Published in final edited form as:

Exp Neurol. 2012 January ; 233(1): 22–32. doi:10.1016/j.expneurol.2011.05.023.

Depression, stress, epilepsy and adult neurogenesis

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Abstract

Epilepsy and depression share an unusually high coincidence suggestive of a common etiology. Disrupted production of adult-born hippocampal granule cells in both disorders may contribute to this high coincidence. Chronic stress and depression are associated with decreased granule cell neurogenesis. Epilepsy is associated with increased production – but aberrant integration – of new cells early in the disease and decreased production late in the disease. In both cases, the literature suggests these changes in neurogenesis play important roles in their respective diseases. Aberrant integration of adult-generated cells during the development of epilepsy may impair the ability of the dentate gyrus to prevent excess excitatory activity from reaching hippocampal pyramidal cells, thereby promoting seizures. Effective treatment of a subset of depressive symptoms, on the other hand, may require increased granule cell neurogenesis, indicating that adult-generated granule cells can modulate mood and affect. Given the robust changes in adult neurogenesis evident in both disorders, competing effects on brain structure are likely. Changes in relative risk, disease course or response to treatment seem probable, but complex and changing patterns of neurogenesis in both conditions will require sophisticated experimental designs to test these ideas. Despite the challenges, this area of research is critical for understanding and improving treatment for patients suffering from these disorders.

Keywords

epilepsy; dentate gyrus; basal dendrite; neuronal migration; neuronal plasticity

Introduction

Unambiguous evidence of ongoing neurogenesis in mammals has revolutionized views of neuroplasticity in the adult brain. Neurogenesis is a natural feature of the mature brain, persisting into old age in both animals (Altman and Das, 1965; Kaplan and Hinds, 1977; van Praag et al., 2002) and humans (Eriksson et al., 1998). Ongoing production of hippocampal dentate granule cells has received much attention because of the role of the hippocampus in learning, memory and cognition (for review see Lisman, 1999; Knierim et al., 2006; Rolls and Kesner, 2006). Although it will take years of study to fully elucidate the purpose of

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these new cells, multiple lines of evidence indicate they are important for these key hippocampal functions (for review see Deng et al., 2010). In addition, emerging research implicates dysregulation of granule cell neurogenesis in several diseases, including depression and epilepsy.

Epilepsy is a multifarious and debilitating disease affecting 1–2% of the population. Epilepsy is defined clinically by the occurrence of two or more unprovoked seizures. Seizures can originate from different regions of the brain, depending on the type of epilepsy syndrome. The present review focuses on temporal lobe epilepsy, a common and difficult to treat form of the disease with consistent hippocampal involvement. While seizures are the defining feature of epilepsy, the disease is frequently associated with other disorders, including cognitive problems, memory disturbances, anxiety and depression. Only recently, however, have these co-morbidities been targeted as an important area of research in epilepsy (NIH, Epilepsy Research Benchmarks, 2007). Intriguingly, the relationship between epilepsy and depression is bidirectional, with a history of depression associated with increased risk for developing epilepsy (Forsgren and Nyström, 1990; Hesdorffer et al., 2006; 2007). The mechanisms underpinning this relationship remain to be discovered. Disrupted granule cell neurogenesis, however, may be a potential common factor. In the present article, this idea is explored further following a review of the literature describing key features of disrupted granule cell neurogenesis in temporal lobe epilepsy, chronic stress and depression.

Part I: Neurogenesis in epilepsy

Adult hippocampal granule cell neurogenesis is disrupted in temporal lobe epilepsy

Basic research in temporal lobe epilepsy has relied on a variety of animal models, such as kindling and status epilepticus. In the kindling model, repeated electrical stimulation of the brain leads to a persistent lowering of the seizure threshold (Goddard et al., 1969), although animals do not exhibit spontaneous seizures unless kindling stimulations are repeated over a prolonged period (Sayin et al., 2003). In commonly-used status epilepticus models, animals receive a precipitating injury to the brain, such as treatment with a chemoconvulsant drug like pilocarpine or kainic acid, to induce status epilepticus and acute cell loss. This acute injury is followed by a phase lasting days to weeks in which spontaneous seizures are infrequent or absent, termed the “latent period.” 24/7 video-EEG monitoring of treated animals indicates that as the latent period progresses, the probability that animals will exhibit spontaneous seizures gradually increases, such that after a few weeks animals exhibit frequent seizures (Williams et al., 2009). Latent periods are also a recurring feature of human epilepsy, in which it can sometimes take years for the appearance of the first clinical seizure following a precipitating injury like head trauma (Kharatishvili and Pitkänen, 2010). A key implication of the latent period is that the initial injury is not sufficient to support epileptic seizures. Although the injury is the proximal cause the disease, other changes must occur before epilepsy develops. Surprisingly, a little over a decade ago it was discovered that the latent period is associated with a dramatic increase in granule cell neurogenesis in rodent models of temporal lobe epilepsy (Bengzon et al., 1997; Parent et al., 1997; Parent et al., 1998; Gray and Sundstrom, 1998), and it has now been shown that many of these new cells survive for at least one year (Jessberger et al., 2007). Indeed, of all the factors that regulate granule cell neurogenesis, seizure activity is among the most potent of neurogenic stimuli. Further studies have demonstrated that increased granule cell neurogenesis is a common feature of most epilepsy models, as well as models of hypoxia-ischemia (Miles and Kerner, 2008) and traumatic brain injury (Emery et al., 2005; Ernst and Christie, 2006; Sun et al., 2007) that can lead to epilepsy.

