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REVIEW ARTICLE

Adult Neurogenesis in Epileptogenesis: An Update for Preclinical Finding and Potential Clinical Translation

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Abstract: Epileptogenesis refers to the process in which a normal brain becomes epileptic, and is characterized by hypersynchronous spontaneous recurrent seizures involving a complex epileptogenic network. Current available pharmacological treatment of epilepsy is generally symptomatic in controlling seizures but is not disease-modifying in epileptogenesis. Cumulative evidence suggests that adult neurogenesis, specifically in the subgranular zone of the hippocampal dentate gyrus, is crucial in epileptogenesis. In this review, we describe the pathological changes that occur in adult neurogenesis in the epileptic brain and how adult neurogenesis is involved in epileptogenesis through different interventions. This is followed by a discussion of some of the molecular signaling pathways involved in regulating adult neurogenesis, which could be potential druggable targets for epileptogenesis. Finally, we provide perspectives on some possible research directions for future studies.

Keywords: Epileptogenesis, adult neurogenesis, drug target, optogenetic, chemogenetic, neural circuit.

1. INTRODUCTION

Epilepsy is a multifarious and deliberating disease, characterized by excessive or hypersynchronous spontaneous recurrent seizures (SRS) affecting ~1% of the population [1, 2]. The term "Epileptogenesis" refers to the process by which a normal brain becomes epileptic and involves a complex epileptogenic network. Anti-epileptic drugs (AEDs) are the first-choice treatment for epilepsy in clinical practice. Although there are currently ~30 AEDs with diverse molecular targets, these AEDs are generally symptomatic in controlling seizures (also called anti-seizure drugs) but are not disease-modifying in epileptogenesis [3]; no effective pharmacological prevention or cure has been identified for epilepsy. Thus, progress towards deeper and alternative insights into the mechanisms of epileptogenesis is critical for developing better therapies to prevent epilepsy in order to ease the significant burden on patients with epilepsy.

Neurogenesis, the process of generating functionally integrated neurons, is traditionally believed to occur only during embryonic stages in the mammalian Central Nervous System (CNS), but its persistence throughout adulthood in mammals (adult neurogenesis) [4-9] has recently become generally accepted. Adult neurogenesis occurs specifically in the Subgranular Zone (SGZ) of the Hippocampal Dentate Gyrus (DG) and the Subventricular Zone (SVZ) of the forebrain lateral ventricles. Specifically in the SGZ, adult-born neurons still make up about 6% of the Granular Cell Layer (GCL) in adult rats [10]. Accumulative evidence suggests that adult neurogenesis is extremely crucial for learning and memory, including encoding of temporal information into memories, spatial memory, context-dependent memory, and pattern separation, as well as cognitive flexibility [11-19]. Meanwhile, adult neurogenesis is also implicated in a variety of pathological CNS diseases, including psychiatric disorders (schizophrenia, major depression, addiction and anxiety) [20-25], neurodegenerative diseases (Parkinson's disease, Alzheimer's disease and Huntington's disease) [26], and epilepsy.

Emerging evidence from both animal models and human data suggests a critical role of neurogenesis in epilepsy, especially in epileptogenesis. Recently, the field of "adult neurogenesis in epilepsy" has been propelled by technical advances, including genetic marking with retroviruses, transgenic animal models that allow visualization and specific manipulation of newborn neurons, and virus-mediated tracing methods, as well as optogenetic/chemogenetic intervention methods. In this review, we mainly concentrate on the role of adult neurogenesis in epileptogenesis. We review pathological changes that occur in adult neurogenesis in the epileptic brain and the functional relevance of neurogenesis

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in epileptogenesis through different updated interventions. Furthermore, we discuss some molecular signaling pathways regulating adult neurogenesis, which can be potential druggable targets for epileptogenesis, and propose some perspectives for future studies.

2. ADULT NEUROGENESIS IN THE EPILEPTIC BRAIN

2.1. Seizure-induced Cell Proliferation

Epileptogenesis is usually triggered by initial epileptogenic insults, such as status epilepticus (SE), childhood febrile seizures, head trauma, and stroke, followed by a latent period between initial insults and later chronic spontaneous recurrent seizures [27]. Different studies have been performed to identify the dramatic disturbances in adult neurogenesis in SGZ and SVZ based on various types of epileptogenic insults (Table **1**), including pilocarpine and kainic acid (KA)-induced SE, as well as kindling stimulation [28-34]. Parent *et al*. (1997) used exogenous nucleotide bromodeoxyuridine (BrdU) mitotic labeling to assess cell proliferation and found a transient upregulation of neurogenesis after pilocarpine-induced SE [28]. A subsequent study using a KA-induced SE model provided further evidence that on both the ipsilateral and contralateral sides of KA injection, neurogenesis increased compared with controls [29]. Additionally, in kindling models, cell proliferation increased in animals that experienced more than 9 fully amygdala kindled seizures [31]. Examination of the hippocampus from temporal lobe epilepsy (TLE) patients also suggested increased cell proliferation [35, 36], which was consistent with studies in animal models.

