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REVIEW

Postnatal neurogenesis as a therapeutic target in temporal lobe epilepsy

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Summary   After it was first identified that seizures increase neurogenesis in the adult brain of laboratory animals, the idea that postnatal neurogenesis may be involved in epilepsy became a topic of widespread interest. Since that time, two perspectives have developed. They primarily address temporal lobe epilepsy (TLE), because the data have either been based on animal models of TLE or patients with intractable TLE. The first perspective is that postnatal neurogenesis contributes to the predisposition for seizures in TLE. This premise is founded in the observations showing that there is a dramatic rise in neurogenesis after many types of insults or injuries which ultimately lead to TLE. As a result of the increase in neurogenesis, several changes in the dentate gyrus occur, and the net effect appears to be an increase in excitability. One of the changes is the formation of a population of granule cells (GCs) that mismigrate, leading to ectopic granule cells in the hilus (hilar EGCs) that exhibit periodic bursts of action potentials, and contribute to recurrent excitatory circuitry. Atypical dendrites also form on a subset of GCs, and project into the hilus (hilar basal dendrites). Hilar basal dendrites appear to preferentially increase the glutamatergic input relative to GABAergic synapses, increasing excitability of the subset of GCs that form hilar basal dendrites. The alternate view is that postnatal neurogenesis is a homeostatic mechanism in epilepsy that maintains normal excitability. This idea is supported by studies showing that some of the new GCs that are born after seizures, and migrate into the correct location, have normal or reduced excitability.

Here we suggest that both perspectives may be important when considering a therapeutic strategy. It would seem advantageous to limit the numbers of mismigrating GCs and hilar basal

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dendrites, but maintain normal neurogenesis because it is potentially homeostatic. Maintaining normal neurogenesis is also important because it has been suggested that a decrease in dentate gyrus neurogenesis contributes to depression. It is challenging to design a strategy that would achieve these goals, and it is also difficult to propose how one could administer such a therapy prophylactically, that is, as an ''antiepileptogenic'' approach. Another issue to address is how a therapeutic intervention with these goals could be successful if it were administered after chronic seizures develop, when most patients seek therapy. Although difficult, a number of approaches are possible, and technical advances suggest that there are more on the horizon.

Contents

Background

Postnatal neurogenesis

It is now widely accepted that neurogenesis occurs throughout the lifetime of mammals (Gage et al., 2008). The two places where this is best established include the dentate gyrus subgranular zone (SGZ; Fig. 1) and the subventricular zone (SVZ), adjacent to the ventricular walls (Gage et al., 2008). Here we focus on the dentate gyrus primarily, because a substantial body of research about neurogenesis in epilepsy has focused on dentate gyrus neurogenesis. Temporal lobe epilepsy (TLE) is emphasized, because pathophysiology in the dentate gyrus is most relevant to this type of epilepsy. However, other types of epilepsy may also be important to consider, because it is possible that pathology in the dentate gyrus, or its effects on downstream targets (the hippocampus and elsewhere) contribute to other types of seizure syndromes. It is also important to bear in mind that the SVZ appears to generate cells that migrate into diverse parts of the brain, beyond the site of termination that is considered to be the main target, the olfactory bulb (Shapiro et al., 2009). Because of the potential for the SVZ to generate cells that migrate to diverse locations, it is possible

that many types of epilepsy are influenced by the postnatal neurogenesis in the SVZ. Another consideration is that some types of neurons may be generated by cells outside the SGZ and SVZ. A recent report suggested that oligodendrocyte precursors that express NG2 (NG2 cells) in the piriform cortex may become cortical neurons (Rivers, 2008), which is potentially important in epilepsy, because the piriform cortex is an area which is epileptogenic, and sustains injury in animal models of epilepsy (Gale, 1992; Loscher and Ebert, 1996; McIntyre and Gilby, 2008).

In the postnatal dentate gyrus, the majority of progenitors reside in the SGZ, which is situated just below the granule cell layer (GCL), at the border with the hilus (Fig. 2). Early progenitors are radial glia-like type 1 cells, which can be identified by expression of the astrocytic marker glial-fibrillary acid protein (GFAP), nestin or other markers (Fig. 2). Although classification into type 1a cells, type 2a cells, type 2b cells, and type 3 cells, implies a sequential maturation in this order, it has not been proven definitively. However, it is clear that the progenitors typically commit to a neuronal fate and become GCs. Thus, under normal conditions, migrating GCs move into the GCL, where it is thought that they initially reside within the ''inner'' third of the layer, close to the hilus, before moving to the center and outer parts of the layer (Gage et al., 2008; Ge et al., 2008;
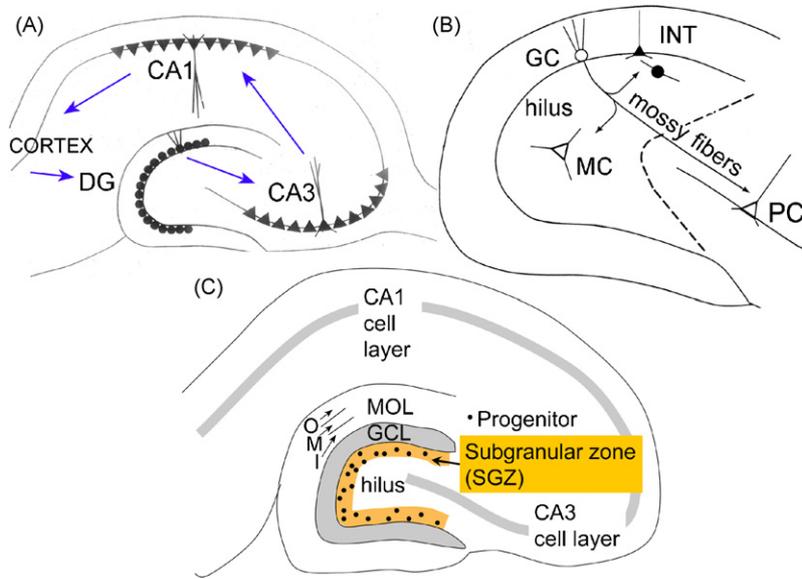
Figure 1   Postnatal neurogenesis in the hippocampus. (A) A schematic of the hippocampus of the rodent in cross section showing the subfields (CA1, CA3, and dentate gyrus), and the major glutamatergic pathways (the trisynaptic circuit; blue arrows). (B) A schematic of the dentate gyrus illustrating major subtypes and the major output of GCs, the mossy fiber pathway. INT = GABAergic neuron; MC = mossy cell. The dotted line demarcates the border between the hilus and the CA3 subfield. (C) A schematic showing the location of the subgranular zone (SGZ; orange), where most progenitors are thought to reside in the adult dentate gyrus. MOL = molecular layer; GCL = granule cell layer; I = inner molecular layer; M = middle molecular layer; O = outer molecular layer.