The striking changes in granule cell neurogenesis have led to the hypothesis that temporal lobe epilepsy develops when large numbers of adult-generated granule cells integrate abnormally into the dentate gyrus (Parent and Murphy, 2008). Before further discussion of the merits and weaknesses of this hypothesis, however, it should be noted that it reflects one of several proposed mechanisms of temporal lobe epilepsy. The epileptic brain is characterized by a host of alterations, including, but not limited to, changes in ion channels, changes in synaptic properties, inflammation, glial changes, cell loss and widespread circuit changes (beyond just the hippocampus) (Jacobs et al., 2009). It is unlikely that any single factor accounts for all cases of temporal lobe epilepsy, or that any individual patient's epilepsy reflects the impact of a single mechanism. More likely, epilepsy reflects a combination of many changes in the brain, with some features playing more prominent roles in some patients, while different combinations of changes are predominant in others. Indeed, many forms of epilepsy (e.g. some cortical epilepsies) may not substantively involve the hippocampus at all, although the incidence and disease burden of temporal lobe epilepsy should not be understated. Nonetheless, the present review should be taken with the caveat in mind that even if newborn granule cells contribute significantly to epileptogenesis in temporal lobe epilepsy, they are likely only part of the story.

The dentate as a key regulator of excitatory/inhibitory balance in the brain

Dentate granule cells are glutamatergic excitatory neurons that sit at the entrance to the hippocampus, acting as the intermediaries between entorhinal cortex and the hippocampal CA3 and CA1 pyramidal cells. The dentate, therefore, is ideally situated to act as a "gate", limiting the amount excitatory input entering the hippocampus (Hsu et al., 2007). A key element of the dentate gate is evident from morphological studies by Acsády and colleagues (1998). Essentially, robust innervation of excitatory CA3 pyramidal cells by granule cells is offset by numerically superior innervation of GABAergic inhibitory interneurons by granule cells. The high ratio of inhibitory to excitatory contacts is unusual, being significantly greater than principal neurons in cortex (Acsády et al., 1998). The inhibitory neuron contacts of granule cells provide robust feedforward and feedback inhibition and serve as important structural components of the dentate gate (Lawrence and McBain, 2003). More direct evidence for the dentate gate has been provided by Ang and colleagues (2006), who were able to use voltage sensitive dyes to demonstrate invasion of neuronal activity into the dentate following activation of entorhinal afferents, and subsequent prevention of activity spread beyond the dentate. Finally, failure of this gating function is evident in several models of epilepsy (Heinemann et al., 1992; Behr et al., 1998; Gloveli et al., 1998; Pathak et al., 2007; Shao and Dudek, 2011). In part for this reason, a large body of literature in the epilepsy field has focused on the dentate (Dudek and Sutula, 2007). While there are many mechanisms in the brain for regulating the balance between excitation and inhibition, it appears that the ability of the dentate to control excitation is unusually pronounced and robust. Disruption of this gating function, therefore, may have disproportionate effects on the excitatory/inhibitory balance in the brain.

Abnormal integration of adult-generated granule cells in temporal lobe epilepsy

If the dentate is critical for maintaining excitatory/inhibitory balance in the limbic system, and this function fails in some forms of epilepsy, the question follows: what causes this failure? Loss of inhibitory interneurons (Dudek and Sutula, 2007) and other factors likely play roles. For the purposes of the present review, however, three unique pathologies of the dentate are worthy of attention. These pathologies have been identified among dentate granule cells in the epileptic brain, and all lead to the formation of recurrent excitatory circuits among granule cells. The first of these, termed mossy fiber sprouting, was described almost three decades ago (Tauck and Nadler, 1985; Sutula et al., 1989; Okazaki et al., 1999; Nadler, 2003). Mossy fiber sprouting occurs when granule cell axons, called mossy fibers,

sprout into the dentate inner molecular layer (Fig. 1) and form excitatory synaptic connections with neighboring granule cells. The recurrent excitatory connections created by this sprouting are hypothesized to promote hyperexcitability within the hippocampus (for review see Sutula and Dudek, 2007). Mossy fiber sprouting has been found in both animals and humans with temporal lobe epilepsy, and is considered by some to be a hallmark pathology of the disease. The second form of pathology occurs when granule cells migrate to ectopic locations within the dentate hilus rather than correctly integrating into the granule cell body layer (Fig. 2). Displacement of these cells into the dentate hilus, a primary target region of granule cell axons, likely accounts for the extensive innervation of ectopic granule cells by neighboring granule cells in rodents (Scharfman et al., 2000; 2002; 2003; Pierce et al., 2005). Ectopic granule cells have also been identified in tissue from humans with epilepsy (Parent et al., 2006). The third pathology arises when granule cells develop basal dendrites projecting into the dentate hilus (Fig. 3, right; Spigelman et al., 1998; Buckmaster and Dudek, 1999). In rodents, mature granule cells typically possess only apical dendrites, which project into the dentate molecular layer where they are innervated by afferents from entorhinal cortex (Fig. 3, left). By contrast granule cells with basal dendrites receive significant recurrent input from neighboring granule cells, as evidenced by both anatomical and physiological studies (Ribak et al., 2000; Austin and Buckmaster, 2004; Shapiro and Ribak, 2006). While the number of granule cells with basal dendrites clearly increases in epileptic rodents, rigorous quantitative studies have yet to be conducted in human tissue, although abnormal granule cells have been observed in tissue from epileptic patients (Scheibel and Scheibel, 1973, von Campe et al., 1997; da Silva et al., 2006). Finally, the recent twist to this story is that the overwhelming majority of these abnormal granule cells are newly-generated. The young age of abnormal cells has been confirmed using pulse-chase bromodeoxyuridine (BrdU) labeling (Parent et al., 2006; Walter et al., 2007; Murphy et al., 2011), viral labeling (Jessberger et al., 2007) and timed radiation experiments (to ablate specific cohorts of adult-generated cells; Kron et al., 2010). These studies have further revealed that newborn granule cells exhibit critical periods during which they are vulnerable to developing specific abnormalities. Conversely, granule cells already mature at the time of an epileptogenic insult are only minimally affected.