The response in adult neurogenesis is also intriguing at different stages after initial SE. Increased neurogenesis after acute seizures returns to baseline or even below baseline level about 1 month after the initial seizure episode in rats [28, 37, 38]. Hattiangady *et al*. (2004) employed doublecortin (DCX) as a marker of newly born neurons and reported that neurogenesis declined at 5 months post-KA administration [37]. Accordingly, another study by Heinrich and colleagues reported a gradual decrease in neurogenesis by 1 week and below baseline by 4-6 weeks after the initial seizure episode [38]. One possible explanation is that the potential for adult neurogenesis might be reduced due to the "exhaustion" of the neural stem cell (NSC) pool or alterations in the neurogenic niche providing support for NSCs [37, 39, 40]. Moreover, the degree of abnormal adult neurogenesis is also associated with the severity of the initial SE, which is also a key determinant factor for later chronic SRS. It was demonstrated that SE severity influenced the long-term outcome instead of short-term neurogenesis in a hippocampal kindling model; animals exhibiting less severe SE states (partially convulsive) had more newborn Dentate Granule Cells (DGCs) survive after 4 weeks (long-term) compared with the fully convulsive group, while SE of varying severity triggered similar neurogenesis after 1 week (short-term) [41, 42]. On the contrary, Uemori *et al*. (2017) found in a pilocarpine-induced SE model that seizure-induced damage and aberrant adult neurogenesis observed 10 days after seizure induction were dependent on the frequency of severe seizures (falling and jumping); fewer severe seizures were associated with enhanced neurogenesis and the generation of ectopic hilar DGCs, while the opposite effects were exerted by more severe seizures [43].

Interestingly, conflicting results were observed when evaluating adult neurogenesis in neonatal rats. In contrast to the increased cell proliferation observed after acute epileptogenic insults in adult animals, neurogenesis decreased after acute SE in young pups, and a modest increase in neurogenesis even at 2 months after SE was found [44-47]. Thus, it seems that the change of adult neurogenesis depends on the developmental state of the brain at the time of the initial seizure induction.

Generally, adult neurogenesis is transiently upregulated by initial epileptogenic insults, and then returns to baseline or even below baseline during the SRS period (Fig. **1**). The change of adult neurogenesis is influenced by many important factors, including the severity of initial epileptogenic insult, the stage of epileptogenesis, and the age of brain. Notably, as epileptogenesis is involved in a multifarious process, whether other various epileptogenic insults lead to similar change of adult neurogenesis still needs to be widely verified.

2.2. Abnormal Maturation and Integration of Adult-generated GCs

In addition to the quantitative changes in neurogenesis after acute SE, major qualitative alterations have also been reported [48-50]. Seizure-induced changes in the local environment were found to accelerate the functional integration of adult-generated DGCs, which affected not only the newborn DGCs generated immediately after seizure, but also impacted subsequent generations [51]. Some populations of seizure-generated DGCs show severe morphological abnormalities that may critically affect dentate connectivity. In striking contrast to cells born under normal conditions, which typically have a single dendrite arising from the apical portion of the cell body branching in the outer GCL or inner molecular layer, seizure-generated DGCs tend to extend additional basal dendrites toward the hilus [52, 53]. In the rat pilocarpine model, about a third of adult-born DGCs that were 2 weeks old at the time of SE or born 4 days after SE developed Hilar Basal Dendrites (HBDs) [54]. This leads to a dramatic shift in the percentage of granule cells with HBDs: from 1% in controls to ≈20% in epileptic animals [55]. Moreover, newly generated DGCs display a significantly greater percentage of HBDs as compared to mature DGCs following SE [56, 57]. Meanwhile, granule cells with HBDs received significant recurrent inputs from neighboring granule cells, as evidenced by both anatomical and electrophysiological studies [52, 58, 59].

In addition to aberrant dendritic growth, SE also alters the migration of adult-born neurons. In the adult rat SVZ, prolonged seizures increased neuroblast migration to the olfactory bulb and induced a portion of neuroblasts to exit the migratory stream prematurely and enter non-olfactory forebrain regions [34]. Although the vast majority of newborn DGCs during adult life migrated into the GCL, DGCs were found in rodent models of epilepsy to migrate instead into the hilus or through the GCL into the inner molecular

Table 1. Impact of seizures on neurogenesis, survival, morphology, and integration of adult-born GCs in different epilepsy models.