Zhao et al., 2008). For the present discussion, it is notable that there may be less organization of the new GCs within the GCL in the epileptic brain and many GCs that migrate outside it (discussed further below).

Normal GCs develop dendrites that extend into the molecular layer and reach the hippocampal fissure. The nor-mal inputs to the GCs that lie in the molecular layer, such as the perforant path, appear to innervate normal GCs in a similar manner as those that are born in adult life (van Praag et al., 2002). However, in TLE, this may not be true, because the perforant path fibers originate in layer II of the entorhinal cortex, which is an area of damage in patients
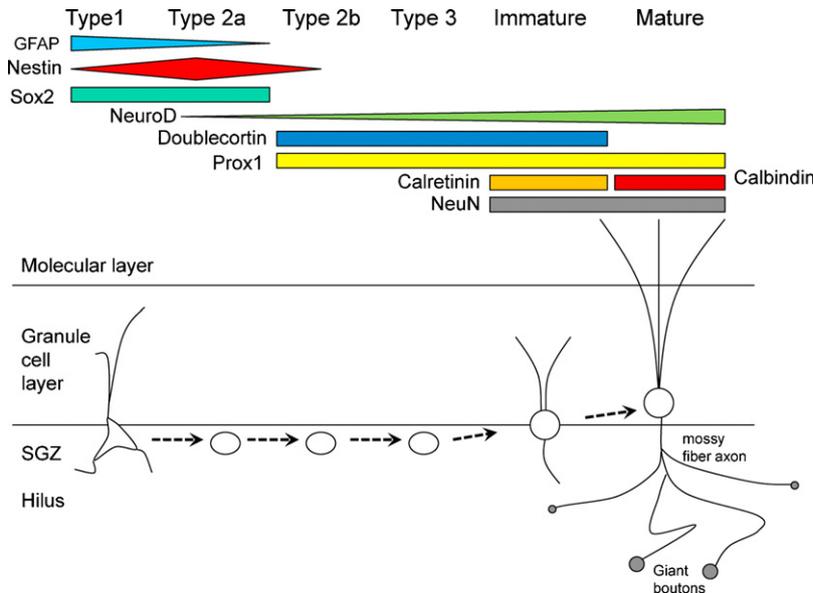
Figure 2   Sequential maturation of progenitors in the normal adult dentate gyrus. Top: stages of progenitor maturation with patterns of expression of selective markers indicated in color. Bottom: schematic illustration of progenitor division in the subgranular zone (SGZ) or the dentate gyrus. In the SGZ, type 1 (radial glia-like progenitors, analogous to the type B cells of the SVZ; Seri et al., 2004) become types 2a, 2b, and 3 cells. Most of the neurons become GCs, distinguished by calretinin immunoreactivity when they are immature, and calbindin immunoreactivity after maturity. GFAP, glial-fibrillary acid protein. From Kempermann et al. (2004) and Kempermann (2006).

with TLE (Scharfman, 2002). In rodent models of TLE, layer III is the area that is damaged primarily, so the issue is not easily studied (Scharfman, 2002).

The GC axon, also called a ''mossy fiber,'' projects to stratum lucidum of area CA3, and collateralizes in the hilus (Amaral et al., 2007; Ribak and Shapiro, 2007). GCs that are generated postnatally develop axonal projections which are very similar to the GCs born during development, i.e. the mossy fiber pathway appears the same (Faulkner et al., 2008; Gage et al., 2008; Ge et al., 2008; Toni et al., 2008; Zhao et al., 2008). In SE models of TLE, new neurons appear to develop a normal mossy fiber projection (Parent et al., 1999; Jessberger et al., 2007a,b), except for those that enter the hilus, which contribute to the plexus of mossy fibers that are in the inner molecular layer (Scharfman et al., 2000).

Although the cells that immediately arise as a result of progenitor division do not typically survive long-term, those that do survive and become GCs appear to persist (Kempermann et al., 2003). Several factors can alter the numbers of GCs that ultimately survive, such as age (Cuppini et al., 2006) and learning (Leuner et al., 2004). GCs that are born after adult SE appear to survive for the rest of the lifespan, similar to GCs that develop in the normal adult brain (Scharfman et al., 2000; McCloskey et al., 2006; Jessberger et al., 2007a,b), although some studies suggest this is not true. The discrepancies are likely to be due to the fact that some experiments examined the cells that resulted from SE-induced proliferation, rather than SE-induced neurogenesis (Parent et al., 1997; Hattiangady et al., 2004).

