE will be considered. Data from animal models of epilepsy and tissue specimens of patients with pharmacologically intractable TLE will be compared.

DENTATE GYRUS NEUROGENESIS IN LABORATORY ANIMALS: THE CURRENT PERSPECTIVE

Initially, it was agreed that neurogenesis in the adult brain largely occurs in three areas: the subventricular zone, the olfactory bulb, and the dentate gyrus. Many now would agree that adult neurogenesis can occur at other sites, such as the striatum (Parent et al., 2002; Dayer et al., 2005). In addition, although the present review focuses on neurons, it is important to consider proliferation of other types of cells, such as glia. Gliogenesis is particularly important to any discussion of epilepsy, where changes in astrocytes and microglia have long been considered a piece of the etiological puzzle.

The focus of this review in the dentate gyrus is neurogenesis, because the dentate gyrus is the primary site in the temporal lobe where the majority of neurogenesis is thought to occur in the normal adult brain, and the temporal lobe is key in TLE. In the rat, neurogenesis occurs in a zone that lies within the first 50–100 μm of the granule cell layer, the subgranular zone (SGZ), and new neurons are thought to derive from radial glia which in turn divide into so-called D cells that ultimately become dentate gyrus granule cells (Seri et al., 2004). In addition to the granule cell fate, other fates are possible, because progenitors can differentiate into glia and GABAergic neurons (Dayer et al., 2005). However, these fates appear to be relatively rare compared to the proportion of cells that become granule cells. It should be noted that the extent to which the rodent data can be generalized to man is unclear, and direct correspondence should not be assumed.

The newly born granule cells have been studied extensively. They rapidly send axon projections to their normal target zone, the mossy fiber pathway (Hastings and Gould, 1999; Markakis and Gage, 1999). Their dendritic trees resemble other granule cells, although some aspects of their dendrites and spines have been suggested to be immature (Toni et al., 2004; Pierce et al., 2005), particularly if they develop in an aged animal (Rao et al., 2005). In addition, they appear to develop electrophysiological properties like other granule cells (van Praag et al., 2002). The demonstration of functional integration of newly born dentate granule cells into hippocampal circuitry (Scharfman et al., 2000; van Praag et al., 2002; Jessberger and Kempermann, 2003) and the fact that they appear to mediate long-term potentiation (LTP) in the dentate gyrus (Schmidt-Hieber et al., 2004), has led to the hypothesis that adult neurogenesis may be important in learning and memory (Gould, 1999; Snyder et al., 2001; Shors, 2004).

MODULATION OF DENTATE GYRUS NEUROGENESIS BY NEURONAL ACTIVITY AND SEIZURES

One characteristic of adult neurogenesis in rodents that has important translational implications is that the rate of proliferation is modifiable, both by environmental cues and pathological conditions. Neuronal activity exerts a strong influence on proliferation rate. As first shown by

Bengzon and colleagues (Bengzon et al., 1997), neuronal depolarization or repetitive discharge —induced either by electrical or pharmacological stimulation—increases the rate of neurogenesis in the dentate gyrus. There are only a few exceptions, such as the increase in neurogenesis that follows NMDA receptor blockade (Nacher et al., 2001) using MK-801, a noncompetitive antagonist of NMDA receptors, or CGP 43487, a competitive antagonist. Depletion of norepinephrine, which would decrease the likelihood of norepinephrine-mediated, dentate granule cell potentiation (Harley, 1991), also increases neurogenesis (Kulkarni et al., 2002).

Given that the majority of studies show that increased neuronal activity increases neurogenesis in the dentate gyrus, it is not surprising that seizure activity also increases neurogenesis. Bengzon et al. (1997) demonstrated this initially using a single afterdischarge, and subsequent studies showed that virtually all methods of seizure induction led to increased neurogenesis.

For example, status epilepticus initiated by administration of the chemoconvulsant pilocarpine intraperitoneally (Parent et al., 1997) or unilateral kainic acid intracerebroventricularly (Gray and Sundstrom, 1998) led to a bilateral increase in neurogenesis. Amygdala kindling (Parent et al., 1998; Scott et al., 1998) is another example of seizure induction in rodents that increases neurogenesis. Electroconvulsive shock also increases neurogenesis in rodents (Madsen et al., 2000; Scott et al., 2000). Subsequent studies have provided further support of these initial investigations (Covolan et al., 2000; Nakagawa et al., 2000; Ferland et al., 2002; Jiang et al., 2003).

