



Review

Neurogenesis in the epileptic brain: a brief overview from temporal lobe epilepsy

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Abstract:

Dentate granule cell neurogenesis persists throughout life in the hippocampus of mammals. Alterations in this process occur in many neurological diseases, including epilepsy. Among the different types of epilepsy, the most frequent is temporal lobe epilepsy (TLE). Therefore, a number of laboratory studies use animal models of TLE to observe the fate of neuronal cells after seizures. Hippocampal neurogenesis is very sensitive to physiological and pathological stimuli. Seizures, as pathological stimuli, alter both the extent and the pattern of neurogenesis, which is associated with cognitive function. Various alterations in neurogenesis are observed depending on the amount of time that has elapsed after the seizures. In acute seizures, neurogenesis generally increases, whereas in chronic epilepsy, neurogenesis decreases. Moreover, several methods currently used for the treatment of brain disorders such as TLE can also have significant impacts on cognitive functions. This review is focused on the recent findings regarding neurogenesis in animal models of TLE.

Key words:

dentate gyrus, seizures, pilocarpine, kainic acid, antiepileptic drugs

Abbreviations: AED(s) – antiepileptic drug(s), DG – dentate gyrus, KA – kainic acid, MGE – medial ganglionic eminence, PILO – pilocarpine, SE – status epilepticus, SGZ – subgranular zone, SRMS – spontaneous recurrent motor seizures, SVZ – subventricular zone, TLE – temporal lobe epilepsy

Introduction

Neurogenesis is a developmental process that involves the proliferation, migration and differentiation

of neuroblasts and the synaptic integrations of newborn neurons. Proliferation of new cells continues into old age, even in humans [20]. There are two major neurogenic regions in the brain: the dentate gyrus (DG) of the hippocampus and the subventricular zone (SVZ) of the brain [38, 44]. The neurogenic cells of the SVZ may constitute a population of undifferentiated cells that can be recruited after tissue injury [19, 45, 48]. The newly born granule cells in the DG have been extensively studied over the last several years. They send axonal projections to their normal target zone, the mossy fiber pathway [27]. Their dendritic

trees resemble those of other granule cells, although some aspects of their dendrites and spines have been suggested to be immature [51]. Moreover, the newly born granule cells appear to develop electrophysiological properties similarly to other granule cells [77]. The functional integration of newly born dentate granule cells into the hippocampal circuitry [35, 60] and their ability to mediate long-term potentiation in DG [63] has led to the hypothesis that neurogenesis in the adult brain may play a key role in learning and memory [67, 69], as well as cognitive dysfunction in some diseases, such as temporal lobe epilepsy (TLE), Alzheimer's disease and major depressive disorders. Hippocampal neurogenesis is very sensitive to physiological and pathological stimuli. Seizures, as pathological stimuli, alter both the extent and the pattern of neurogenesis, although the overall effects depend on the type of seizure [40].

Animal models of TLE

Epilepsy is one of the oldest and most well-known ailments of the brain, affecting 50 million people worldwide [58]. According to epidemiological studies, approximately 70–80% of epilepsy patients achieve remission, but there are still patients who are refractory to currently available treatments [41, 46, 57].

Understanding the molecular mechanisms associated with seizure development can be addressed by dividing all *in vivo* animal models into two categories: models of seizures and models of epilepsy. The difference between these two groups is those models of epilepsy are characterized by multiple spontaneous recurrent seizures (TLE evoked by pilocarpine or kainic acid), whereas models of seizures are characterized by generalized seizures in response to a single exposure to a potent neurotoxin [3, 47]. The inherent distinction between the two types of models might foster a better understanding of critical elements in the evolution of seizures. Among the many different animal models of epilepsy, the most well known and most frequently used is TLE. Because human TLE is the most common type of epilepsy, animal models of this condition are thought to be some of the best for helping us understand the problem of epileptogenesis and the neuronal alterations that take place in the brain after convulsions. Several well-characterized animal models of

