DOI 10.1007/s11055-019-00892-z
Neuroscience and Behavioral Physiology, Vol. 50, No. 2, February, 2020

Hippocampal Neurogenesis in Epileptogenesis

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Translated from Rossiiskii Fiziologicheskii Zhurnal imeni I. M. Sechenova, Vol. 104, No. 10, pp. 1152–1162, October, 2018. Original article submitted July 24, 2018. Revised version received September 6, 2018.

This review presents data on the characteristics of the reorganization of the hippocampus associated with impairment to neurogenesis in epileptiform states of different etiologies. Data on the effects of convulsive states of different severities and frequencies on the levels of proliferation, migration, and insertion of new cells into the hippocampal neural network are presented and anomalies in newly formed granule cells are described. The focus is placed on possible explanations of existing contradictions in anybody assessment of the importance of neurogenesis in epilepsy.

Keywords: neurogenesis, epileptogenesis, hippocampus, proliferation.

Hippocampal neurogenesis in adult mammals. The views that the brain is essentially unable to undergo regeneration and that neurogenesis does not occur in adult mammals have long been held. However, Altman's studies in 1962 demonstrated that mitotically active precursor cells persist in the brains of adult animals and operate as the sources for new neurons [1]. Several subsequent studies showed that neurogenesis in the adult state occurs in almost all mammals, including humans [2–4]. Two main neurogenic niches exist in the brain: the subventricular zone of the lateral ventricles and the subgranular zone of the dentate gyrus of the hippocampus.

The subgranular zone of the dentate gyrus of the hippocampus is one of the niches containing stem cells in the adult mammal brain. The narrow strip between the granule cell layer and the hilus contains a unique microenvironment, which allows a population of neuronal stem cells to be maintained. Neuronal stem cell proliferation occurs here, with their subsequent differentiation into dentate gyrus granule cells. Dentate gyrus granule cells formed in the adult body pass through several sequential stages of development before functional integration into the hippocampal neural network. Cells of the first type, or glial-like cells, constitute a population of neural stem cells and give rise to proliferating intermediate precursor cells (type 2). These in turn give rise to neuroblasts (type 3), which then differentiate into mature dentate gyrus granule cells. Apart from the population of neuronal precursor cells, this area also contains other cell types, expressing cytokines, growth factors, and neurotransmitters, including GABA. These cells are believed to create the conditions required for neurogenesis [5].

Hippocampal neurogenesis in adult animals is functionally linked with learning and memory. With age, the level of neurogenesis decreases, which coincides in time with decreases in the ability of the brain to recover after trauma. Neurogenesis is believed to play a key role in maintaining mental health and recovery after stroke, as well as in depression, Huntington's disease, and Parkinson's disease [6–10]. However, the role of neurogenesis in the pathogenesis of Alzheimer's disease and epilepsy is ambiguous. For example, some investigators take the view that the process of neurogenesis is impaired in Alzheimer's disease, while others believe that the level of neurogenesis is increased [11–13]. It may be that the contradictions can be explained in terms of the fact that different investigators have analyzed levels of neurogenesis at different stages of disease and at different ages. In addition, it has been suggested that an increased level of neurogenesis in Alzheimer's disease is compensatory in nature [14]. In epilepsy, the functional importance of neurogenesis remains incompletely understood.

Hippocampal neurogenesis in adult mammals in epileptogenesis. Epilepsy-associated changes in the an-

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atomical structure of the dentate gyrus and hilus may be of prime importance for the initiation and development of convulsive states. The hippocampus of patients with temporal partial epilepsy shows numerous cellular anomalies, including decreases in the numbers of pyramidal cells in fields CA1 and CA3, along with hippocampal astrogliosis. Impairments seen in the hilus, known as endosphorial sclerosis, constitute one of the most characteristic signs of temporal partial epilepsy [15]. In addition, the dentate gyrus shows branching of mossy fibers, dispersion of the granule layer, the appearance of ectopic cells in the hilus, and increases in the density of the basal dendrites of neurons [16]. The rodent hippocampus responds to pilocarpine, which induces status epilepticus, with similar changes: branching of mossy fibers, dispersion of the granule cell layer, the appearance of ectopic cells, and increases in the density of basal dendrites [17]. Increased levels of neurogenesis also contribute to the development of epilepsy, though the functional significance of neurogenesis in the development of epileptiform states remains undetermined. We will consider the probable consequences of aberrant neurogenesis, leading to impairments in hippocampal function, in more detail.