The mechanism of the increased cell proliferation after seizures is largely unknown, although 5HT-1_A (Radley and Jacobs, 2003; Zucchini et al., 2005) and galanin type 2 receptors appear important (Mazarati, 2004). Furthermore, neuropeptide Y (NPY) via its Y1 receptor (Howell et al., 2005), and fibroblast growth factor 2 (FGF-2) (Yoshimura, 2001) may contribute. Sonic hedgehog (Shh) signaling has also been implicated in seizure-induced progenitor proliferation (Banerjee, 2005).

A role for seizure-induced injury in stimulating proliferation is suggested by studies in culture, which show that kainic acid-induced injury precedes the increase in proliferation (Sadgrove et al., 2005). However, events associated with seizure-induced damage, such as up-regulation of neurotrophins, could be more important than damage per se (Hagihara, 2005; Scharfman et al., 2005). Besides neurotrophins, cysteine protease cystatin C, which is expressed on astrocytes and microglia after status epilepticus, may play a role in seizure-induced increase in neurogenesis (Pirttila, 2005). An argument against a fundamental role of seizure-induced cell death is the fact that a proliferative progenitor response to seizures can occur independent of cell death (Smith, 2005).

Seizures may exert their effect by facilitating certain steps during progenitor differentiation. In other words, do seizures stimulate the transition from Type 1 (GFAP-immunoreactive, radial glia-like cells) to Type 2a or Type 3 (doublecortin-immunoreactive)? Interestingly, after NMDA receptor antagonism, which increases neurogenesis, there is an increase in radial glia-like (Type 1) cells (Nacher et al., 2001). To address this question, Huttman et al. (2003) examined Type 1 cells using transgenic FVB/n mice expressing GFP in cells with the GFAP promoter. They found a greater number of Type 1 cells in the SGZ at a time after kainic acid-induced status epilepticus when neurogenesis is likely to be maximal (72 h). This result suggested a greater proportion of proliferating Type 1 cells (Huttmann et al., 2003). An increase in the number of proliferating astrocytes with radial glia-like features has also been reported seven days after kainic acid-induced status, based on expression for ribonucleotide reductase, an endogenously expressed cytoplasmic marker of cell proliferation (Zhu et al., 2005). Interestingly, this study also found that the number of clusters of proliferating cells in the SGZ

increased after seizures, but GFAP expression in each cluster was unchanged, suggesting that more Type 1 cells were recruited into the cell cycle after seizures.

Jessberger et al. (Jessberger et al., 2005) examined Type 3 cells (doublecortin immunoreactive) after kainic acid-induced status and found that status stimulated division. They did not find evidence of increased numbers of Type 1 cells, but they evaluated animals nine days after status, a time when some could have differentiated. Therefore, there is evidence that seizures can influence the proliferation of both primitive GFAP-expressing precursors and more committed neuronal-like precursors.

Seizures also modify the survival of new neurons (Ekdahl et al., 2001). The severity of seizures appears to play an important role, with more severe seizures decreasing survival of new neurons (Mohapel et al., 2004; Scott and Burnham, 2004). However, the spontaneous seizures that follow status epilepticus do not appear to influence survival (Scharfman et al., 2000; Ekdahl et al., 2003; McCloskey et al., 2006). It is important to consider that the net increase in granule cells is not only a function of the number of surviving new neurons, but it also depends on the numbers of mature neurons that may die due to seizure-induced apoptosis. Although granule cells are relatively resistant to seizure-induced death, it has been shown that granule cells die by apoptosis after seizures in laboratory animals (Sloviter et al., 1996; Bengzon et al., 2002), and granule cell loss is evident in severely sclerotic tissue from individuals with intractable TLE (for review, see Scharfman and Pedley, 2006). Seizures also may have other effects on new neurons that complement their ability to increase the rate of proliferation. This possibility is raised by a recent study showing that the granule cells born in mice after severe seizure are able to more rapidly develop dendrites and other structural features of mature granule cells (Overstreet-Wadiche et al., 2006). They also appear to integrate more readily into the circuitry of the dentate gyrus (Overstreet-Wadiche et al., 2006). These data suggest that, in addition to the previous demonstration that seizures increase the rate of dentate gyrus neurogenesis, seizures also facilitate the maturation and assimilation of new cells into the hippocampus. Based on these results, one might conclude that seizures are one of the most robust means to increase functional, mature dentate granule cells in the adult brain.