Types of Epilepsy	Species	Region	Findings	Refs.
Pilocarpine-induced epilepsy model	Rat	SVZ	Increased neuroblasts at 7 days after SE, returned after 21days; Increased neuroblast migration to the olfactory bulb	Parent, J. M. *et al*. (2002)
	Rat	SVZ	No increase in cSVZ neurogenesis; Increased cSVZ gliogenesis	Parent, J. M. *et al*. (2006)
	Rat	SGZ	Increase in neurogenesis 3, 6, and 13d after SE, recovered by 27 d; Ectopic location	Parent, J. M. *et al*. (1997)
	Rat	SGZ	induced HBDs which are postsynaptic to mossy fibers	Ribak, C. E. *et al*. (2000)
	Rat	SGZ	Adult-born DGCs located at the hilar/CA3 border several weeks after SE and they were synchronized with CA3 pyramidal cells	Scharfman, H. E *et al.* (2000)
	Rat	SGZ	Perforant path activation led to robust activation of newborn hilar GCs	Scharfman, H.E *et al*. (2003)
	Rat	SGZ	HBDs were longer than control; 20% HBDs of newborn neurons in epileptic rat, <2% in control; HBDs were adjacent to astrocytic process in the hilus	Shapiro, L. A. *et al*. (2005)
	Rat	SGZ	More ectopic hilar GCs, more frequent seizures	McCloskey, D. P. *et al*. (2006)
	Rat	SGZ	Progenitors migrated aberrantly to the hilus and ML in rat DG; Ectopic DGCs were found in the hilus and ML	Parent, J. M. *et al*. (2006)
	Mouse	SGZ	2 weeks or 1 month after seizures, the length and complexity of dendrites of immature (~12d) GCs were both increased; Dendrite outgrowth correlated with the severity of initial seizures; 5-16 days after seizure, PP stimulation evoked glutamatergic input to newborn GCs	Overstreet-Wadiche, L. S. *et al.* (2006)
	Mouse	SGZ	~50% of immature GCs exhibited aberrant HBDs compared with only ~9% of immature GCs; newborn cells were even more severely impacted than immature cells	Danzer, S. *et al*. (2007)
	Mouse	SGZ	Positive correlations were found between seizure frequency and the percentage of hilar ectopic GCs; the amount of MFS; the extent of mossy cell death	Hester, M. S *et al*. (2013)
	Rat	SGZ	Low incidence of severe seizures enhanced neurogenesis and the generation of ectopic hGCs; High incidence of severe seizures impaired GCL and reduced newly-generated cells	Uemori, T. *et al.* (2017)
KA-induced epilepsy model	Rat	SGZ	KA-induced seizures led to neurogenesis	Bengzon, J. *et al.* (1997)
	Rat	SGZ	1 week after KA, neurogenesis was increased bilaterally; > 6-fold ipsilateral, 3-fold contralateral	Gray, W. P. *et al.* (1998)
	Rat	SGZ	Neurogenesis began to increase at day 3, peaked at day 5 and returned to baseline at day 10	Nakagawa, E. *et al*. (2000)
	Rat	SGZ	Induced HBDs which are postsynaptic to mossy fibers	Ribak, C. E. *et al*. (2000)
	Rat	SGZ	Adult-born DGCs located at the hilar/CA3 border several weeks after SE and they were synchronized with CA3 pyramidal cells	Scharfman, H. E *et al.* (2000)
	Rat	SGZ	DCX-expressing cells were increased 16 days after ICV or IP KA; Conversely, neurogenesis declined after 5 months	Hattiangady, B. *et al.* (2004)
	Mouse	SGZ	Increased cell proliferation and new neurons persisted for months; Stimulus stimulated the division of late type-3 progenitor cells (expressing DCX)	Jessberger, S. *et al.* (2005)

(Table 1) contd….

Types of Epilepsy	Species	Region	Findings	Refs.
KA-induced epilepsy model	Mouse	SGZ	GCL dispersion within the lesion is negatively associated with ipsi neurogenesis, the contra exhibits neurogenesis without local neuronal loss; similar survival rate in KA as in control	Kralic, J. E. *et al*. (2005)
	Mouse	SGZ	Early, transient increase in neurogenesis bilaterally, becoming microglial cells and astrocytes instead of neurons; later, neurogenesis stops in ipsi but not in contra	Heinrich, C. *et al*. (2006)
	Rat	SGZ	Granule cells born after SE extended abnormal HBDs and became morphologically and functionally integrated; GCs born before SE didn't show aberrant dendritic growth	Jessberger, S. *et al*. (2007)
Perforant path stimulation	Rat	SGZ	Prolonged, focal seizure discharges increased mitotic activity	Parent, J. M. *et al*. (1997)
	Rat	SGZ	Neurogenesis began to increase after 5 consecutive stage I seizures	Nakagawa, E. *et al*. (2000)
Hippocampal kindling model	Rat	SGZ	1 and 40 kindling stimulations induced neurogenesis	Bengzon, J. *et al*. (1997)
	Rat	SGZ	SE of varying severity triggered similar short-term (1 week) proliferation of neural progenitors; More new neurons survived at 4 weeks after partially convulsive SE compared with fully convulsive	Mohapel, P. *et al*. (2004)
Amygdala kindling model	Rat	SGZ	9 or more class 4/5 kindled seizures increased cell proliferation in DG	Parent, J. M. *et al*. (1998)
	Rat	SGZ	No significant change during focal seizures; Neurogenesis was enhanced by 75-140% after generalized seizures	Scott, B. W. *et al*. (1998)
Electrovonculsive seizure	Rat	SGZ	A single seizure increased the number of newborn cells , surviving for > 3 months; dose-dependent mechanism	Madsen, T. M. *et al*. (2000)
Flurothyl kindling model (forebrain seizures)	Mouse	SGZ	Significant increases in either 1 or 8 fluorothyl-induced seizures; Increases were observed at 1 and 3 days after 1 seizures, and at 0, 1, 3 and 7 days after 8 seizures	Ferland, R. J. *et al*. (2002)
Electrically induced, self-sustained SE	Rat	SGZ	The degree of survival of newly generated neurons was determined primarily by the initial SE instead of additional seizures	Ekdahl, C. T. *et al*. (2003)
	Rat	SGZ	A substantial proportion of the mature GCs at 6 months are generated during the first 2 weeks after SE and survive	Bonde, S. *et al*. (2006)
TLE	Human	SGZ	Progenitors migrated aberrantly to the hilus and ML in rat DG; Ectopic DGCs were found in the hilus and ML	Parent, J. M. *et al*. (2006)