Functional significance of abnormal granule cells in epilepsy

While intriguing, morphological studies alone are not adequate to prove that abnormal integration of adult-generated granule cells impairs the dentate gate or contributes to epileptogenesis. Physiological, as well as functional, studies are also needed. While numerous studies have taken these approaches, results have been conflicting.

One approach has been to use single-cell physiology to determine whether newborn granule cells from epileptic animals are hyperexcitable relative to newborn cells from control animals. The presumption is that more excitable cells would be pro-epileptogenic. Studies of ectopic dentate granule cells, which appear to be almost exclusively newborn (Walter et al., 2007; Kron et al., 2010), have revealed that many of these neurons burst (Scharfman et al., 2000). Bursting is not typical of normal granule cells, and this property has been suggested to be pro-epileptogenic. Ectopic granule cells also exhibit higher ratios of excitatory to inhibitory inputs than normal granule cells (Zhan et al., 2010). By contrast, newborn granule cells correctly located in the granule cell body layer in epileptic animals have been found to be less excitable than age-matched cells from controls, raising the possibility that some newborn cells integrate to perform a homeostatic role (Jakubs et al., 2006). These findings introduce an important point: morphological heterogeneity among newborn granule cells in the epileptic brain must, in many cases, reflect significant functional differences among these cells. Indeed, even among newborn cells correctly located in the granule cell layer in epileptic animals, significant morphological heterogeneity has been found. The majority of

newborn granule cells from this region possess fewer dendritic spines than age-matched cells from control brains; however, a subset of new cells (roughly 10%) has large numbers of dendritic spines (implying increased excitatory input). Moreover, these cells tend to have enlarged somas, thick apical dendrites, long basal dendrites and robust innervation from sprouted mossy fiber axons (Murphy et al., 2011). Until physiological studies can be conducted on the range of abnormal granule cells present in the epileptic brain, the functional significance of new cells will remain difficult to predict.

A second approach used to assess the role of new granule cells in epilepsy has been to reduce or block adult neurogenesis following an epileptogenic insult. The rationale for these experiments is that if new granule cells contribute to epileptogenesis, blocking neurogenesis should be protective. Again, these studies have produced mixed results. Specifically, serotonin 1A receptor blockade, which reduced neurogenesis, failed to mitigate spontaneous seizures in the rodent-pilocarpine model of epilepsy (Radley and Jacobs, 2003). Importantly, however, this treatment also failed to block mossy fiber sprouting. Since this pathology can be attributed largely to newborn granule cells (Kron et al., 2010), it implies that substantial numbers of new cells are still present despite serotonin 1A receptor blockade. Similarly, enzymatic depolysialylation of NCAM did not delay kindling epileptogenesis (Pekcec et al., 2007) or reduce seizure frequency in an electrical status model of epilepsy (Pekcec et al., 2008). Although this treatment was effective at reducing the number of new granule cells, however, it did not alter the percentage of granule cells with aberrant basal dendrites, implying again that substantial numbers of new cells were present. Hippocampal irradiation to block neurogenesis was also ineffective at delaying kindling progression, although a subtle, yet significant, reduction in seizure severity was observed during the kindling process (Pekcec et al., 2010). By contrast, treatment of animals with the anti-mitotic agent cytosine-b-D-arabino-furanoside following an epileptogenic brain insult reduced granule cell neurogenesis and the frequency of spontaneous seizures (Jung et al., 2004). Importantly, this treatment also significantly reduced the number of ectopic granule cells. Similarly, treatment with the cyclooxygenase-2 inhibitor, celecoxib, which reduced granule cell neurogenesis, was effective at reducing seizure frequency and ectopic granule cell number (Jung et al., 2006). The ability of these latter treatments to reduce neurogenesis and the accumulation of abnormal cells may account for the studies contrasting findings. Nonetheless, all agents used to date have effects in addition to reducing granule cell neurogenesis, so the possibility that the effect (or lack of effect) of these agents reflects other drug targets cannot be excluded. Finally, it should be noted that agents which reduce neurogenesis presumably do so indiscriminately, blocking both the formation of cells destined to become abnormal (i.e. ectopic granule cells) and cells that might integrate normally. The net effect of anti-neurogenic treatments, therefore, might be variable and difficult to predict.