SEIZURE-INDUCED NEUROGENESIS AND ITS RELEVANCE TO ANIMAL MODELS OF EPILEPSY

Although an intriguing phenomenon, and striking in its robust nature, the significance of seizure-induced neurogenesis to TLE has remained elusive. Is it relevant to epileptogenesis in TLE? Is it relevant to other aspects of TLE? Or might it simply be one of many phenomenons that have been reported in animal models of epilepsy for which there is no critical role?

In vivo studies

Arguments against a role of seizure-induced neurogenesis in epileptogenesis are based on studies which demonstrate that the newly born neurons do not necessarily survive for long periods of time (Bengzon et al., 2002; Mohapel et al., 2004). If the neurons do not live for long periods of time, it would seem unlikely that they could be influential. However, a transient population of new cells could be important (Fig. 1). Furthermore, some newly born cells can survive for long periods of time. This may depend on the severity of the initial seizures used to stimulate proliferation. The reason for this suggestion is based on studies of seizure severity (Mohapel et al., 2004), and also the fact that long survival was described in a study that truncated status severely (Scharfman et al., 2000).

Other studies have also suggested that seizure-induced neurogenesis may not have a profound influence on chronic epilepsy. Using pilocarpine to initiate status and subsequent recurrent

seizures, Parent et al. (1999) administered radiation during the days immediately after status, when neurogenesis normally increases greatly. They found that animals still developed spontaneous seizures, suggesting that a reduction in neurogenesis could not prevent all seizures that developed in this animal model. However, it might have reduced seizures, a question that was unanswered because it was not the focus of the study. Indeed, the answer would have required rigorous seizure quantification.

A second study provided strong evidence that seizure-induced neurogenesis can influence chronic seizures in animal models. This study used i.c.v. infusion of the mitotic inhibitor arabinoside-C to reduce neurogenesis, and quantified both neurogenesis and seizures. They showed that reduction of new neurons after lithium-pilocarpine-induced status epilepticus was associated with a reduction in chronic seizure frequency (Jung et al., 2004). A caveat was that arabinoside-C influenced glia in area CA1, so factors besides reduced neurogenesis may be why seizure frequency declined. A selective means to ablate newly born neurons after seizures would be extremely valuable to evaluate their functional role.

In vitro studies

Experiments in vitro support the hypothesis that seizure-induced neurogenesis may contribute to increased excitability in animals that have had status followed by chronic seizures. These data were initially surprising because they did not support the prevailing view at the time, that new neurons in the adult brain would benefit CNS function.

The data were based on the new neurons that develop in the hilus, the region outside the granule cell layer that lies between the dentate gyrus and area CA3 (for review, see Scharfman, 1999). These cells are commonly termed “ectopic” granule cells because of their location outside the layer (Parent et al., 1997; Dashtipour et al., 2001; Scharfman et al., 2000). After pilocarpine-induced status epilepticus, it was found that a substantial population of new granule cells develop in this location (Parent et al., 1997; Scharfman et al., 2000).