layer after SE [28, 37]. Similar ectopically located DGCs were also reported to appear in the epileptic human hippocampus [60]. Accompanying their abnormal localization, the electrophysiological features of ectopic granule cells are different from cells born under normal conditions. Bursting is not typical of normal DGCs, while many of these ectopic DGCs burst in synchrony with CA3 pyramidal cells, and this property has been suggested to be pro-epileptogenic [61]. Meanwhile, it was also shown that ectopic DGCs exhibited higher ratios of excitatory to inhibitory inputs than normal DGCs [62]. Combining retroviral birth dating with rabies virus-mediated retrograde trans-synaptic tracing, Du *et al*. (2017) found substantial hippocampal circuit remodeling after an epileptogenic insult. Prominent excitatory monosynaptic inputs (from other DGCs, CA3, and CA1 pyramidal cells) were all increased for early-born and adult-born DGCs [63]. Using the same retrograde tracing technology, a more recent study by Zhu *et al*. (2019) also revealed that newborn DGCs formed excessive de novo excitatory connections, as well as recurrent excitatory loops [64]. Conversely, seizure-generated DGCs had less excitatory but increased inhibitory input that resulted in overall decreased excitability compared with newborn DGCs induced by running [65]. These findings suggest that seizure-induced adult neurogenesis may play a compensatory role in epileptogenesis.

In general, although controversy exists, there are abundant pathologies identified among DGCs, including changed cell proliferation, abnormal maturation, and functional integration in the epileptic brain, which are thought to contribute to epileptogenesis through the establishment of hyperexcitatory networks. However, whether these abnormal newborn DGCs are causal or resultant factors for epileptogenesis remains to be determined.

3. FUNCTIONAL SIGNIFICANCE OF ADULT NEUROGENESIS IN EPILEPTOGENESIS

While intriguing, morphological and electrophysiological studies are only correlation studies. They are not adequate to definitively establish that the integration of adult-born DGCs