In addition to the potential confounding effects of new granule cell heterogeneity, it is now clear that all of these studies are limited by an unforeseen complexity in the contributions of differentially aged adult-generated cells to potentially epileptogenic changes. Newborn granule cells go through several critical periods during which they are selectively vulnerable to developing specific abnormalities (Fig. 4). At the time of an epileptogenic insult, the oldest granule cells (>7 weeks) appear to be relatively resistant to disruption, although reductions in spine density and subtle dendritic changes are evident (Murphy et al., 2011). Notably, reduced spine density, indicative of reduced afferent input, might reflect homeostatic changes among these cells. Younger granule cells ($\approx$ 4 weeks) contribute to mossy fiber sprouting quickly after the insult (within one month) and can form basal dendrites. Granule cells one-two weeks old at the time of the insult also develop basal dendrites and exhibit somatic hypertrophy (Murphy et al., 2011), but exhibit little mossy fiber sprouting until two-three months after the insult. Granule cells born after the insult migrate to ectopic locations in the hilus and form basal dendrites, but again, exhibit little

mossy fiber sprouting until months after the insult (Walter et al., 2007; Kron et al., 2010). Notably, the recruitment of cells born a few weeks before an epileptogenic insult into pathological circuits reveals that all efforts to date to interfere with epileptogenesis by blocking neurogenesis applied anti-neurogenic treatments too late (Radley and Jacobs, 2003; Jung et al., 2004; Jung et al., 2006; Pekcec et al., 2007; Pekcec et al., 2008; Pekcec et al., 2010). Anti-neurogenic treatments should be begun at least four weeks before an epileptogenic insult to eliminate juvenile granule cells (Fig. 4). Future studies of this design will better test the role of adult neurogenesis in epilepsy.

While epilepsy is associated with increased neurogenesis and aberrant integration of new cells in early stages of the disease, animals examined five months after kainic acid treatment to induce epileptogenesis exhibited dramatically reduced neurogenesis (Hattiangady et al., 2004). Impaired neurogenesis is particularly pronounced in rodent hippocampi that become sclerotic (Danzer, 2008), a condition in both animals and humans with temporal lobe epilepsy characterized by hippocampal cell loss, gliosis and shrinkage (Fig. 5). Extensive cell loss in this condition may lead to disruption of the neurogenic niche, in which progenitor cells are lost entirely or cell proliferation, survival or differentiation are disrupted. Hattiangady and Shetty (2010) found that while neurogenesis was profoundly reduced or absent in damaged rodent hippocampi, cell birth continued, indicating the progenitor cells are still present. The progeny of these progenitor cells, however, differentiated into glia rather than neurons.

In summary, good evidence exists from animal models to indicate that the dentate has an important role in maintaining the excitatory/inhibitory balance in the brain. It is also clear that the dentate is altered by the accumulation of granule cells with abnormal connections in many animal models of temporal lobe epilepsy. More limited evidence suggests this also may be the case in humans (Parent et al., 2006). The functional significance of these aberrant new cells remains uncertain, with both pro-epileptogenic and anti-epileptogenic roles proposed. For consideration of co-morbid conditions in epilepsy, however, it is hard to imagine – whatever the role of the newborn granule cells – that the epileptic dentate functions in the same manner as a normal dentate.

Part II: Co-morbidity between depression and epilepsy

Epidemiological studies have revealed an unusually high co-morbidity between depression and epilepsy. Patients with epilepsy are at high risk for major depression relative to the general population (O'Donoghue et al., 1999; Tellez-Zenteno et al., 2007). Individuals with a history of major depression and/or suicide attempts are at increased risk for developing new onset epilepsy (Forsgren and Nyström, 1990; Hesdorffer et al., 2006; 2007). The incidence of depression is 5–20 times higher and epilepsy 4–7 times higher for each group, respectively (for review see Kanner, 2009). Moreover, the high incidence of depression in patients with epilepsy does not appear to simply reflect the burden of living with a debilitating disease, because depression incidence does not correlate with epilepsy severity (Attarian et al., 2003).

Animal studies also support a correlative link between depression and epilepsy. Epileptogenesis in animal models of temporal lobe epilepsy is followed by the appearance of behavioral symptoms consistent with anxiety/depressive disorders. For example, immobility in the forced swim test, a measure of despair-like symptoms, is increased in rats using the kindling, kainic acid and pilocarpine models of epilepsy, while sucrose preference, a measure of anhedonia, is decreased (Koh et al., 2007; Mazarati et al., 2007; 2008; 2009). Similarly, mice rendered epileptic using the pilocarpine model consistently exhibit increased anxiety in a range of behavioral tests (Gröticke et al., 2007; 2008; Müller et al., 2009a;

2009b). Although not widely reported, these animals are well known among vivarium staff for being aggressive and difficult to handle (unpublished observations). While animal models of human behavior remain controversial, these findings are consistent with the possibility that persistent changes in the physiology and circuitry of the epileptic brain, rather than seizure incidence or disease burden, are responsible for the high risk of depression in epilepsy.

There is currently no established mechanism to account for the co-incidence of epilepsy and depression, reflecting the immature state of research in this area. To begin exploring whether a causal, mechanistic relationship exists, it is reasonable to examine pathological features the disorders have in common. One such feature is dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis. The HPA axis regulates the stress response in mammals, and hyperactivity is a hallmark of depression in humans (Pariante and Lightman, 2008) and is a feature of epilepsy in both animals (Mazarati et al., 2009) and humans (Zobel et al., 2004). Interestingly, chronic stress can precipitate the onset of depressive episodes, and can increase the severity of ongoing depressive periods (Kessler, 1997; Kendler et al., 1999; Gold and Chrousos, 2002; Caspi et al., 2003; Melchior et al., 2007). Dysregulation of the HPA axis in epilepsy, therefore, might lead to changes which increase the risk of depression. Epileptogenesis, on the other hand, might be exacerbated by excess hormone release during chronic stress or depression. Hippocampal neurons possess high levels of corticosteroid receptors (Reul and de Kloet, 1985; Herman et al., 1989; Cameron et al., 1993) and stress is the most cited seizure precipitant among patients with epilepsy (Temkin and Davis, 1984; Haut et al., 2007; Hall et al., 2009). Both corticotropin-releasing hormone and corticosterone increase neuronal excitability on the hippocampus, likely accounting for their ability to provoke seizures (Baram and Hatalski, 1998; Joëls, 2009). Moreover, corticosterone treatment of rodents accelerates kindling epileptogenesis (Karst et al., 1999; Taher et al., 2005; Kumar et al., 2007).