The very fact that a large population of abnormally situated granule cells develops after status epilepticus in laboratory animals indicates that seizures, or seizure-induced neurogenesis, may lead to disorganization of the dentate gyrus, a potential problem for normal information processing in the hippocampal formation. This can be appreciated simply by the axonal projection of the new hilar granule cells, which projects both to area CA3, like a normal granule cell, and to the inner molecular layer (Scharfman et al., 2000). It is also supported by ultrastructural studies showing increased excitatory afferent input to ectopic granule cells in the hilus (Dashtipour et al., 2001; Pierce et al., 2005). Furthermore, physiological recordings in hippocampal slices showed that the ectopic granule cells discharged spontaneous bursts of action potentials, which is unusual for granule cells (Scharfman et al., 2000). The spontaneous discharges were synchronized with area CA3 pyramidal cell population discharges, suggesting that the activity was abnormal (Scharfman et al., 2000). Epileptiform burst discharges are not normally recorded in granule cells that are located in the granule cell layer, even after exposure to convulsants (Scharfman, 1994). The network burst discharges could play a role in the recurrent seizures that occur in these animals, because each burst could activate target neurons in CA1, the contralateral hippocampus, and ultimately the cortex. These discharges could also reverberate in the dentate-CA3 network because the ectopic cells have axon projections that contribute to the network of mossy fiber axons which sprout into the inner molecular layer (Scharfman et al., 2000). However, potential for the new neurons to innervate GABAergic neurons, or for the new neurons to express GABA like other “epileptic” granule cells (Gutierrez, 2005), remain unclear, and could dampen excitability.

In light of the possibility that the new granule neurons could influence the dentate gyrus and area CA3, it is important to consider the evidence that the abnormal network of ectopic granule

cells could contribute to seizure activity in the pilocarpine animal model. To date, this question has not been fully addressed. However, it is known that after a spontaneous seizure in this animal model of epilepsy, c-fos is expressed in the ectopic granule cells, suggesting that at the very least, they are activated during a spontaneous seizure (Scharfman et al., 2001). In addition, quantification of the number of ectopic granule cells is correlated with seizure frequency (McCloskey et al., 2006). When this population is reduced, seizure frequency is also reduced (Jung et al., 2004). The similarity in the time to maturity of new ectopic neurons and the time to spontaneous seizures is suggestive, but not definitive proof that the maturation of new cells contributes to spontaneous seizures. Therefore, an increase in ectopic granule cells after status could contribute to epileptogenesis (Fig. 2). Epileptogenesis after status epilepticus may not only be due to factors associated with seizure-induced damage, but also seizure-induced cell birth.

SEIZURE-INDUCED NEUROGENESIS AND ITS RELEVANCE TO TLE

What is the evidence that seizure-induced neurogenesis of ectopic granule cells is relevant to patients with TLE? In addition, how do the new granule cells that develop in the correct location, that is, the granule cell layer, possibly contribute to TLE pathophysiology?

Neurogenesis in the granule cell layer

Regarding the new granule cells that develop in the granule cell layer after seizures, that is, normally positioned granule cells, initial studies suggested a discordance between the data in laboratory animals and TLE. Thus, in studies of tissue resected from patients with intractable TLE, Blümcke and colleagues found little evidence of newly born granule cells in the granule cell layer (Blümcke et al., 2001). They reported that in pediatric cases less than 2 years old, evidence was present, but supportive data were sparse in older patients. A more recent study of tissue resected from patients with pharmacologically resistant TLE provided substantial evidence for progenitor cells, but similar to the findings of Blumcke and colleagues; there was no strong evidence that the progenitors ultimately became neurons. This conclusion was based on the lack of coexpression of markers of progenitors with antibodies to NeuN, a neuronal nuclear antigen found in all adult neurons (Crespel et al., 2005). Instead, the progenitors expressed markers of a glial phenotype, such as nestin, and vimentin (Blümcke et al., 2001; Crespel et al., 2005). Other studies of tissue specimens from patients with intractable TLE showed that there was decreased expression of cell markers that reflect immature neurons (Mathern et al., 2002). These data are consistent with studies discussed above, that few immature neurons exist in the individuals with TLE that come to surgery. They are also consistent with the animal studies showing that the most severe cases are associated with new neurons that do not survive for long periods of time (Mohapel et al., 2004). However, at some point in the course of TLE, neurogenesis is likely to be increased, based on the evidence of new granule cells in a recent study (Parent et al., 2006).

The different reports from studies of TLE may be due to the difference in the severity of the epilepsy as discussed above, or other factors. The age of the patient at the onset of epilepsy or epileptogenesis may play a role, because studies in rodents show that seizures during development lead to a different outcome relative to seizures during adulthood (Sankar et al., 2000; McCabe et al., 2001; Cha et al., 2004; Porter et al., 2004). There are also technical issues that can lead to different conclusions about neurogenesis in TLE: markers of an immature neuron vary in the duration of their expression, potentially causing distinct interpretations about the extent of proliferation.