A number of in vivo experimental models of temporal partial epilepsy display significant increases in the proliferative activity of precursor cells and accelerated maturation of neurons at the initial stages of epileptogenesis. However, the level of proliferation is decreased at the later stages. In particular, cell proliferation in the dentate gurus has been shown to increase by factors of 5–10 after some latent period (lasting several days or weeks) after convulsive seizures induced by pilocarpine or kainate [18–20]. In the dentate gyrus, this sharp increase in the level of proliferative activity is due to active proliferation of glial-like neuronal precursor cells [21].

Studies have shown that 75–90% of cells newly formed after convulsive seizures start to express mature neuron markers within four weeks [19, 22]. In addition, it has been suggested that convulsive seizures accelerate the maturation and integration of newly formed neurons [23].

The level of proliferation returns to initial about 3–4 weeks after a convulsive seizure [19]. It should be noted that chronic temporal partial epilepsy is accompanied by a decreased level of neurogenesis. Proliferative activity has been shown to drop significantly by five months after administration of kainate [24].

The functional role of newly formed granule cells. One approach to understanding the role played by neurogenesis in adult mammals in epileptogenesis is provided by selective inhibition of the process of neurogenesis induced by epileptiform activity. if newly formed granule cells promote epileptogenesis, inhibition of neurogenesis should have a protective effect. This hypothesis was tested in a model of epilepsy, i.e., kindling induced by stimulation of the amygdala. Attachment of polysialic acid to neuronal cell adhesion molecules is important for neurogenesis to occur in the adult brain [25]. This reaction can be blocked by administration of endoneuraminidase (EndoN) [26, 27]. Administration of EndoN into the amygdala has been shown to decrease the level of hippocampal proliferation, though this led to a decreased convulsive threshold. The number of ectopic granule cells in the hilus decreased significantly [20, 27]. This demonstrates that partial inhibition of the aberrant migration of newly formed granule cells did not prevent the epileptogenesis process, at least in kindling, which is a model of epilepsy in humans. Further studies using the same model demonstrated that administration of EndoN did not prevent the development of spontaneous seizures [27].

On the other hand, Jung et al. [25] used prolonged infusions of cytosine-β-D-arabinofuranoside, an antimitotic agent, to block neuron proliferation in the pilocarpine model of epilepsy. These studies demonstrated that the probability of developing spontaneous repeating seizures decreased significantly, pointing to the important role of newly formed cells in the development of convulsive activity after administration of pilocarpine. However, it is interesting to note that decreases in the proliferative activity of neurons had no effect on features such as branching of mossy fibers.

Thus, inhibition of neurogenesis in some cases decreased the frequency of convulsive seizures and promoted recovery of cognitive functions, which supports the suggestion that aberrantly inserted newly formed cells are proepileptogenetic [28]. However, in other cases, inhibition of neurogenesis has been shown to increase convulsive readiness, increasing the frequency of convulsive seizures and their duration [29]. Termination of neurogenesis after manifestation of disease can also decrease seizure frequency, though duration increases [28]. Recent studies have demonstrated that low-intensity convulsive seizures decrease the level of neurogenesis, while intense seizures promote the differentiation of neural stem cells into glial cells, leading to gliosis [30]. This emphasizes the importance of understanding the etiology and pathogenesis of disease, particularly epilepsy.

The functional role of newly formed ectopic hilar granule cells. One of the proposed functions of the dentate gyrus is the "gatekeeper" function. As the proportion of inhibitory innervation of granule cells is greater than the proportion of excitatory innervation [31], the dentate gyrus limits the number of excitatory signals, thus controlling the level of arousal. In fact, innervation of GABAergic interneurons by granule cells is a negative feedback mechanism controlling hippocampal arousal [32]. In rodents experiencing epileptiform activity, the dentate gyrus fails to cope with this task [33, 34]. The cause of impairments to hippocampal function may be the reorganization of neuronal connections induced by aberrant neurogenesis. Within the framework of the fact that aberrant granule cells contribute to the development of impairments to neural networks in epileptogenesis, it can be suggested that these cells undergo functional integration into hippocampal neural networks. Shifts in the ratio of excitation and inhibition can occur as a result of insertion

of newly formed cells with different electrophysiological characteristics [35] and aberrant synaptogenesis.