Recordings from new neurons in the adult brain have shown that they develop characteristics similar to GCs born during development (Laplagne et al., 2006). However, when adult-born neurons are young, they demonstrate increased excitability. For example, new neurons appear to have T-type Ca^{2+} channels that facilitate Na^+-dependent action potential generation, and long-term potentiation (LTP) is easier to induce (Schmidt-Hieber et al., 2004). Other studies of postnatal neurogenesis show that it plays an important role in LTP of the perforant path input (Wojtowicz, 2008). Another characteristic of young GCs that are born in the adult is that they have a depolarized equilibrium potential for chloride, making them depolarize in response to GABA more than adult cells (Ge et al., 2006; Markwardt and Overstreet-Wadiche, 2008). There also are additional changes in GABAergic transmission that also increase in excitability of young neurons (Karten et al., 2006; Ge et al., 2007).

Postnatal neurogenesis as a contributing factor in epileptogenesis

Overview
Studies of dentate gyrus neurogenesis in the 1990s noted that postnatal neurogenesis is dynamic, regulated by many genes, and epigenetic factors. Activity is a major regulator of neurogenesis, so it might have been predicted that seizures would also. In 1997, it was shown that single after-discharges increased neurogenesis, as did convulsants such as pilocarpine and kainic acid (Bengzon et al., 1997; Parent et al., 1997). Because these convulsants are commonly used
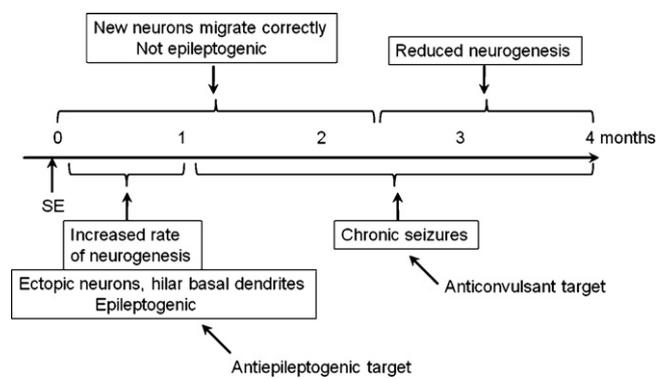

Figure 3 Timeline of changes in postnatal neurogenesis in a SE model of TLE illustrates the changes that would be potential therapeutic targets. After SE (time 0), animals initially exhibit many changes in the dentate gyrus, including a dramatic increase in the rate of neurogenesis that lasts the first weeks after SE (Parent et al., 1997; Scharfman et al., 2000), and some neurons that migrate incorrectly appear to be epileptogenic (Scharfman et al., 2000, 2007; Scharfman, 2004). Others, that migrate normally, appear to have no such effect (Jakubs et al., 2006). Long term, after chronic seizures have developed, there is a reduction in neurogenesis (Hattiangady et al., 2004; Kuruba et al., 2009). The timing that these phases exhibit is only estimated in the schematic.

to initiate an epileptic state in laboratory animals, the new data suggested potential relevance of seizure-induced neurogenesis to epilepsy, and became a topic of widespread interest. It has now been shown that almost every method to induce seizures leads to an increase in the rate of dentate gyrus proliferation or neurogenesis (kainic acid i.c.v. (Gray and Sundstrom, 1998); kainic acid i.p. (Scharfman et al., 2000); kindling (Parent et al., 1998; Scott et al., 1998); electroconvulsive shock; (Scott et al., 2000)), and this occurs in both rats and mice (Jessberger et al., 2005; Overstreet-Wadiche et al., 2006). However, there are exceptions: experimental febrile seizures (Bender et al., 2003), and immature animals treated with convulsants (Porter, 2008), or several episodes of convulsant administration (Liu et al., 2003) do not appear to exhibit a change in the rate of neurogenesis thereafter, or the rate declines. Because other aspects of neurogenesis may be altered, such as maturation and survival of newly generated neurons (Liu et al., 2003; Porter, 2008), it remains important to use caution in generalizing the data from animal models that evaluate adult animals using SE as the initiating mechanism to induce a state of epilepsy.