TLE exist, and they reflect, at least in part, the complex partial seizures observed in patients with TLE [59]. Administration of chemical convulsants, including the glutamate analogue kainic acid (KA) and the cholinergic agonist pilocarpine (PILO), and electrical stimulation of the amygdala or hippocampus (kindling model) are the most frequently studied animal models of TLE. PILO and KA can be systemically or intracerebrally injected into animals and can rapidly produce seizures with an acute episode of status epilepticus (SE). The majority of rodents that survive the initial SE develop spontaneous seizures after a quiescent period of several days to several weeks [11]. The PILO model is well characterized in rats [12, 74] and in various strains of mice [68, 73]. According to the results from many different studies, PILO induces neurochemical alterations in neurons and glial cells, which in turn change the cellular environment by altering the expression levels of receptors, trophic factors, enzymes and proteins from cytoskeleton, altering the phosphorylation of macromolecules, etc. [65]. Additionally, cell death associated with prolonged convulsions can result in reactive gliosis. Taken together, these alterations can cause brain damage and persistent hyperstimulation. The mechanism of seizure induction for the KA model is very similar to the PILO model. Experimental evidence indicates that KA causes cell death in the hippocampus, the entorhinal cortex and the medial thalamic nuclei [5, 6, 64]. The kindling model involves the repeated application of a subconvulsive stimulus delivered through a bipolar electrode implanted into a limbic structure, such as the amygdala, hippocampus or entorhinal cortex [2]. Pitkanen and Sutula [52] reported neuronal damage, gliosis, neurogenesis and mossy fiber sprouting after using the kindling model of epilepsy.

Neurogenesis: basic and new findings

As mentioned in the Introduction, neurogenesis takes place in specific brain regions throughout life. These regions are the subgranular zone (SGZ) of the DG in the hippocampus and the subventricular zone (SVZ) of the anterior lateral ventricles [21, 22, 44, 72]. According to recent data, newly born neurons from the SGZ are functionally integrated into the hippocampal circuitry [53, 79], and they have passive membrane

properties, action potentials, and functional synaptic inputs similar to those found in mature granule cells [78]. The highest level of neurogenesis within the neurogenic zones occurs during prenatal development. However, generation of new neurons in the adult hippocampus has been one of the most provocative research topics for the last several years. The interest in neurogenesis in adolescence and adulthood increased rapidly because of the importance of hippocampal function in learning and memory in both the normal and the diseased/injured brain [40]. Alterations in cognitive function are commonly observed in TLE, Alzheimer's disease, cranial irradiation and traumatic brain injury [1, 16, 17, 54, 56]. Additionally, methods currently used to treat brain disorders can also significantly impact cognitive functions [14, 66].

Neurogenesis and acute seizures

Animal studies revealed that there are many conditions that affect the rate of cell proliferation, migration and differentiation and hence affect the process of neurogenesis. These changes are usually caused by environmental and pathological conditions. One of the most common abnormal conditions that has a significant impact on neurogenesis is a seizure. Many different studies have been performed to identify the disturbances in neurogenesis based on the types of convulsions (Tab. 1). Moreover, the same methods producing seizures can produce different types of neurogenesis alterations.

Electrical stimulation increases the rate of neurogenesis by neuronal depolarization or repetitive dis-

charge [7]. Dramatic increases in neurogenesis were observed in the SGZ following PILO- and KA-induced SE [7, 26, 50] or kindling stimulation. Examination of the hippocampus from young TLE patients (2 years old) also suggested increased cell proliferation [8]. Although the molecular mechanisms underlying the seizure-induced increase in neurogenesis are unclear, several potential mechanisms have been proposed:

1. Up-regulation of the factors promoting proliferation and survival of neurons (including NGF – nerve growth factor, BDNF – brain-derived neurotrophic factor, FGF-2 – fibroblast growth factor, and VEGF – vascular endothelial growth factor) [4, 10, 15, 23, 25, 43].
2. Positive impact of increased levels of the inhibitory neurotransmitter γ -aminobutyric acid (GABA) on the proliferation of neural progenitors, the migration and differentiation of neuroblasts, and synaptic integration of newborn neurons in the DG a short time after a seizure [24].
3. Increase of neurogenesis in the presence of high levels of neuropeptide Y (NPY) [32, 33, 61, 62], which produces an increase in neural stem cell proliferation as a consequence of modulation of neuron-restrictive silencing factor (NRSF) activity [36].