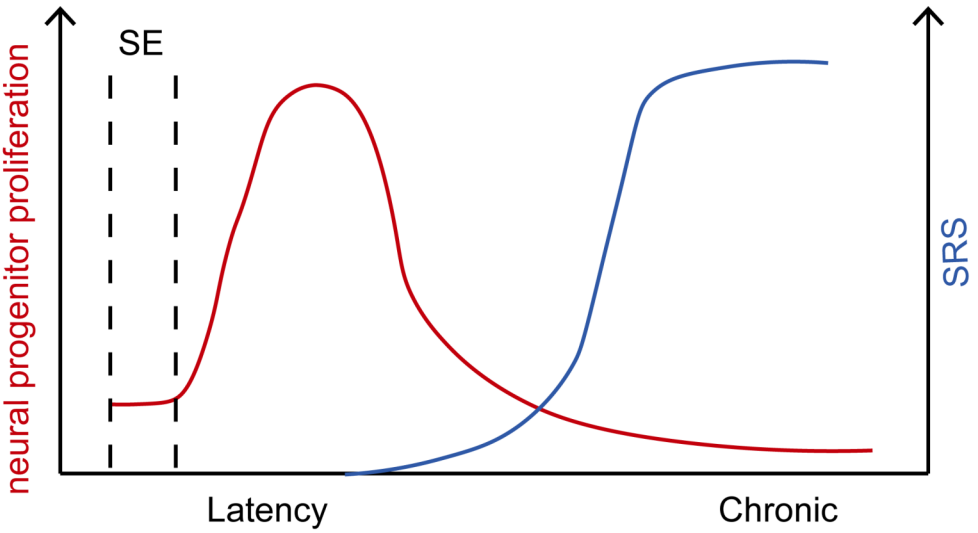

Fig. (1). Changes of neural progenitor proliferation and SRS in epileptogenesis over time. Epileptogenesis is usually triggered by initial epileptogenic insults, such as status epilepticus (SE), followed by a latent quiescent period between initial insults and later chronic spontaneous recurrent seizures (SRS). The quiescent latency lasts ranging from several days to several weeks and ends at the time of the appearance of the first spontaneous seizure. Frequency of SRS increases with time and gradually becomes stable. On the other hand, seizure activity leads to a dramatic increase in neural progenitor proliferation judged by Ki67 expression or short-pulse bromodeoxyuridine (BrdU) labeling in the DG after SE. Neural progenitor proliferation returns to baseline levels approximately 3 to 4 weeks following the initial SE episode. At later stages following SE, the potential for adult neurogenesis might even be reduced, probably due to an "exhaustion" of the NSC pool. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

contributes to epileptogenesis. Thus, subsequent studies have used different intervention approaches to block or reduce adult neurogenesis (loss of function) to assess its real role in epileptogenesis (Table **2**).

Using a variety of antimitotic agents or radiation to limit adult neurogenesis before an epileptogenic brain injury, early studies have produced conflicting results. Raedt and colleagues used low-dose radiation to suppress hippocampal adult neurogenesis in a kindling model of TLE and found that radiated rats developed severe seizures more rapidly, while the final establishment of the permanent fully kindled state was not influenced [66]. Meanwhile, other studies showed no detrimental or protective effects of newborn DGCs on hippocampal network function [65-68], suggesting that hyper-excitability within the epileptic hippocampal circuitry might be compensated for by more inhibited newborn DGCs. By contrast, studies demonstrated that decreasing DGC neurogenesis by using antimitotic agents, including cytosine-b-D-arabinofuranoside (Ara-C) or a selective Cyclooxygenase-2 (COX-2) inhibitor, reduced the frequency of SRS and suppressed epileptogenesis [69, 70]. Nonetheless, all approaches discussed above (anti-mitotic agents, radiation, *etc*.) have other non-specific effects apart from reducing newborn DGCs; meanwhile, the role of adult neurogenesis may vary since different epilepsy models are applied. Thus, the effect (or lack of effect) of these approaches is not adequate to define the precise role of adult neurogenesis in epileptogenesis.

A conditional and inducible transgenic cell ablation strategy was used to ablate adult neurogenesis more selectively and at specified time points [71-73]. In a pilocarpine-induced SE model, Nestin-δ-HSV-thymidine kinase-EGFP (Nestin-TK) transgenic mice were used to achieve selective ablation of dividing neural stem/progenitors by ganciclovir (GCV) administration. Remarkably, in this way, ablation of adult neurogenesis for 4 weeks before acute seizures led to a reduction in the frequency of SRS, which lasted for nearly 1 year [72]. A subsequent study extended these findings by beginning ablation from 5 weeks before SE until 3d after the epileptogenic insult, using a conditional and inducible diphtheria-toxin receptor (DTr) expression strategy. This approach produced a 50% reduction in the frequency of SRS and a 20% increase in the duration of SRS [73]. More recently, more than 4 weeks of continuous and concurrent ablation of seizure-induced neurogenesis in the Nestin-TK mice after SE was reported to reduce the formation of SRS by 65% [74], while the therapeutic effective time was very limited. Whether adult neurogenesis in later phases of epileptogenesis may consistently contribute to epileptogenic circuits and lower the therapeutic efficacy of targeting early adult neurogenesis still remains to be studied.

In addition, although these above studies indicate that abnormal hippocampal newborn DGCs contribute to epileptogenic circuits, it remains to be determined how these abnormal hippocampal DGCs contribute to the onset of SRS. Recently, chemogenetic approaches have been developed as a valuable platform for manipulating neuronal and non-neuronal signal transduction in a cell-type-specific manner in freely moving animals [75]. Compared with ablation, the chemogenetic method only controls the activity of newborn DGCs in an inducible and reversible manner without interrupting neural circuit formation during epileptogenesis. Using this method to inhibit newborn DGCs, Zhou *et al*. (2019) found that epileptic spikes and SRS were both reduced, revealing an essential role for newborn DGCs in the production of epileptic spikes and SRS. Conversely, specific activation of

Table 2. Functional relevance of adult neurogenesis in epilepsy with different interventions.