Although the early studies were intriguing, they did not clarify how a change in neurogenesis might contribute to epileptogenesis or chronic epilepsy. Several hypotheses developed based on anatomical and functional studies. Taken together, they support the concept that SE-induced neurogenesis leads to abnormal GCs, and these neurons contribute to increased excitability. They also suggest that neurons born after SE are heterogeneous, and some of these GCs may not contribute to an increase in excitability. Notably, the neurons that are abnormal appear to primarily develop in the weeks after SE, whereas long afterwards, the ability to generate new neurons declines. The late decline
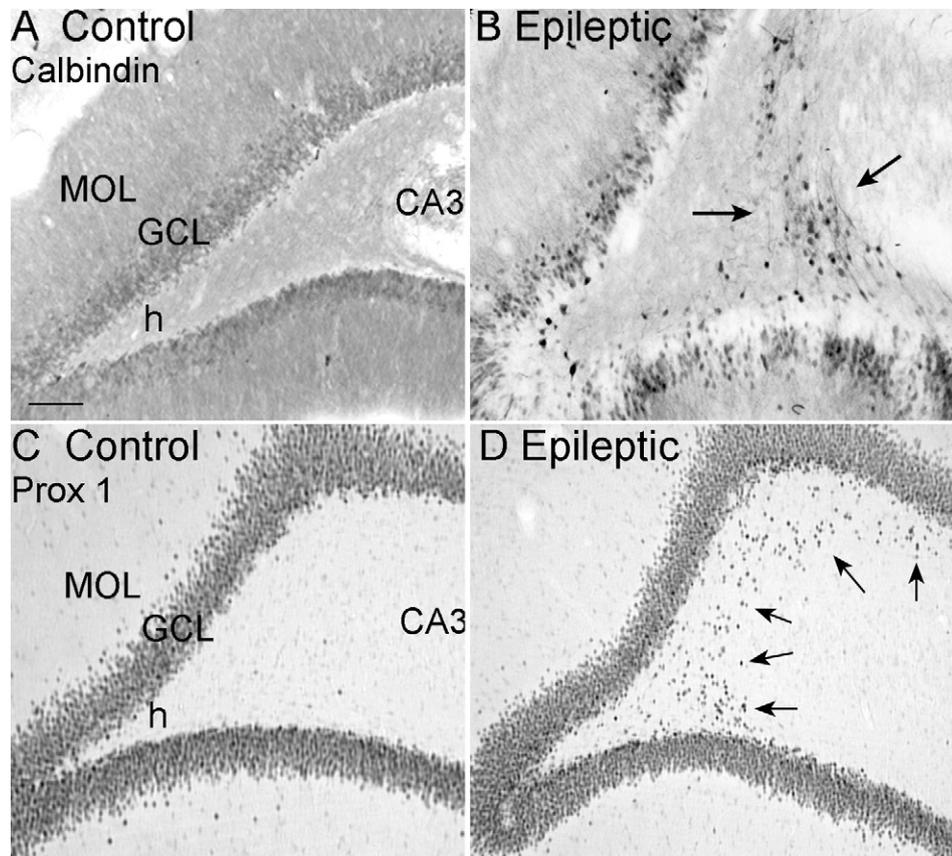
Figure 4 Hilar EGCs. (A) Calbindin (D28K)-immunoreactivity in a control rat labels the cell bodies of GCs, GC dendrites in the molecular layer (MOL), as well as GC axons (mossy fibers) in the hilus (h). Calibration = 100 μm. Calbindin immunoreactivity in an epileptic rat illustrates a population of hilar EGCs near CA3 (arrows). Note that calbindin immunoreactiivty is weak in the GCL in this section, because young GCs do not express calbindin (Goodman et al., 1993), and many mature GCs downregulate calbindin after seizures (Nagerl et al., 2000; Scharfman et al., 2002; Carter et al., 2008). (B) Prox1 immunoreactivity in a different pair of rats demonstrates numerous hilar EGCs in the epileptic rat (arrows).

in neurogenesis is potentially important, because it could be contribute to cognitive impairment and depression in TLE, as discussed elsewhere (Hattiangady et al., 2004; Kuruba and Shetty, 2007; Scharfman and Gray, 2007). Therefore, there is a time-dependent and non-linear relationship between neurogenesis and TLE, diagrammed in Fig. 3. Nevertheless, treatment strategies could be developed, theoretically (Fig. 3 and below).

Changes in neurogenesis in animal models of epilepsy that increase excitability

Hilar EGCs. Recordings from animals that had experienced SE in adulthood, and demonstrated a dramatic rise in neurogenesis thereafter, led to the hypothesis that neurons which became abnormal in the epileptic brain may contribute to the increase in excitability. Evidence for this hypothesis was founded in early observations by Parent et al. (1997), where it was shown that some of the neurons that were born in the dentate gyrus after pilocarpine-induced SE did not necessarily migrate correctly into the GCL. Instead, these cells appeared to migrate into the hilus, an area between GCL and CA3, where they formed ectopic clusters of GCs (hilar EGCs; Fig. 4). Subsequent studies showed that hilar EGCs often

exhibited dendrites that were not typical of GCs, although hilar EGC axons were extremely similar to axons of GCs. Thus, hilar EGCs generated mossy fibers that had the specializations and projection sites of normal GCs, including the inner molecular layer (Scharfman et al., 2000, 2007; Scharfman, 2004), typical of the GC in SE models of TLE that exhibits mossy fiber ''sprouting'' (Scharfman et al., 2000, 2007; Scharfman, 2004). Importantly, the hilar EGCs survived for long periods of time, so once they developed, their effects could persist (Scharfman et al., 2000; McCloskey et al., 2006). Other studies of hilar EGCs also demonstrate their long-term survival (Jessberger et al., 2007a,b). Importantly, hilar EGCs could become a substantial fraction of hilar neurons (Scharfman et al., 2000; McCloskey et al., 2006).

In studies using hippocampal slices from epileptic rats that had pilocarpine-induced SE, many hilar EGCs exhibited spontaneous, rhythmic bursts of action potentials, synchronized with CA3 pyramidal cells and other hilar neurons (Scharfman et al., 2000, 2007; Scharfman, 2004). The burst discharges did not occur if rats were examined before spontaneous, recurrent seizures developed, or in animals without SE (Scharfman et al., 2000). Further studies, based on simultaneous recordings, suggested that bursts of action
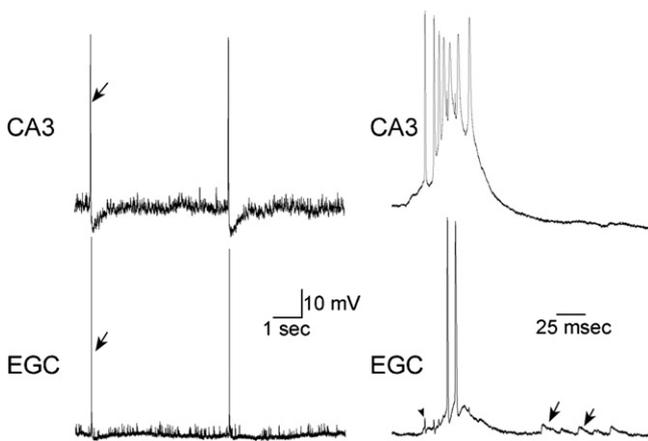
Figure 5 Synchronization of CA3 pyramidal cells with hilar EGCs. Simultaneous intracellular recordings at a slow (left) and fast (right) time base show the synchronization of a hilar EGC with spontaneous bursts in a CA3 pyramidal cell. The arrow points to the capacitative artifact of the first CA3 pyramidal cell action potential in the EGC recording, illustrating that the onset of the burst in the pyramidal cell preceded the onset of the EGC burst. From Scharfman et al. (2007).