Data from studies over the last several years show that the altered neurogenesis due to acute seizure activity has a strong impact on the development of aberrant circuitry [40]. Hippocampal injury in chronic epilepsy may occur as a consequence of acute seizures that disturb cell proliferation.

Neurogenesis and chronic TLE

In rats, the increased neurogenesis observed after acute seizures usually returns to basal levels within 2 months after the convulsions [18]. However, in chronic TLE, which is characterized by high numbers of spontaneous seizures, hippocampus-dependent learning and memory deficits are observed, which can be at least partially linked to decreased neurogenesis [28]. Significant evidence for reduced neurogenesis in the KA model of mouse TLE was shown by Kralic and coworkers [39], who demonstrated a correlation between decreased neurogenesis and increased astrocyte production. Additional studies performed by Lederberger and colleagues [42] using the KA mouse model of TLE showed impaired fate commitment and/or early differentiation of proliferating cells in the lesioned DG.

Tab. 1. Neurogenesis after acute seizures (*in vivo* studies)

Type of seizure	Neurogenesis	Reference
KA (rats)	↑	[43]
KA (rats)	↑	[10]
Electrolytic lesions (rats)	↑	[23]
Kindling (rats)	↑	[7]
KA (rats)	↑	[26]
PILO (rats)	↑	[15]
Kindling (rats)	↑	[4]
PILO (mice)	↑	[33]

↑ increase in neurogenesis, KA = kainic acid, PILO = pilocarpine

The number of spontaneous seizures has a strong impact on the extent of neurogenesis. Significant alterations in the proliferation of neural progenitors and the migration and differentiation of neuroblasts were strongly associated with high numbers of spontaneous seizures. Heinrich and coworkers [30] showed a decrease in neurogenesis at 1 week and a virtual loss of all neurogenesis by 4–6 weeks after the first seizures. However, the opposite results were shown by Bonde et al. [9] in the electrically evoked SE rat model: no changes in neurogenesis (up to 6 months after SE) were reported. Moreover, no effects on neurogenesis were observed by Cha et al. [13], who found that the hippocampus was capable of generating new neurons several weeks after SE and that recurrent seizures enhanced the production of new neurons in a rat PILO model of epilepsy. Hattiangady and coworkers [29] showed that in the rat, severely diminished dentate gyrus neurogenesis in chronic TLE was not associated with either decreased production of new cells or reduced survival of newly born cells in the subgranular zone and in the granular cell layer. Rather, it was linked to a dramatic decline in the neuronal fate choice of newly generated cells. In chronic TLE, newly born cells differentiated primarily into glial cells, which was different from the neuronal fate that was observed in normal animals.

Waldau and colleagues [76] tested the hypothesis that spontaneous recurrent motor seizures (SRMS) in chronic TLE could be reduced by grafting neural stem cells that are capable of adding new GABA-ergic interneurons and glial-derived neurotrophic factor-ex-

pressing astrocytes into the epileptic hippocampus. They showed that the grafted neural stem cells decreased the number of spontaneous recurrent motor seizures in the rat model of chronic TLE. SRMS were reduced by 43%, and stage V seizures were reduced by 90%. This evidence confirms that this therapy effectively diminishes SRMS in chronic TLE. Based on the results obtained from different animal models of epilepsy, we can confirm that decreased neurogenesis depends on the animal model and on the age of the animal at the time of the initial seizure episode (Tab. 2).

Neurogenesis after administration of antiepileptic drugs

Nearly 30% of epilepsy patients suffer from refractory epilepsy and require at least two antiepileptic drugs (AEDs) in combination. Each additional AED added to the standard treatment increases the risk of serious side effects. One very important side effect may be the alteration of neurogenesis. This can be very problematic, especially for children, because neurogenesis is most vigorous at early ages and because any reduction may cause learning and memory impairments. Treatment with AEDs takes at least 2–3 years and, in many situations, lasts a lifetime. While the most desirable effect is the reduction of seizures, long-term medication with AEDs may affect neuronal excitability and impair cognition and memory [49]. Reduced neurogenesis is often associated with alterations in some of the hippocampus-dependent cognitive functions [34, 55]. However, seizures are known to stimulate neurogenesis [37, 50]. This is why the problem of long-term treatment of epilepsy patients with AEDs is an important issue with respect to neurogenesis.