Interventions	Timepoints of Intervention	Species	Animal Models	Findings	Refs.
Inhibition of neurogenesis by antimitotic Ara-C	from 1 day before SE for 14 days	Rat	Pilo-induced epilepsy	Reduced frequency and duration of seizures; No obvious difference of neuronal damage	Jung K. H. *et al*. (2004)
Inhibition of neurogenesis by COX-2 inhibitor	from 1 day after SE to 14 or 28 days after SE	Rat	Pilo-induced epilepsy	Reduced frequency and duration of seizures; Neuroprotective effect	Jung K. H. *et al*. (2006)
Inhibition of neurogenesis by radiation	1 day before starting kindling	Rat	Hippo kindling model	Decreased ADT and developed more severe seizure more rapidly	Raedt, R. *et al*. (2007)
Inhibition of neurogenesis by Levetiracetam	from 1 day after SE for 25 days	Mouse	KA-induced epilepsy	Decreased the mean duration of seizures 58 days later	Sugaya, Y. *et al*. (2010)
Inhibition of neurogenesis by radiation	1 day before starting kindling	Rat	Amygdala kindling model	No effects on kindling acquisition and kindled seizures	Pekcec, A. *et al*. (2011)
Genetic ablation of neurogenesis (Nestin-TK)	GCV for 4 weeks until injection of Pilo	Mouse	Pilo-induced epilepsy	Reduced frequency of SRS; Restored cognitive function	Cho, K. O. *et al*. (2015)
Reduction of neurogenesis by X-irradiation or genetic ablation (GFAP-TK)	from 6 weeks of age (3 doses of X-irradiation, 3 days between doses) 7 weeks later, KA; from 6 weeks of age (VGCV for 6 weeks) 2 weeks later, KA	Mouse	KA-induced epilepsy	Increased the acute effects of KA (decrease in the latency to the first convulsive seizure, increased number, duration and mortality)	Iyengar, S. S. *et al*. (2015)
Genetic ablation of neurogenesis (NestinCreER^{T2}:: DTr)	from 3 weeks of age for 4 weeks (tamoxifen, weekly), 1 week later, Pilo; DT began the 3rd day after SE daily for 5d	Mouse	Pilo-induced epilepsy	Reduced seizure frequency; Increased seizure duration	Hosford, B. E. *et al*. (2016)
Inhibition of neurogenesis by MAM	both 4 weeks ahead of and after SE; with intervals of 48 hours for 4 weeks	Mouse	Pilo-induced epilepsy	eHGCs, MFS and HBDs were eliminated; No alterations in frequency, duration, or severity	Zhu, K. *et al*. (2017)
Inhibition of neurogenesis by ephrin-B3	from 7 days after SE for 7 days	Rat	Pilo-induced epilepsy	Reduced seizure frequency; Reduced amplitudes and mean duration of EEG seizures	Liu, T. *et al*. (2018)
Chemogenetic excitation/inhibition of newborn neurons (RV-hM3Dq/RV-hM4Di)	3 days after SE, RV-hM4Dq/hM3Di injected; 2.5 months later, EEG recording, 1-3 d baseline, 4-6 d CNO	Mouse	Pilo-induced epilepsy	Inhibition reduced epileptic spikes and SRS; Activation increased epileptic spikes and SRS	Zhou, Q. G. *et al*. (2019)
Genetic ablation of neurogenesis (Nestin-TK)	GCV for 4 weeks post-SE, EEG recording from 5 to 7 weeks post-SE; GCV for 8 weeks post-SE, EEG recording from 5 to 7 weeks post-SE or EEG recording from 18 weeks to 20 weeks post-SE	Mouse	Pilo-induced epilepsy	4 weeks of ablation, no effect on SRS frequency or duration; 8 weeks of ablation, 65% reduction of SRS frequency, last for 10 days	Varma, P. *et al*. (2019)