potentials in hilar EGCs are initiated by synaptic input from CA3 (Scharfman et al., 2000, 2007; Scharfman, 2004). Thus, simultaneous recordings showed that the onset of burst discharges in CA3 pyramidal cells preceded the onset of bursts in hilar EGCs (Fig. 5; Scharfman et al., 2000, 2007). Although these recordings were conducted *in vitro*, hilar EGCs were also active *in vivo*, and appeared to participate in seizures, because c-fos expression developed in hilar EGCs shortly after a spontaneous seizure in epileptic animals (Scharfman et al., 2002). Interestingly, the numbers of hilar EGCs were correlated with the frequency of stage 5 limbic seizures in the pilocarpine model (McCloskey et al., 2006). These data led to the hypothesis that hilar EGCs may increase dentate gyrus excitability in animal models of TLE, and possibly predispose the hippocampus to seizures (Parent and Lowenstein, 2002; Scharfman, 2004; Kuruba and Shetty, 2007; Scharfman and Gray, 2007; Parent and Murphy, 2008).

Hilar basal dendrites. Another GC abnormality that appears to develop in animal models of TLE is the outgrowth of hilar basal dendrites. Numerous studies have been published that describe these cells in detail anatomically (Spigelman et al., 1998; Buckmaster, 1999; Ribak et al., 2000; Dashtipour et al., 2003; Jessberger et al., 2007a,b; Walter et al., 2007; Thind et al., 2008), and they suggest that the hilar basal dendrites would lead to a greater net excitatory input to the cell, leading the cell to be closer to threshold. By extension, these cells would increase the excitability of the network (Ribak and Dashtipour, 2002; Shapiro and Ribak, 2005; Danzer, 2008; Shapiro et al., 2008).

Why hilar basal dendrites form after SE is not completely clear at the present time, but it appears that the increase in immature neurons that occurs after SE may be one contributing factor, because immature GCs appear to be predisposed to develop hilar basal dendrites (Walter et al., 2007). Because the neurotrophin BDNF (brain-derived neu-

rotrophic factor) increases after SE (Scharfman, 2005a,b), and it facilitates the formation of hilar basal dendrites (Danzer, 2008), SE-induced increases in BDNF in the dentate gyrus may also contribute to the emergence hilar basal dendrites on GCs after SE.

Despite the striking changes in hilar basal dendrites in the literature, there have been few published recordings from GCs with hilar basal dendrites, so the functional influence of these neurons is not clear at this time. Nevertheless, computational modeling would suggest a potentially important role (Morgan and Soltesz, 2008).

Summary and caveats

Dentate gyrus neurogenesis changes dramatically after severe insults or injury in the adult rodent, and this leads to a dramatic rise in the rate of neurogenesis. The net effects include generation of abnormal GCs, which appear to increase excitability, as well as normal GCs, which do not necessarily increase excitability. The implications are that targeting the changes that cause increased excitability may be important in acquired TLE. In addition, one might want to prevent the aspects of neurogenesis that do not contribute to an increase in excitability, and long-term, one would want to preserve postnatal neurogenesis so that cognitive function and mood are maintained. We propose that the characteristics to target therapeutically include EGCs and hilar basal dendrites, while the adult-generated neurons that migrate normally and behave normally should be preserved, as well as the neurogenic niche (Fig. 3).

It is important to emphasize that this strategy is based on a number of assumptions that have yet to be proved. For example, there has been no proof that increased neurogenesis, hilar EGCs or hilar basal dendrites are essential to epileptogenesis or chronic seizures. It was shown that hilar EGC number correlates with seizure frequency (McCloskey et al., 2006), but correlative data are not definitive. Hilar EGCs occur in patients with intractable TLE (Parent et al., 2006), which suggests that what is studied in the animal model has relevance to human TLE, but the relationship between EGCs and human TLE is not clear at this time. Two studies were conducted using the lithium-pilocarpine model of epilepsy by Jung and colleagues, and provided evidence that reducing neurogenesis and hilar EGCs was accompanied by a reduction in seizures (Jung et al., 2004, 2006). However, the procedures that were used to limit neurogenesis also had other effects besides those that reduced neurogenesis (Parent, 2005). One argument has been that SE is sometimes followed by seizures relatively soon thereafter, sooner than new GCs, and hilar basal dendrites, would be likely to mature and form strong interconnections. However, new neurons and process outgrowth develop quite rapidly after SE (Shapiro et al., 2007). Furthermore, the days after SE may be accompanied by changes in neurons that were almost mature at the time of SE, causing disruption to the end stages of their maturation. In addition, the earliest of seizures could be an acute response to the metabolic effects of SE, which can be severe, and not reflect the seizures which develop long-term. Below we consider potential therapeutic strategies based on the assumption that abnormal GCs contribute to epileptogenesis, and are an important target for intervention.