One typical feature of aberrant neurogenesis induced by convulsive seizures is migration of anomalous newly formed granule cells to the hilus of the dentate gyrus rather than to the granule cell layer. These cells are termed ectopic hilar granule cells. Ectopic cells insert into the neural network of the dentate gyrus and receive excitatory innervation from other granule cells. Their axon collaterals have been shown to form projections in field CA3, forming synaptic contacts with mossy fibers from granule cells and GABAergic interneurons innervating pyramidal cells in field CA3 [36]. Thus, cyclic connections form [37], leading to overexcitation of the hippocampus and exacerbation of epileptiform activity. in addition, hilar ectopic granule cells have been shown to be characterized by permanently increased activity as compared with granule cells in the dentate gyrus [36]. Despite the fact that hilar ectopic granule cells make up a small percentage of dentate gyrus granule cells, their arousal can lead to activation of a large population of dentate gyrus granule cells and induce epileptiform activity as a result of reciprocal synaptic contacts [36]. Cyclic connections have also been shown [38] to form between granule cells in the healthy brain, though in smaller numbers and, probably, only transiently. Thus, the formation of cyclic connections between granule cells may not be a unique feature of the dentate gyrus in the epileptic brain, though their relative number may be increased due to epileptiform activity or epileptiform activity may stabilize these connections, such that cyclic connections can make a significant contribution to the process of epileptogenesis [39]. This hypothesis has been considered in detail in Gulyaeva's review [40].

Scharfman et al. [41] used a pilocarpine model of epilepsy to show that hilar ectopic granule cells express *c-fos* (an early response gene) after spontaneous seizures, which confirms their active involvement in the formation of epileptic connections. Studies using the pilocarpine model of epilepsy also demonstrated that the number of hilar ectopic granule cells correlates with the number of spontaneous convulsive seizures [17, 42].

The functional role of newly formed dentate gyrus granule cells. A significant proportion of newly formed cells migrate to the granule layer of the dentate gyrus, where they are integrated into the existing neural network. However, in the epileptic brain, these cells have a series of structural and functional features. Pun et al. [43] showed that newly formed granule cells play a leading role in the branching of mossy fibers. This group used animals with knockout of the gene responsible for PTEN synthesis, which was excluded only in newly formed granule cells; the result was overactivation of the mTOR signal pathway and the anomalous development of these cells. Increases in the numbers of these knockout cells correlated with increases in the branching of mossy fibers, i.e., the axons of ectopic granule cells. It should be noted that animals in which the number of cells knocked out was minor and branching of mossy fibers was not seen displayed epileptiform activity [44]. Branching of mossy fibers has been demonstrated in many models of epilepsy [16, 45, 46]. Mossy fibers form contacts with the apical dendrites of granule cells, and only a small proportion of these cells form contacts with GABAergic interneurons [47]. This reorganization of the dentate gyrus promotes the formation of a focus of epileptogenesis. However, studies have been reported showing that newly formed granule cells are most subject to overarousal immediately after induction of a convulsive seizure, before branching of mossy fibers is seen [48], i.e., the functional significance of increased branching of mossy fibers in epileptogenesis remains incompletely understood. Furthermore, studies have shown that repeated convulsive seizures in WAR rats do not lead to increased branching of mossy fibers [49].

The second morphological feature of newly formed granule neurons in the epileptic brain consists of basal dendrites of dentate gyrus neurons, which usually disappear during cell development [50]. Increases in the number of basal dendrites are seen in different models of epilepsy [47, 51, 52]. Ribak et al. [53] were the first to identify the involvement of the basal dendrites of granule neurons in the cyclic connections of the hippocampus due to formation of synaptic connections with mossy fibers. Murphy et al. [54] found that granule cells form basal dendrites immediately after induction of convulsive seizures following administration of kainate. However, at this time there are only small numbers of newly formed cells. This indicates that basal dendrites also form on those granule cells appearing before seizures and that newly formed granule cells are not the only type of cell underlying morphological changes as a result of epileptiform activity.