Granule cell dispersion and seizure induced neurogenesis

Houser (1990) described a dispersed appearance of the granule cell layer characterized by an irregular widening of the granule cell layer. Fifty percent of patients with hippocampal sclerosis have a dispersed granule cell layer (Lurton et al., 1998). Clinically, there is a strong correlation between granule cell dispersion and a history of seizures in the first four years of life (Houser, 1990; Lurton et al., 1998). Complicated or prolonged febrile convulsions appear to be particularly associated with granule cell dispersion, while simple febrile convulsions are not (Lurton et al., 1998). Animal studies also support the observation that granule cell dispersion is associated with an initial, severe period of status epilepticus (Suzuki et al., 1995; Bouilleret et al., 1999). While dispersion of the granule cell layer has been hypothesized to be due to an initial excessive production of new neurons with later pruning, new evidence suggests it is not the case. Indeed, reelin deficiency and displacement of mature neurons, rather than neurogenesis, underlies granule cell dispersion in the epileptic hippocampus, as recently demonstrated by Heinrich et al. (2006).

Ectopic granule cells

There is some support that the ectopic location of granule cells increases in patients with TLE. For example, Houser et al. discussed that some granule cells were present in the hilus in tissue showing granule cell dispersion (Houser, 1990). Other studies of tissue resected from patients with intractable TLE demonstrated granule-like cells in the hilus (Sloviter et al., 1991; Thom, 2002). The evidence that they were granule cells was based on their similar morphology to granule cells, and their expression of calbindin. Importantly, more recent studies using a granule cell-specific marker have shown that ectopic granule cells exist in patients with intractable TLE (Parent et al., 2006).

It is important to point out that some studies do not detect ectopic granule cells in tissue from patients with intractable TLE. This could be due to the fact that they are not always present. Alternatively, they may not exist in subsets of TLE with severe hippocampal damage, when hilar neurons of all kinds are lost. Patients without severe sclerosis may contain more ectopic granule cells. Indeed, it would be interesting to study those patients, so that more comprehensive understanding of ectopic granule cells in all patients with TLE could be obtained.

Even in those tissue samples that have been examined, however, it is possible that the ectopic cells are underestimated. This is because multiple markers for these cells are not always used. This is true for studies of progenitors in the hilus, as well as hilar ectopic granule cells. For example, NG2-immunoreactive progenitors that exist in the hilus in some patients with intractable TLE have recently been identified (Sosunov et al., 2003); previous studies had not examined NG2 immunoreactivity.

Another reason why ectopic granule cells may be underestimated is that patients with a long period of chronic seizures prior to surgery, or a long history of antiepileptic (AED) therapy, may have reduced numbers of ectopic granule cells relative to those that are more rapidly recommended for surgical resection. This may occur because the more severe seizures damage the cells (Mohapel et al., 2004). Little is known about the effects of AEDs on dentate gyrus neurogenesis, although it has been shown that chronic treatment with valproate increased neurogenesis in the normal rodent dentate gyrus (Hao et al., 2004). Thus, tissue from patients with TLE for many decades may not show evidence of hilar progenitors or ectopic hilar granule cells, because the cells had developed at initial stages of the disease, but did not survive.

If this is the case, how could these cells be important to epileptogenesis, or epilepsy? It could be that they initially were born early in the process of epileptogenesis, and stimulated abnormal

circuits to develop (Fig. 1). After the abnormal circuits developed, increased excitability could persist even if the ectopic granule cells died, assuming that the new circuits became independent of ectopic granule cells.

Reduced neurogenesis after chronic seizures as a mediator of cognitive dysfunction

Given the emerging role of adult neurogenesis in hippocampal-dependent learning and behaviour (Shors, 2004; Aimone et al., 2006; Dranovsky and Hen, 2006), changes in neurogenesis in chronic epilepsy may alter cognitive function and mood because it changes the production and/or integration of newly born neurons within the dentate gyrus. Central to this hypothesis has been the work of Hattiangady and colleagues (2004), who demonstrated that dentate gyrus neurogenesis initially rose after status epilepticus, and then declined in subsequent months, during the time of recurrent seizures. Interestingly, neurogenesis in the dispersed dentate gyrus has also been reported to be significantly reduced (Kralic et al., 2005). The cause of reduced neurogenesis is unknown, but may reflect disruption of the SGZ, and appears to also occur in patients with chronic epilepsy (Mathern et al., 2002; Crespel et al., 2005). It is tempting to suggest that a chronic reduction in neurogenesis may lead to cognitive dysfunction and depression in patients with TLE.