Therapeutic strategies

General strategies

Hilar EGCs
In light of the discussion above, a therapeutic strategy might include preventing hilar EGC formation. Although reasons why hilar EGCs form are not clear at this time, there appear to be two factors that contribute. One is the rapid increase in proliferation that occurs early after insult or injury. This is likely to lead to a surge in the production of new GCs, some of which will become hilar EGCs. Therefore, reducing the initial increase in proliferation that follows an initial insult could be an important strategy to reduce hilar EGCs. However, one of the problems with this idea is that some of the new neurons that would potentially be reduced might not be hilar EGCs, but neurons that would migrate into the GCL and potentially maintain excitability rather than increase it (Jakubs et al., 2006).

To target only those neurons that migrate incorrectly, one approach would be reducing stromal derived factor-1 (SDF-1), a ''go'' signal for migration (Bagri et al., 2002) that appears to be upregulated after seizures (Jung et al., 2008). Alternatively, it might be useful to preserve reelin, which is a ''stop'' signal for neuronal migration of GCs away from the GCL (Frotscher, 1997). Recent studies have demonstrated that hilar neurons which co-localize GABA and somatostatin also express reelin, and may prevent GCs from migrating into the hilus (Gong et al., 2007). These neurons are typically lost after SE because of their vulnerability, and the loss of the hilar reelin appears to cause hilar EGC formation (Gong et al., 2007). A third strategy is to reduce the abnormal activity that develops in hilar EGCs, i.e., the spontaneous rhythmic burst discharges. The periodic discharges appear to develop because CA3 pyramidal neurons project to hilar EGCs, and CA3 pyramidal cells develop intermittent burst discharges (Scharfman et al., 2000, 2007; Scharfman, 2004). Methods to prevent the circuits that develop among hilar EGCs, CA3 and other neurons seem particularly important, because the ongoing network activity increases over time (Scharfman et al., 2000). Therefore, this circuitry could contribute to a progression of pathophysiology (Sutula and Hermann, 1999; Pitkanen and Sutula, 2002; Sutula, 2004). Even if hilar EGC formation could not be prevented, stopping the activity in these circuits might be valuable. Another strategy would be to reduce the survival of the hilar EGCs, when they form. Normalizing the lifespan of adult-generated neurons after SE could be extremely effective, because any increase in excitability that would be caused would self-terminate. In summary, it may be useful to target three characteristics that contribute to hilar EGCs and the presumed disruption of normal excitability they cause: the changes in expression of factors like SDF-1 and reelin that normally control migration, the formation of recurrent excitatory circuits that include hilar EGCs, and persistence of hilar EGCs.

Hilar basal dendrites
Preventing or reversing the formation of hilar basal dendrites seems a logical strategy given the evidence that they are likely to increase excitability (Shapiro et al., 2008). However, how to do so is difficult to propose, because the reasons

Table 1 Therapeutic strategies to target abnormal postnatal neurogenesis in epilepsy.

Antiepileptogenic	Anticonvulsant
Prevent hilar EGCs and hilar basal dendrites	Suppress dentate excitability
Control rate of neurogenesis Decrease migratory ''go'' signals Increase migratory ''stop'' signals Reduce survival Reduce process outgrowth Increase inhibitory innervation	Anticonvulsants Targeted inactivation Surgical transection Stem cell therapy

Antiepileptogenic (left) and anticonvulsant (right) strategies to address characteristics of postnatal neurogenesis that appear to contribute to the predisposition for seizures in adult SE models of TLE. For detailed description, see text.

why hilar basal dendrites form are not clear. It was shown that a large percentage of neurons with hilar basal dendrites are immature at the time of SE (Walter et al., 2007), suggesting that a cause of hilar basal dendrite formation is disruption of normal maturation of the dendritic tree. However, another study showed that many GCs with hilar basal dendrites form after SE (Jessberger et al., 2007a,b). It has also been shown that SE disrupts the normal interactions between radial glia and immature GCs, which could play a role in the formation of hilar basal dendrites (Shapiro et al., 2005). The elevation in neurotrophins after SE may be important, because they stimulate process outgrowth. For example, brain-derived neurotrophic factor (BDNF) levels rise in the mossy fibers after SE, and remain elevated for long periods of time (Scharfman, 2005a,b). It is not clear if that neurotrophin pool would be accessible to the extracellular milieu in sufficient concentrations to be trophic for hilar basal dendrites, but even if not, there are many other examples of growth factors and cytokines that increase and decrease after SE in the hilus (Scharfman, 2005a,b). Together, they may create a stimulus for hilar basal dendrite formation.

Thus, it is difficult to propose an intervention to prevent hilar basal dendrites from developing, or a strategy to reverse the process after the fact. However, even if the dendrites cannot be prevented from forming, or reversed, manipulations to increase the relative numbers of GABAergic synapses on hilar basal dendrites may be useful. This idea is suggested by quantitative studies of hilar basal dendrites, which showed that the majority of synapses are excitatory (Thind et al., 2008).

Seizures vs. co-morbidity
The main targets for treatment of seizures in TLE that are discussed above include preventing EGC formation and hilar basal dendrites, or the increase in excitability they cause (Table 1). These could be addressed in a preventative (antiepileptogenic) manner or long after the problems develop and seizures become chronic, i.e., in an anticonvulsant manner (Fig. 3 and see below). However, it is also important to consider the potential that a long-term reduction in proliferation rate occurs in the chronic disease, and leads to cognitive impairment and co-morbidities such

as depression. Therefore, a strategy that would be potentially useful to reduce co-morbidities late in the course of the disease would be to increase the rate of neurogenesis. Presumably, stimulation of the rate of neurogenesis would be most useful if seizures were under control by AEDs, because increasing neurogenesis during a period of uncontrolled seizures could have adverse effects by disrupting normal maturation and migration.