It is important, however, to distinguish between acute modulatory effects of stress and stress hormones on neuronal excitability, seizures and behavior, and the hypothesis that comorbid HPA-axis dysregulation mediates the development of either epilepsy or depression. Specifically, the epileptic brain is characterized by an imbalance between excitation and inhibition. Agents that increase excitation or reduce inhibition will tend to promote seizures, while agents that reduce excitation or increase inhibition will tend to restrain seizure activity. These agents are not considered “disease modifying” because they only alter seizure frequency when present. Anticonvulsant drugs provide the best example of this phenomenon. While these drugs are effective at controlling seizure activity when taken by the patient, they are ineffective at preventing epilepsy or altering the course of the disease (Temkin, 2001; 2009). When the drugs are removed the seizures return. Acute effects of stress and stress hormones may act in similar fashion, albeit in the opposite direction. Therefore, although acute pro-convulsant effects of stress hormones are extremely interesting, and may yet hold the key to explaining the high coincidence of epilepsy and depression, it will be necessary to demonstrate that these agents are disease modifying (e.g. able to produce a persistent reduction in seizure threshold) to support the hypothesis that HPA-axis dysregulation accounts for the coincidence of depression and epilepsy.

Part III: Neurogenesis in stress/depression

Granule cell neurogenesis is reduced by stress and increased by treatments that mitigate stress

Among the many effects of stress, one that emerges as a potential disease modifier is altered neurogenesis. Stressful stimuli such as sleep deprivation (Mirescu et al., 2006), subordination to a dominant animal (Gould et al., 1997; Kozorovitskiy and Gould, 2004),

social isolation (Stranahan et al., 2006) and exposure to predator odor (Tanapat et al., 2001) all reduce granule cell neurogenesis, although not necessarily by the same mechanisms (for review see Duman, 2004; Lucassen et al., 2010; Schoenfeld and Gould, 2011). Similarly, depression models in rodents are associated with decreased neurogenesis (Malberg and Duman, 2003).

Corticosterone again stands out as the mediator of these effects. Corticosterone treatment dramatically reduces neurogenesis in rodents (Cameron and Gould, 1994; Brummelte and Galea, 2010). Adrenalectomy has the opposite effect (Cameron and Gould, 1994), suggesting that baseline levels of adrenal hormones suppress neurogenesis. Moreover, adrenalectomy blocks the anti-neurogenic effects of stressful stimuli (Tanapat et al., 2001) and treatment with the glucocorticoid receptor antagonist mifepristone prevents reductions in neurogenesis in chronically-stressed animals (Oomen et al., 2007). Even more subtle differences in circulating corticosterone levels appear to account for strain differences in neurogenesis rates between Sprague-Dawley and Lister-Hooded rats (Alahmed and Herbert, 2008). In contrast to these stress- and corticosterone-mediated reductions in neurogenesis, treatments which might be considered anxiolytic, including exercise (Ernst et al., 2006), environmental enrichment (Nilsson et al., 1999; Brown et al., 2003), electroconvulsive therapy (Madsen et al., 2000) and antidepressant medications (Malberg et al., 2000) all increase granule cell neurogenesis, the latter in both animals and humans (Boldrini et al., 2009). By reducing or increasing the number of new cells added to the hippocampus these stimuli can induce changes in brain structure and function that persist indefinitely.

An emerging – yet still controversial – story links effective treatment of depression to increased granule cell neurogenesis. In 2003, Santarelli and colleagues demonstrated that irradiation treatment to eliminate neurogenesis blocked the antidepressant effects of fluoxetine in a chronic unpredictable stress paradigm in rodents, implying that the neurogenic effect of this class of drugs is important for their efficacy. Similar findings in rodents were obtained for the antidepressant effects of the cannabinoid receptor agonist HU210 (Jiang et al., 2005). Later studies challenged these findings, however, with the demonstration that increased neurogenesis is not required for all effects of drugs with antidepressant properties (Holick et al., 2008; Singer et al., 2009). Instead, enhanced neuronal plasticity may be important (Wang et al., 2008; Bessa et al., 2009). Recent studies provide some clarification, with the demonstration that these agents likely act by multiple mechanisms – some requiring adult neurogenesis and some not (Surget et al., 2008; David et al., 2009). Conflicting findings may also reflect limitations of ablation strategies, which may be confounded by compensatory circuit changes. As with ablation studies to block epileptogenesis, application of antimitotic agents after treatment begins also leaves intact adult-generated granule cells born in prior weeks. Variability among different rodent strains in baseline rates of neurogenesis further complicates these studies (David et al., 2010). New transgenic and cell-silencing approaches are likely to provide more definitive tests of the neurogenic hypothesis of depression in the future. Nonetheless, it seems likely that increased neurogenesis, probably acting in combination with other neuroplastic changes among adult-generated cells, accounts for some of the beneficial effects of antidepressant therapies. Indeed, the delay between cell birth and cell maturation may explain why antidepressant medications take several weeks to relieve symptoms of depression even though their acute effects on neural transmission are almost immediate.