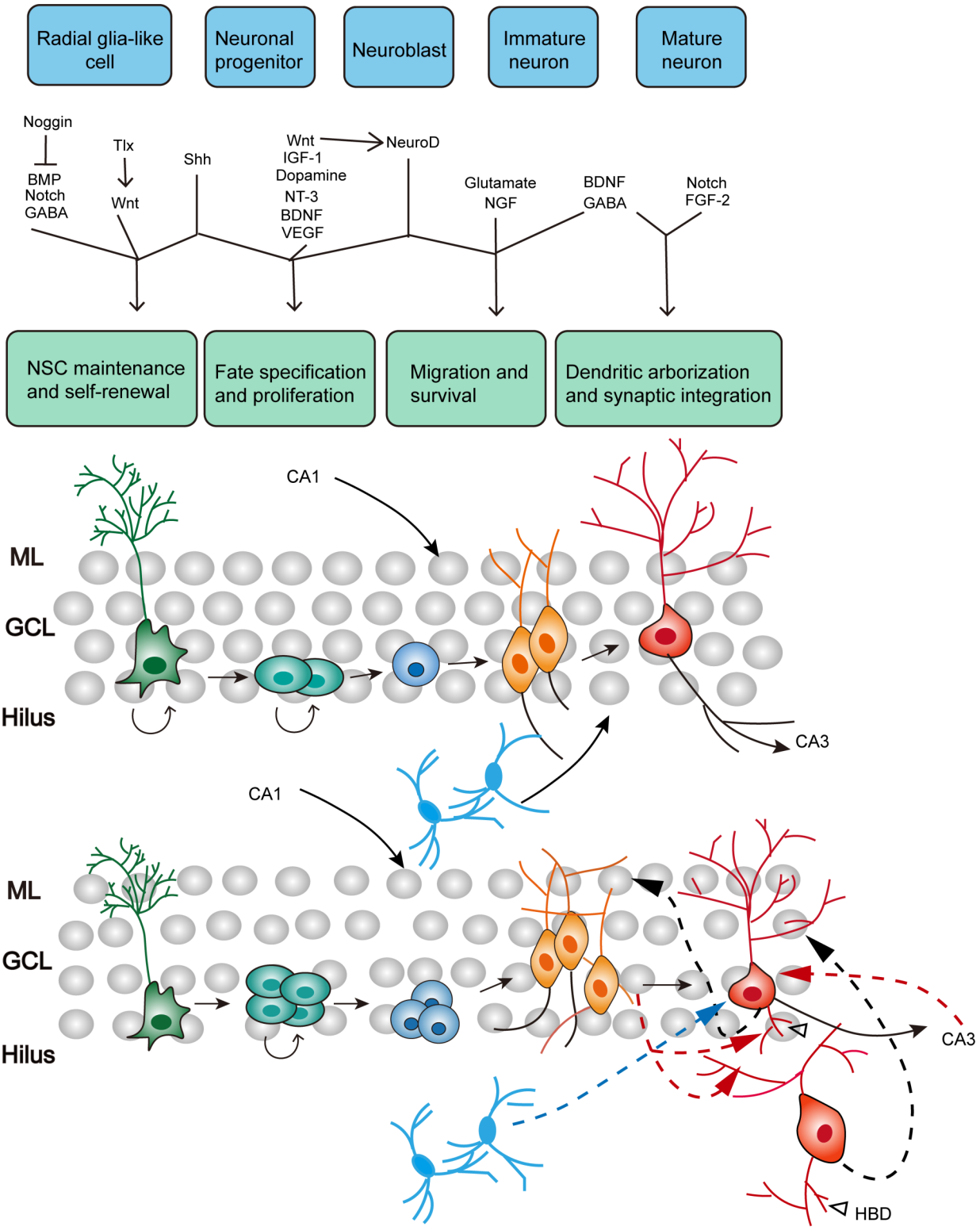

Fig. (2). Hippocampal circuitry remodeling in the epileptic brain and signaling pathways regulating adult hippocampal neurogenesis. Upper panel: Schematic of the hippocampus in normal physiological conditions, sparse DGC-DGC connections are shown. Newborn neurons in the SGZ pass through several consecutive developmental stages. Different signaling pathways exert stage- and cell-specific effects. Lower panel: Schematic of the epileptic brain demonstrating increased recurrent DGC-DGC connections and preferential inputs from hilar ectopic DGCs to adult-born DGCs; back projections from CA3 pyramidal cells preferentially onto adult-born DGCs. Inhibitory inputs (blue dashed line) onto adult-born DGCs from interneurons are maintained, while those onto early-born DGCs are diminished. Increased excitatory inputs (red dashed line) and outputs (black dashed line) indicate their contributions to epileptogenesis. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

newborn DGCs dramatically increased the frequency of epileptic spikes and SRS, indicating that activation of newborn DGCs was sufficient to activate epileptic neural circuits [64]. This is the first research published that focused on attempting to activate newborn DGCs (gain of function) rather than merely ablating them, which indicates that newborn DGCs are necessary and sufficient for remodeling hippocampal neural circuits underling induction of SRS during epileptogenesis.

However, uncertainty still remains as to the exact contribution of newborn DGCs to epileptogenesis. In 2015, Iyengar and colleagues demonstrated that ablating newborn neurons before a challenge with (KA) increased the severity of the resulting seizures, suggesting that the newborn DGCs before SE may serve a protective role during acute seizures [76]. On the other hand, another study by Cho *et al*. (2015) reported that there was no observed effect from ablation on acute SE induced by pilocarpine [72]. Meanwhile, in this work, investigators found that pre-SE ablation was effective at reducing later SRS, whereas pre- plus post-SE ablation, which provided near-complete ablation, turned out to be not effective. Using a transgenic mouse model to reduce neurogenesis by deleting the transcription factor NeuroD1 from progenitors, Brulet and colleagues found that although this approach produced a partial reduction in neurogenesis, SRS was similar between control and knockout mice treated by pilocarpine [77]. Considering these contradictory findings, there is a possibility that functionally heterogeneous populations of adult-born neurons exist. In other words, adult-born neurons are a mixture of hyper- and hypo-excitable cells. To address this hypothesis, there remains a need to develop specific methods to target or modulate subpopulations of adult-born neurons that are structurally or functionally abnormal. Besides, differences among mouse strains, timepoints, seizure models, or other technical aspects all contribute to these conflicting findings. Future studies will need to use improved tools to precisely distinguish detrimental and protective adult-generated neurons.