Prevention (antiepileptogenic approaches)

Irradiation

Low doses of irradiation can reduce proliferating cells selectively compared to postmitotic neurons, because of the sensitivity of the dividing cell. Interestingly, it has been noted clinically that low-dose irradiation to a seizure focus can be advantageous (Jenrow et al., 2006), although this effect may not be due to an influence of irradiation on neurogenesis.

With respect to the use of irradiation to modify the potential influence of neurogenesis in epilepsy, one of the first studies used this approach to ask whether new neurons born in SE models contributed to mossy fiber sprouting. Mossy fiber sprouting is an example of synaptic reorganization that is thought to contribute to epileptogenesis by increasing recurrent excitatory circuitry in the dentate gyrus (Dudek and Sutula, 2007; Sutula and Dudek, 2007). It was hypothesized that new neurons might be likely to contribute to the novel excitatory circuitry, and low-dose irradiation might preferentially block progenitor division without additional effects on mature cells (Parent et al., 1999). The reduction in neurogenesis that occurred after low-dose irradiation did not appear to impair mossy fiber sprouting (Parent et al., 1999), and it was not noted if the seizures in the animals were affected. Subsequent studies have attempted to address the influence of irradiation on seizures, using the kindling model. Mixed results have been obtained. In one study that used whole brain irradiation before the first kindling stimulus, afterdischarge threshold was reduced during kindling, but there was no net effect on the kindled state (Raedt et al., 2007). In another study, irradiation was aimed at the amygdala because it was the focus, i.e., the site that was chosen for kindling. Different effects were demonstrated, depending on when irradiation was conducted relative to stages during kindling acquisition (Jenrow et al., 2006). These studies suggest that irradiation can influence seizures, but it is not clear how, and whether it is due to reduction of neurogenesis by irradiation. Because neurogenesis is not the only effect of irradiation (Fike et al., 2007), other methods have been developed, such as genetic manipulations.

Genetic manipulations

Mice that have genetic manipulations allow deletion of the progenitor pool and are potentially powerful because they are more specific than irradiation (Beech et al., 2004; Saxe et al., 2006). They also have the potential to be tailored temporally. These inducible, conditional genetic manipulations could be a foundation for gene therapy, although it would be unlikely that gene therapy would be available in the near future. Nevertheless, gene therapy has substantial

potential, as discussed elsewhere (Noe et al., 2006; Vezzani, 2007).

One strategy that has been used effectively in rodents to reduce neurogenesis selectively is to insert thymidine kinase in the progenitors that express glial-fibrillary acid protein (GFAP), the radial glia-like progenitors (Fig. 2). Upon systemic exposure to the anti viral agent ganciclovir, thymidine kinase phosphorylates ganciclovir only in GFAP-expressing cells. Phophorylated ganciclovir becomes a toxic thymidine analogue, which will lead to the death of any of the radial glial cells that begin to divide. After several weeks of exposure, most of the radial glia naturally divide, and therefore, most will have died. This is a powerful approach, but there is a caveat in using the mice to address consequences of SE. The reason is that injury leads to a division of mature astrocytes (which express GFAP) into reactive microglia (Faulkner et al., 2004). Because mature astrocytes express GFAP, there would be a loss of reactive microglia after SE, which could change the progression from SE to chronic seizures.

Another strategy is to target nestin-expressing cells. Nestin is expressed in progenitors like radial glia, as well as other types of progenitors (Fig. 2). One caveat with this approach is that nestin is present in non-progenitors, but a new strategy circumvents the problem by targeting the nestin promoter that is specific for progenitors (Yu et al., 2008). The newer method is also advantageous in other ways, because some stem cells appear to remain after treatment with ganciclovir. Although normally dormant, it appears to be possible to induce division in this dormant population long after ganciclovir treatment is over (Yu et al., 2008). Therefore, such a strategy could potentially reduce neurogenesis as a preventative measure, but then restore it much later, allowing one to prevent seizures but maintain a neurogenic niche long-term.

There are a number of approaches that could potentially be used in the future. Increasing the expression of proteins that normally induce apoptosis of the newly generated neurons, such as BAX or decreasing those that impair apoptosis (Bcl-2) could be advantageous. Another strategy would be to reduce levels of neurotrophins such as BDNF that increase neurogenesis, foster survival, process outgrowth, and plasticity (Scharfman, 2005a,b; Binder, 2007). Both strategies would require selective targeting to avoid the adverse consequences of excess apoptosis, or neurotrophin depletion, making the desired goals seem difficult to achieve at the present time.

Pharmacological approaches

Currently available anticonvulsants may be useful in the antepileptogenic context suggested here, because they might reduce excitability, and in so doing, prevent some of the stimulus for epileptogenesis. In other words, if one assumes that epileptogenesis is stimulated by a large increase in neuronal activity (i.e., SE), and is perpetuated by new GCs with increased excitability, drugs that reduce excitatory activity could be effective in blocking epileptogenesis. Bumetamide might be a logical choice, if the new GCs that accumulate in the dentate gyrus after SE have increased excitability due to depolarized responses to GABA (Overstreet-Wadiche et al., 2006), which are due the $Na^+K^+/2Cl^-$ transporter that bumetamide inhibits (Kahle

and Staley, 2008). However, blocking the excitatory effects of GABA in normal adult-generated GCs lead to defects in their development (Ge et al., 2007). Other anticonvulsants, such as valproic acid, may be useful because valproic acid appears to normalize neurogenesis (Jessberger et al., 2007a,b), although other agents that have been suggested to normalize neurogenesis, such as endoneuramidase-N, has not shown efficacy in reducing seizures in an animal model of TLE (Pekcec et al., 2008). Even if these drugs would not stop seizures, both valproic acid and endoneuramidase-N may be useful in preventing detrimental effects of chronic seizures on the neurogenic niche, and as a result, stabilizing cognition or mood in patients with TLE (Jessberger et al., 2007a,b; Scharfman and Gray, 2007; Pekcec et al., 2008).