Finally, increased neurogenesis may be important for recovery from depression, but the converse does not appear to be true, in that experimental manipulations to reduce neurogenesis do not produce depression-like behaviors in rodents (David et al., 2010). Selective ablation of granule cell progenitors by overexpressing the pro-apoptotic gene *Bax*, however, does increase anxiety-related behaviors in mice. These animals avoided

threatening environments, such as brightly lit and open arms of an elevated plus maze, suggesting increased anxiety (Revest et al., 2009). Given the association between stress and depression (Kessler, 1997; Kendler et al., 1999; Gold and Chrousos, 2002; Caspi et al., 2003; Melchior et al., 2007), it is not unreasonable to speculate that reduced neurogenesis might be a risk factor for depression by increasing anxiety.

Part IV: Granule cell neurogenesis: a common mechanistic target of stress and epilepsy?

Functional role of adult-generated granule cells

Chronic stress, depression and epilepsy are all associated with disrupted adult neurogenesis. Given the frequent coincidence of these conditions, their relative effects on neurogenesis almost certainly interact. The significance of these interactions, however, will largely depend on the functional role of adult-generated granule cells, an area of considerable uncertainty. In perhaps the simplest view, the primary function of adult neurogenesis is to replace older granule cells as they senesce. A key assumption of this “replacement” model is that all granule cells are functionally similar; new cells are added to the circuit so that they can take over the role of aging cells. An alternate model of adult neurogenesis proposes, broadly speaking, that newborn granule cells are functionally distinct from mature granule cells, contributing to hippocampal processing in ways that mature granule cells cannot. For example, the addition of new cells has been proposed to be important for pattern separation, and neurogenesis throughout life may provide temporal encoding for memories. These ideas are covered in depth elsewhere (Deng et al., 2010), the main point here being that newborn granule cells may occupy a unique functional niche in the brain. Consistent with this idea, physiological studies clearly demonstrate that newborn granule cells exhibit a number of distinctive properties, including greater plasticity, enhanced excitability and a reduced threshold for long-term potentiation relative to mature granule cells (Snyder et al., 2001; Schmidt-Hieber et al., 2004; Saxe et al., 2006; Ge et al., 2007).

Different models of new granule cell function predict different consequences to altered granule cell neurogenesis in chronic stress, depression and epilepsy. Should new granule cells simply replace older granule cells, transient changes in neurogenesis might exert only minimal effects on hippocampal function. Deficits in cell numbers might easily be made up for by increased neurogenesis at a later date, increased survival of new cells, or reduced turnover of mature cells. Alternatively, if newborn granule cells indeed represent a functionally distinct population with a unique role in brain processing, even subtle changes in neurogenesis rates could significantly impact brain function. It is tempting to speculate that this latter scenario, if correct, might link disrupted granule cell neurogenesis to the high coincidence of epilepsy and depression.

Impact of reduced neurogenesis on the development of epilepsy

During chronic stress and depression, neurogenesis is decreased, while neurogenesis is increased during the development of epilepsy. Despite the opposing direction of these changes, both may be epileptogenic. As described in part I, increased neurogenesis after an epileptogenic brain injury may be maladaptive, as a majority of these cells integrate abnormally (Murphy et al., 2011) and may impair the dentate gate. Curiously, reduced granule cell neurogenesis may also impair the dentate gate. Recent work by Lacefield and colleagues (2010), for example, examined the impact of blocking granule cell neurogenesis in two separate experiments, one using X-irradiation and the other using a transgenic approach. Animals were examined 6–12 weeks later. Physiological recordings revealed that activity synchronization in the dentate was actually increased in the absence of new cells. This finding can be interpreted in a couple ways. Adult-generated cells may be an important

component of the dentate gate and their loss impairs its function. Alternatively, the absence of newborn cells in the dentate may lead to compensatory changes among remaining cell populations, and these changes, in turn, exert a net destabilizing effect. Consistent with this latter idea, Singer and colleagues (2011) found a significant reduction in immunoreactivity for the inhibitory synaptic marker vesicular GABA transporter (VGAT) in the dentate six weeks after, but not immediately after, genetic ablation of newborn cells. They also observed a corresponding reduction in miniature inhibitory post-synaptic current frequency, attesting to the functional significance of this change. The temporal dissociation between new cell ablation and VGAT reductions implies that the change is compensatory rather than a direct consequence of ablation. Importantly, both studies suggest that reduced neurogenesis, while not directly causing epilepsy, may lower the threshold for epileptogenesis to occur – either by enhancing synchronization or reducing inhibition – regardless of whether changes reflect direct or indirect consequences of newborn granule cell loss. In essence, reduced numbers of healthy granule cells born prior to an epileptogenic insult might compound the negative impact of increased numbers of abnormal cells born after an epileptogenic insult. Consistent with this idea, both environmental enrichment (Auvergne et al., 2002) and exercise (Arida et al., 1998) delayed kindling epileptogenesis in rodents, and environmental enrichment was protective in the kainic acid model (Young et al., 1999). Environmental enrichment and exercise increase granule cell neurogenesis, providing correlative evidence in support of the idea the greater numbers of healthy granule cells may be protective, although the possibility that other effects of these treatments were actually operative cannot be excluded.