Results obtained by Chen et al. [14] using topiramate and lamotrigine, two commonly applied second-generation AEDs, indicated that topiramate but not lamotrigine promoted aberrant neuron regeneration in the hippocampus after SE. Similarly to lamotrigine, levetiracetam suppressed the development of spontaneous electroencephalographic (EEG) seizures and aberrant neurogenesis following KA-induced SE [71]. Moreover, Jessberger and coworkers showed that valproic acid (VPA – classical antiepileptic drug and mood stabilizer) potentially blocked seizure-induced neurogenesis, an effect that appeared to be mainly mediated by inhibiting histone deacetylases (HDAC) and normalizing HDAC-dependent gene expression

Tab. 2. Neurogenesis after chronic spontaneous seizures (*in vivo* studies)

Type of seizure	Neurogenesis	Reference
KA (rats)	↓	[28]
PILO (rats)	↓	[13]
KA (mice)	↓	[39]
KA (mice)	↓	[42]
KA (mice)	↓	[30]
Electrical stimulation (rats)	no change	[9]
KA (rats)	↑	[29]

↓ decrease in neurogenesis, ↑ increase in neurogenesis, KA = kainic acid, PILO = pilocarpine

within the epileptic dentate area [36]. Additional studies performed on VPA indicated that it reduced cell proliferation in the dentate SGZ and impaired the ability of treated rats to successfully perform a hippocampus-dependent spatial memory test [75]. Moreover, the NMDA antagonist MK801 and two GABA_A agonists, phenobarbital and diazepam, reduced numbers of newly born neurons in the brains of infant rats [70]. In the DG, many of the newly formed cells differentiated toward a neuronal phenotype; phenobarbital and MK801 significantly reduced the number of new neurons in that structure [70]. These results showed that NMDA receptor- and GABA_A receptor-mediated enhancement disturbed cell proliferation and, in fact, inhibited neurogenesis.

Conclusions

There is no doubt that adult hippocampal neurogenesis is very important for proper learning and memory. It is obvious that defective neurogenesis may contribute to progressive memory dysfunction [31]. The most popular animal model of TLE is widely used to better understand the process of epileptogenesis and to find the best way to protect neurons. It is very important for patients suffering from epilepsy to receive a medication that will be able to stop the process of epileptogenesis and protect neurons with minimal side effects, especially learning and memory disturbances. Results from animal models show that at early time points after acute seizures or SE, hippocampal neurogenesis and abnormal recruitment of newly born neurons into hippocampal circuitry increases, whereas the chronic phase of epilepsy is associated with substantially decreased hippocampal neurogenesis.

It is difficult to unambiguously determine if the reaction of increased neurogenesis after seizures increases or decreases the likelihood of epileptogenesis. However, recent studies have shown that seizure-induced neurogenesis has a pro-epileptogenic role in the formation of the epileptic hippocampus. The process of epileptogenesis generates ectopic granule cells that are born after SE and, instead of migrating to the granule cell layer, migrate to the hilus or to the inner molecular layer of the DG [48]. This situation is abnormal and may be one of the stimuli that induce epi-

leptogenesis. Seizure activity or high levels of inflammation, which are main epileptogenic factors, have a strong impact on plasticity, migration patterns, morphology and the afferent synapses of the newly born cells. To answer the question of whether or not seizure-induced neurogenesis increases or decreases the likelihood of epileptogenesis, more advanced studies are necessary. These studies should focus on the integration of newly born cells into the existing neuronal network and on how this integration contributes to the excitability of this network.

Determining the best combination of AEDs is equally important because they can have a positive impact on neurogenesis. Therefore, studies concerning the problems of increased neurogenesis in TLE, learning and memory impairments and mood disorders are essential to better understand seizure development and to determine how to stop the process of epileptogenesis.

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