SUMMARY AND PERSPECTIVE

A substantial body of evidence now exists which demonstrates that seizures increase the rate of dentate gyrus neurogenesis in adult rodents. The consequences for our understanding of epileptogeneis and chronic epilepsy remain to be fully elucidated, but some surprising suggestions have been made already. For example, hilar ectopic granule cells develop after severe seizures, and appear to contribute to epileptogenesis rather than resolve it by replacing damaged hilar neurons. Furthermore, although there appears to be an initial surge in neurogenesis after an initial period of seizures in normal animals, chronic recurrent seizures may not be as influential, and indeed are associated with the opposite—reduced neurogenesis. These findings from animal models have been echoed by studies of tissue from patients with intractable TLE, because there is little evidence for ongoing, increased proliferation, yet there are abnormally situated neurons that could reflect abnormal development of new neurons in the history of the patient.

How to use our growing understanding of dentate gyrus neurogenesis in epilepsy for therapeutic benefit is an important question. From studies to date, one would predict that interventions early in the process of epileptogenesis that would reduce new ectopic granule cells would impede the development of recurrent seizures. In contrast, after epileptogenesis has occurred, that is, patients develop chronic seizures, the opposite type of intervention might be beneficial: enhancing neurogenesis might ameliorate cognitive dysfunction and depressive symptoms. Although these clinical possibilities are attractive, it is important to recognize that the effect of such interventions are difficult to predict in the epileptic brain, where multiple seizure-induced changes develop in addition to altered neurogenesis (Scharfman and Pedley, 2006; Scharfman and Schwarcz, in press). Therefore, a greater understanding of seizure-induced neurogenesis will be required before its therapeutic potential can be fulfilled.

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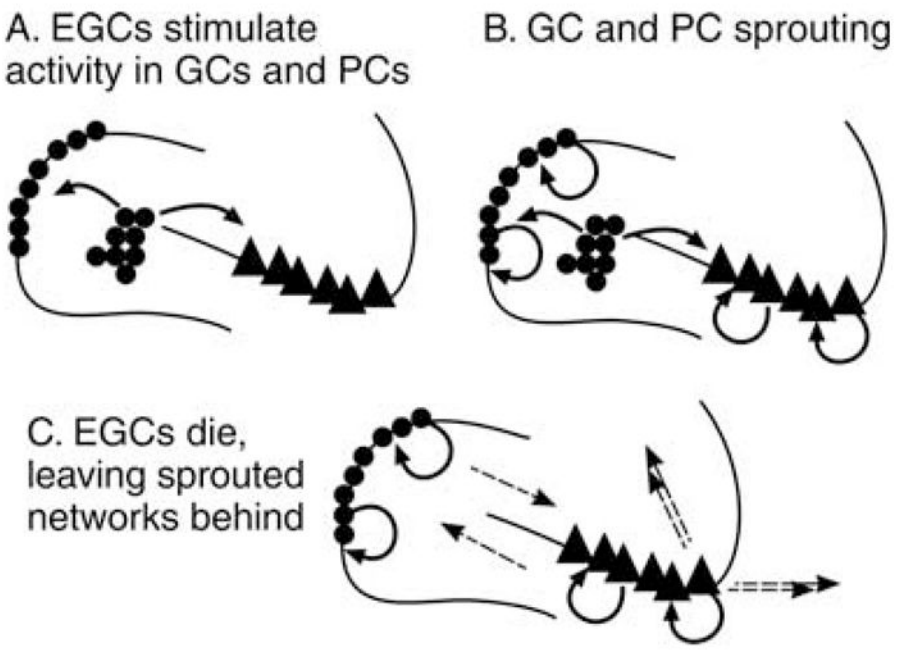

FIG. 1.