Thus, the impairments described in the migration pathways and morphofunctional characteristics of newly formed cells in epilepsy suggest that they have a proepileptic role. However, some investigators have described a protective function of newly formed cells in epileptogenesis [55, 56]. This contradiction is partly explained by the suggestion of Murphy et al. [54] that newly formed granule cells inserted into the granule cell layer can be integrated differently into the existing neural network, forming different numbers of spines, and also forming different dendrites. Thus, some of these cells have a protective function, while others promote epileptogenesis. Newly formed granule cells can be divided into two groups, differing in terms of insertion site and excitability. The first group, which includes most newly formed cells, is characterized by a low density of spines, pointing to low excitability. However, about 10% of newly formed neurons have a high density of spines, and also form long basal dendrites. Cells with basal dendrites have more synaptic contacts with mossy fibers, i.e., greater levels of integration into proepileptogenetic hippocampal networks. Despite the fact that a large propor-

tion of newly formed granule cells are hypoexcitable and migrate into the granule cells layer, where they probably carry out a protective function, cells of the other, smaller, group are hyperexcitable. These also insert into the existing hippocampal network, forming cyclic glutamatergic neural networks. Thus, the overall influence on the epileptogenetic process may depend on the relative contributions of each of these two different cell populations [54]. As previously, what controls and regulates the development of these two cell populations remains unknown. Some authors hold that the number and duration of convulsive seizures have no effect on the speed or other characteristics of neurogenesis in adult animals [57, 58]. However, other investigators have found that the duration and intensity of convulsive seizures may be key factors determining the characteristics of newly formed granule cells [59, 60]. Granule cells formed as a result of intense convulsive seizures are probably more often hyperexcitable, while cells formed as a result of less intense convulsive seizures are mainly hypoexcitable. It has been suggested that the actions of these hyperexcitable cells are opposite in direction to the action of inhibitory neurons in the hippocampus, leading to decreases in inhibitory innervation and promoting the epileptogenetic process [39].

Thus, the ratio of hypo- and hyperexcitable cells due to the intensity of convulsive seizures may be one of the key factors determining the consequences of the epileptogenesis process [39]. In summary, we can say that Murphy et al. [54] suggested a particularly interesting hypothesis with great potential, which can probably help explain the numerous contradictions arising in studies of this question.

Conclusions. Thus, many studies have been reported confirming that convulsive activity at the initial stages of epileptogenesis is associated with increases in the level of proliferation in the hippocampus [18, 19]. However, it remains unknown whether increased proliferative activity in the hippocampus precedes and can promote the development of epileptiform activity. The accumulated data provide evidence that epileptiform activity impairs, one way or another, the sequential stages of neurogenesis, and in particular may affect migration [36] and the rate of differentiation [23] and may alter the nature of dendrite and, probably, axon formation [16, 61]. Epileptiform activity also impairs the integration of newly formed neurons into existing neural networks and alters the normal electrophysiological characteristics of newly formed dentate gyrus granule cells [62]. In addition, some cases show increases in the number of astrocytes [15], which suggests that the direction of differentiation of newly formed cells may also change. The question of why and how all these changes occur remains open.

Summarizing all known data suggests that the question of how all the observed and suggested impairments influence epileptogenesis continues to lack an unambiguous answer. Some studies have confirmed a protective effect of neurogenesis in adult animals [55, 56], while others have found indications that neurogenesis promotes the process of epileptogenesis [52, 56, 60, 62, 63]. There are also data indicating that newly formed granule cells do not play any significant role in epileptogenesis [20, 27, 64], and all the cellular anomalies observed merely accompany epileptogenesis but have no serious consequences. Thus, the question of the significance of neurogenesis induced by epileptiform activity also remains open. As shown above, the contribution of newly formed cells to epileptogenesis probably depends on the ratio of cells with different electrophysiological properties.

This study was supported by the State Assignment on topic No. AAAA-A18-118012290371-3.

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