Further complicating the issue, the timing of stress-induced reductions in neurogenesis relative to an epileptogenic insult could be important. Adult-generated granule cells exhibit several cell age-dependent critical periods, during which they can contribute to different pathologies of the epileptic brain (Fig. 4). Any treatments that reduce neurogenesis, such as chronic stress, will alter the proportions of cells present in each critical period, depending on timing relative to an epileptogenic insult. For example, chronic stress occurring 0–4 weeks before an epileptogenic insult might reduce the pool of granule cells likely to contribute to mossy fiber sprouting and basal dendrite formation (potentially beneficial). Conversely, stress occurring 8–12 weeks before an insult might reduce the number of resistant mature granule cells (potentially harmful). Whether a physiological stimulus like stress could actually alter the number and type of abnormal cells produced by a subsequent insult remains untested; however, work by Kron and colleagues (2010) using timed radiation treatments provides “proof of principle” evidence in support of this idea. Essentially, by exposing rodents to radiation at different time points before an epileptogenic insult, Kron and colleagues were able to selectively eliminate different-age populations of adult-generated granule cells. Loss of different-age cohorts of new cells significantly altered the degree and nature of pathological changes in the dentate following exposure to an epileptogenic brain insult.

Impact of impaired neurogenesis and neuronal integration in epilepsy on depression

Altered neurogenesis and granule cell integration during acute and chronic phases of epilepsy may alter the risk and course of depression. Early in the epileptogenic process neurogenesis is increased (Fig. 6). Distressingly, however, many of these new cells are abnormal (Jessberger et al., 2007; Walter et al., 2007; Parent et al., 2006; Kron et al., 2010). While increased production of normal granule cells following antidepressive therapies appears to be beneficial, increased production of abnormal granule cells in epilepsy may not have the same positive effects. It is not known whether antidepressive therapy in patients with epilepsy increases the production of normal or abnormal granule cells, although clearly this is an important question. Encouragingly, the acute effects of fluoxetine appear to be

anticonvulsant in animal models of epilepsy (Hernandez et al., 2002; Jobe and Browning, 2005); however, long-term studies are needed to elucidate the impact of this class of drugs on neurogenesis and neuronal integration in epilepsy.

In the chronic phase of epilepsy, neurogenesis may drop below normal levels (Fig. 6). While reduced neurogenesis alone does not appear sufficient to cause depression, it could be a risk factor (David et al., 2010). Moreover, disruption of the neurogenic niche in the epileptic brain (Fig. 5c) may limit the utility of antidepressant treatments, just as radiation treatment limits the utility of fluoxetine in rodents (Santarelli et al., 2003). Studies have yet to be conducted to determine whether depressed temporal lobe epilepsy patients with hippocampal sclerosis respond differently to antidepressive therapy relative to epileptic patients without obvious hippocampal damage. A recent study of depressive behavior in rodents rendered epileptic using the pilocarpine model (which produces significant cell loss) however, found fluoxetine to be ineffective (Mazarati et al., 2008). Such studies in humans could provide important guidance for the treatment of depression in patients with epilepsy.

Conclusions

Patients with epilepsy are at increased risk for depression, and prior history of depression increases the risk for new-onset epilepsy. Disrupted adult neurogenesis is a common feature of both disorders, raising the possibility that altered neurogenesis might contribute to this bidirectional relationship. Chronic reductions in neurogenesis following stress and depression would reduce the number of normal granule cells present in the dentate gyrus. A relative paucity of normal granule cells prior to a subsequent epileptogenic insult could magnify the disruptive potential of abnormal cells generated after the insult. Reduced numbers of normal adult-generated cells may also impair the dentate gate, making the hippocampus more vulnerable to seizure spread. Conversely, although neurogenesis is increased acutely in epilepsy, these new cells integrate abnormally, and may not possess the antidepressant qualities normal granule cells appear to have. Reduced neurogenesis in chronic epilepsy may further increase the risk of depression. Clearly, these ideas remain speculative, and even if altered neurogenesis does indeed contribute to the co-morbidity between depression and epilepsy, it is likely to be only one of many factors. Nonetheless, given the high incidence of depression in patients with epilepsy, and the neurogenic effects of all classes of antidepressant medications, it is important to understand the impact of these agents on the epileptic brain.

Acknowledgments

This work was supported by the Charles L. Shor Foundation for Epilepsy Research and the National Institute of Neurological Disorders and Stroke (SCD, Award Numbers R01NS065020 and R01NS062806). The content is solely the responsibility of the author and does not necessarily represent the official views of the National Institute of Neurological Disorders and Stroke or the National Institutes of Health. I would also like to thank Keri Kaeding and Dr. Raymund Pun for helpful comments on earlier versions of this manuscript.

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Figure 1.

Confocal reconstruction of newborn granule cells from a Gli1-CreER^{T2} X GFP reporter mouse born after pilocarpine-status epilepticus. Tamoxifen treatment of these animals leads to persistent expression of GFP in Gli1-expressing granule cell progenitors and all their progeny (Murphy et al., 2011). Two GFP expressing cells are shown; the first with a basal dendrite (arrowheads) and the second (blue asterisk) with an axonal projection into the inner molecular layer (arrows). The section was co-stained with zinc transporter-3 (Znt-3, red), which labels granule cells mossy fiber terminals. In this animal, Znt-3 labeling is present in the hilus, the normal target of mossy fiber axons, and the inner molecular layer (IML),

indicative of mossy fiber sprouting characteristic of epilepsy. DGC-L, dentate granule cell layer. Scale bar = 20 μm .