An illustration of the ways that neurogenesis, and ectopic granule cells (EGCs) could contribute to persistent changes in the circuitry of the hippocampus, even if the ectopic cells did not persist. **(A)** The initial step would be the formation of ectopic granule cells. It is hypothesized that their development would stimulate new circuits to form among neighboring neurons, for example, the granule cells and the CA3 pyramidal cells. In addition, non-principal cells might be involved in these circuits (not shown). **(B)** Some of the new circuits that form could be recurrent excitatory circuits among granule cells (mossy fiber sprouting) or strengthening of the recurrent collaterals among pyramidal cells. These may not all include ectopic granule cells. **(C)** If ectopic granule cells die, the recurrent excitatory circuits that are independent of them may be unaffected by their loss, and interact by preexisting interconnections (dotted lines) which could lead to an influence on downstream targets (double dotted lines).

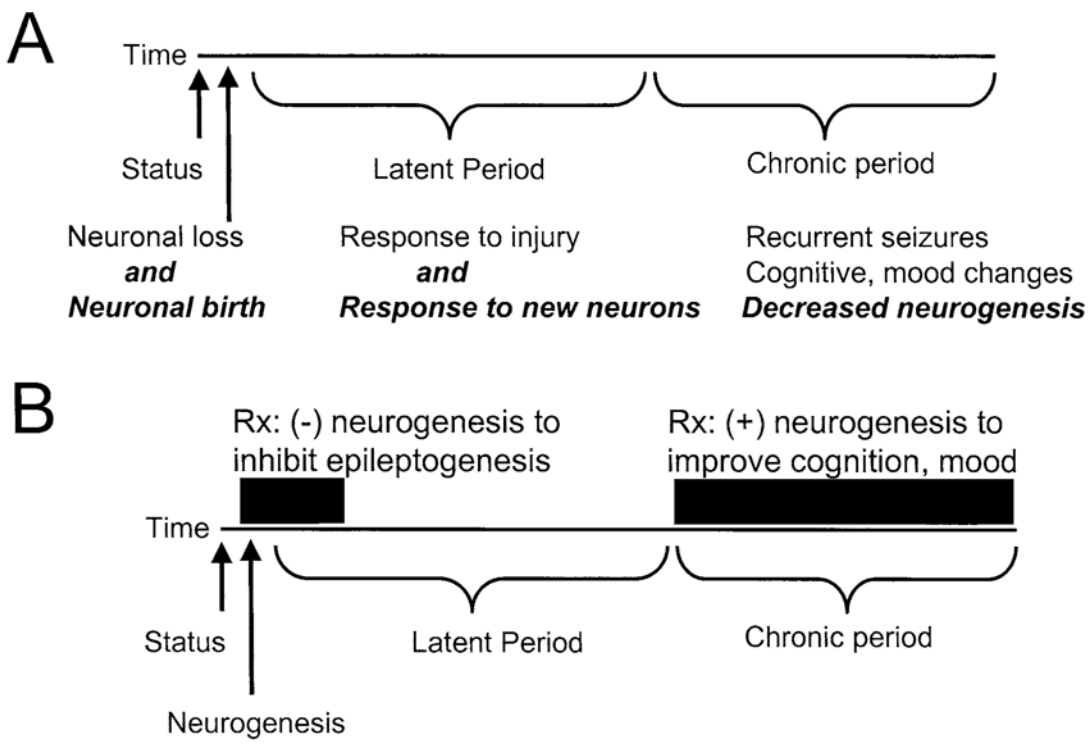

FIG. 2.

A schematic illustrating the ways that seizure-induced neurogenesis may influence epileptogenesis in TLE, and potential for therapeutic intervention. **(A)** A theoretical timeline is shown to reflect the hypothesis that TLE is due to an initial precipitating event, a latent period, and a subsequent chronic state of recurrent seizures. The timeline begins when an initial precipitating insult occurs, such as status epilepticus. It is suggested that status-induced neuronal damage, as well as the increase in neurogenesis following status (italicized text), contributes to epileptogenesis. Reduced neurogenesis in the chronic period may contribute to cognitive changes, which are common in TLE, and animal models of TLE. **(B)** The same timeline is used to suggest therapeutic intervention, which would potentially impede epileptogenesis if neurogenesis were inhibited initially. Increasing neurogenesis during the chronic period might be used to alleviate cognitive dysfunction and depression.