Reversal (anticonvulsant approaches)

Futuristic approaches
The most valuable strategy for the future is probably the hardest — to attempt reversal or recovery of TLE, long after disruption of neurogenesis has occurred and potentially contributed to it. In other words, for the patient who already has recurrent seizures, what anticonvulsant treatment, or potential cure, could be offered that would reverse or reduce the effects of ''aberrant'' neurogenesis? Pharmacotherapy would be one strategy, using drugs that decrease excitability, which is presumed to be initiated by circuits of abnormal GCs with other dentate gyrus neurons. If a compound that preferentially acted on mossy fiber transmission were available, such a drug might be particularly effective, because the normal GCs and hilar EGCs both use these specialized synapses to release glutamate onto their targets and contribute to abnormal network activity. Of the drugs known to modulate mossy fiber transmission, some metabotropic receptor ligands such as DCG-IV are commonly used *in vitro*, but one would need to carefully tailor this approach so that the functions of the mossy fibers that are important to cognitive function would not be impaired, and the drug would not reach other sites in the brain where the receptors are important to normal function.

Two new approaches are attractive, although in early stages of development at the present time. One of these new approaches is to selectively silence neurons of interest, so they do not influence their targets (Slimko et al., 2002; Lerchner et al., 2007). The manner in which silencing is achieved involves expression of an ion channel which will hyperpolarize the cell, such as a chloride or potassium channel (Slimko et al., 2002; Lerchner et al., 2007). In the present context, one might silence the hilar EGCs, because their burst discharges lead to greater activity in the dentate gyrus network than normal, facilitating seizure-like activity. Another possibility is to use this approach to silence CA3 pyramidal neurons, to reduce their ability to generate burst discharges that in turn activate hilar EGCs. It might be best to reduce the activity in a fraction of CA3 neurons rather than the entire population, however, because completely blocking the ability of CA3 pyramidal cells to discharge action potentials would presumably disturb normal hippocampal function.

Another approach is to use light-activated silencing (Zhang et al., 2007), where a miniaturized light source silences neurons that express channelrhodopsins, which are proteins that are sensitive to light. At the present time, this technique is not amenable for sites deep within the brain, but it has already been used *in vivo*, an important first step. Theoretically, if the light could be flashed intermittently to expose EGCs that express the channelrhodopsin protein, it might disrupt the periodic discharges of the EGCs and their associated circuitry. However, it is not clear that a specific protein is expressed in hilar EGCs that would allow one to target them selectively.

Surgical approaches
It already is clear that surgical removal of the hippocampus is effective in reducing seizures in TLE when the hippocampus is a defined and specific focal lesion (Engel et al., 1998; Schmidek and Roberts, 2005; Spencer and Huh, 2008). Although often not considered, it is possible that those patients which benefit the most are those with numerous hilar EGCs, and complex circuitry that develops between the dentate gyrus and residual CA3 neurons. If so, one surgical approach to consider is not only removal, but also transection or ''disconnection.'' In other words, one might transect the circuitry between the dentate gyrus and CA3 network to disrupt the output of the dentate gyrus, and reverberatory activity between CA3, hilar cells (such as EGCs) and GCs. This concept is analogous to subpial transection — instead of removal, transection could be better. However, transection would seem very difficult, from the technical perspective, because of the difficulty in selectively transecting the junction between the dentate gyrus and CA3, which is not easily accessed.

Stem cells
Another potential approach for therapeutic use, and one that has already demonstrated preclinical success (Richardson et al., 2008), is transplantation. Recent studies have shown that transplanted neurons can restore neurogenesis (Kuruba et al., 2009), and GABAergic neurons can reduce seizures (Alvarez-Dolado et al., 2006). Moreover, one study has shown that a specific type of ''stem cell,'' transplanted into the dentate gyrus often matures into normal GCs, which could be used in a restorative manner if neurogenesis declines (Carpentino et al., 2008). Remarkably, these stem cells can lead to abnormal growths if a normal animal is used, but in an animal that has had seizures, the stem cells become GCs and tumors do not appear to develop (Carpentino et al., 2008). Infusion of neuropeptide Y may be a particularly effective strategy after such stem cell infusion, because it stimulates precursor division (Howell et al., 2003; Scharfman and Gray, 2006; Scharfman and Gray, 2007) and reduces seizures (Noe et al., 2006).

As intriguing as these possibilities are, there are many issues that need to be addressed before therapeutic use can truly be considered. For example, if some transplanted neurons become GCs, and they do not migrate correctly, would they increase the hilar EGC population and worsen the condition? If GABAergic neurons were used for a transplant procedure, and they were to project to other GABAergic neurons, seizures might increase due to disinhibition of principal cells. The remarkable plasticity of the dentate gyrus could be advantageous in allowing transplanted neurons to

survive and develop synaptic connections, but be detrimental if inappropriate maturation and integration occur. There are many other issues to resolve, such as administration route, side effects, the type of TLE that should be examined, and whether age and comorbidity would complicate outcome. Still, there are a number of promising possibilities to consider that could improve a devastating condition, i.e., TLE.

Acknowledgements

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