Figure 2.

GFP-expressing granule cells born after status epilepticus (SE) in Gli1-CreER^{T2} X GFP reporter mice develop abnormally. **Control.** Tamoxifen treatment of 5-week-old Gli1-CreER^{T2} X GFP reporter mice leads to GFP labeling of dentate granule cells. Two months after tamoxifen treatment, labeled cells exhibit normal mature morphologies. **SE.** Tamoxifen treatment of Gli1-CreER^{T2} X GFP reporter mice exposed to status epilepticus one day earlier also leads to GFP expression in granule cells. Two months later, however, many more GFP-expressing granule cells are present, and a subset are found ectopically in the dentate hilus (see expansion of the boxed region, right panel). White lines denote the dentate granule cell layer / hilar border. H, dentate hilus. Scale bars = 100 μ m (left, middle), 30 μ m (right).

Figure 3.

Control (left): Confocal reconstruction of a granule cell from a Thy1-GFP expressing control mouse (see Walter et al., 2007; Murphy et al., 2011). The GFP-expressing cell pseudocolored orange shows typical granule cell morphology, with an axon projecting off the base of the soma (arrowhead) and apical dendrites projecting into the dentate molecular layer. Adjacent GFP-expressing granule cells are shown in green. Scale bar = 50 μ m. **SE (right):** Confocal reconstruction of a twelve-week-old hippocampal dentate granule cell born one week before pilocarpine treatment to induce status epilepticus (SE) and the development of epilepsy. BrdU-labeling, used to birthdate the cell, is shown in blue, while GFP-labeling is shown in orange. This cell developed two prominent basal dendrites projecting deep into the dentate hilus. The arrowhead denotes the axon. DGC-L, dentate granule cell layer. IML, inner molecular layer. MML, middle molecular layer. OML, outer molecular layer. Scale bar = 20 μ m.

Figure 4.

Schematic diagram depicting the contributions of different age granule cells to pathologies of the dentate gyrus in epileptic animals. Granule cells that are mature (>7 wks) at the time of status epilepticus (SE, red bar) treatment are resistant to developing major structural pathologies, although reductions in dendritic spine densities are evident and subtle changes in distal dendrite length have been observed. Juvenile granule cells (≈ 4 wks) develop hilar basal dendrites (HBD's) and mossy fiber sprouting (MFS) quickly (within 4 weeks) after SE. Apical dendrite (AD) changes have not been assessed for this age. Immature granule cells (1-2 wks) develop HBD's by 4 weeks after the insult and MFS by 10 weeks. These cells also exhibit distorted AD trees, and while roughly 90% of cells in this group exhibit reduced spine numbers, 10% have large numbers of spines and somatic and dendritic hypertrophy. Newborn cells (generated after the insult) migrate to ectopic locations in the hilus, develop HBD's by 4 weeks and MFS by 10 weeks. AD's have yet to be examined for this age.

Figure 5.

Confocal reconstructions of hippocampi from control (A) and epileptic (B, C) thy1-GFP expressing mice. Animals were examined three months after pilocarpine status epilepticus (B, C) or control treatment (A). A subset of granule cells and pyramidal cells are labeled with GFP in these animals (Feng et al., 2000). **A, A.1;** Images from a control animal reveal the normal hippocampal structure (A) and typical granule cell morphology of labeled cells (A.1, expansion of boxed region in A). Note the absence of basal dendrites and cell bodies in the hilus. **B, B.1;** Images from an epileptic animal with preserved gross hippocampal structure (B). Cell layers are intact, and large numbers of labeled granule cells are present. This animal does not have hippocampal sclerosis. Despite this preservation of gross structure, however, many labeled granule cells are abnormal (B.1, expansion of boxed region in B), with basal dendrites and cell bodies in the hilus (arrows). **C, C.1;** Sclerotic hippocampus from an epileptic animal. Note the red autofluorescence of degenerated cells in the dentate granule cell layer and pyramidal cells layers, and the relative absence of GFP-expressing cells. The expansion (C.1) shows a surviving granule cell with a contorted apical dendrite (arrow) and contracted dendritic tree. H, hilus. CA1, CA1 pyramidal cell layer. CA3, CA3 pyramidal cell layer. Scale bars = 200 μ m (A–C) and 20 μ m (A.1–C.1).

Figure 6.

Schematic model depicting the impact of epileptogenesis on rates and integrative properties of adult-generated granule cells. In the baseline condition, a population of newborn adult-generated granule cells (green circles) is present amongst a larger population of “old” granule cells (gray circles) generated early in development (1). Following an epileptogenic brain injury, newborn cells born before the insult but still in an immature state are vulnerable to disruption. Some immature cells integrate normally (2; green circles with gray centers) and some develop abnormal features (2; red circles with gray centers). The epileptogenic brain injury also increases neurogenesis rates over baseline conditions; however many of these new cells also integrate abnormally, leaving a mixed population of newborn normal (green circles) and abnormal (red circles) cells (2). At this stage, hippocampal function may be compromised by the presence of abnormal cells, which could predispose the patient to depression. In the chronic phase of epilepsy (months to decades), hippocampal sclerosis may develop, which is characterized by cell loss (red X) and gliosis. In this state (3), endogenous neurogenesis may decrease dramatically, and the small numbers of new cells born are still at risk for integrating abnormally (red circles). Previously generated abnormal granule cells are still present (red circles with gray centers). Reduced

neurogenesis and abnormal functioning of the dentate in this state may further increase the risk of depression.