4. SIGNALING MECHANISM REGULATING ADULT NEUROGENESIS: LOOKING FOR NEW POTENTIAL DRUGGABLE TARGETS FOR EPILEPTOGENESIS

4.1. The Challenge for Current AEDs: Control of Seizure but not Epileptogenesis

Although the pathophysiological mechanism underlying epilepsy is multifactorial, it is commonly recognized that epileptic seizures are caused by generalized hyperexcitability and excessive or hypersynchronous activity with enhanced neuronal excitability [1, 78]. There is no doubt that this concept has assisted our discovery of many AEDs with different targets. Currently available AEDs are mostly based on the following main mechanisms: (1) modulation of voltage-gated ion channels, including the voltage-gated sodium, potassium, and calcium channels, which are essential to the intrinsic excitability of neuron, and play a key role in epilepsy [79-86]; (2) inhibition of excitatory synaptic transmission, such as glutamate, one of the predominant excitatory neurotransmitters in the adult mammalian brain, which is closely involved with epilepsy [87-94]; (3) enhancement of inhibitory synaptic transmission, such as GABA, one of the most important inhibitory neurotransmitters in the brain and one that provides a key functional mechanism for AED [95-101].

However, epilepsy is still associated with considerable therapeutic pharmacological treatment challenges. One foremost challenge is drug-resistance, with 30% of epilepsy patients unable to be efficiently controlled through current therapies [102, 103]. Meanwhile, most available AEDs are not without side effects (including ataxia, dizziness, cognitive impairment, and depression) [104, 105]. Another primary challenge is that no one AED is able to inhibit or prevent epileptogenesis. All current AEDs actually work as symptomatic drugs alleviating seizure activity. Apart from the seizure itself, the burden of comorbidities (including depression, anxiety, and cognitive deficits), which are significant in people with epilepsy [106], are not well controlled by AEDs. Without a doubt, investigations of novel therapeutics for epileptogenesis should extend beyond directly manipulating the excitatory and inhibitory imbalance. From this point of view, new concepts and novel targets should be introduced based on a deeper and more comprehensive understanding of the precise mechanism of epileptogenesis, such as abnormal adult neurogenesis.

4.2. Druggable Target of Adult Neurogenesis for Epileptogenesis

Fortunately, recent progress in adult neurogenesis represents a promising target for the intervention of epileptogenesis. The balance between progenitor maintenance, proliferation, and neuronal differentiation is regulated by signals provided by the microenvironment that respond to both physiological and pathological stimuli. Thus, a better understanding of these signaling pathways can lead to a more defined regulation of neurogenesis for treatment in the future. Various signaling pathways and neurochemicals, such as Wnt [107-113], Notch [114-118], sonic hedgehog (Shh) [119-121], Bone Morphogenetic Proteins (BMPs) [122, 123], Brain-Derived Neurotrophic Factor (BDNF) [124-128], vascular Endothelial Growth Factor (VEGF) [129], and neurotransmitters like glutamate and GABA [130-132], as well as inflammatory pathways [133-135], have all been found to be important regulators of neurogenesis (Table **3**). Meanwhile, some of the above have been reported to produce notable changes in epilepsy, suggesting that these signaling pathways take part in certain phases of epileptogenesis. In the following section, we describe potential pathways that may be used to prevent epileptogenesis through modulation of adult neurogenesis (Fig. **2**).

4.3. Wnt/β-catenin

Several studies have addressed the role of Wnt signaling in adult neurogenesis. It was reported that overexpression of Wnt3 increased neurogenesis; in contrast, blocking Wnt signaling reduced neurogenesis significantly, suggesting a critical role of Wnt signaling in progenitor proliferation [113]. Apart from the convincing evidence for the role of this pathway in promoting proliferation, Wnt-signaling was also reported to be required in neuronal differentiation based on the evidence that adult NSCs were not able to transit to

Table 3. Overview of signaling pathways regulating neurogenesis.

Molecules	Effect on Neurogenesis	Species	Region	Refs.
Morphogens				
Wnt	Increases neurogenesis; Involved in the control of neuronal fate commitment	Rat	SGZ	Lie *et al*. (2005)
	Required for progenitor proliferation	Mouse	SVZ	Adachi, K. *et al*. (2007)
		Mouse	SGZ	Mao, Y. *et al*. (2009)
		Mouse	SGZ/SVZ	Qu, Q. *et al*. (2010）
	Required for dendritic development	Mouse	SGZ	Gao, X. *et al*. (2007)
	Required for neuronal differentiation	Mouse	SGZ	Kuwabara, T. *et al*. (2009); Gao Z. *et al*. (2009)
	Required for the survival	Mouse	SGZ/ SVZ	Gao Z. *et al*. (2009)
Shh	Required for progenitor proliferation	Rat	SGZ	Lai, K. *et al*. (2003); Banerjee, S.B. *et al*. (2005)
		Mouse	SGZ/SVZ	Machold R. *et al*. (2003); Ahn, S. *et al*. (2005)
	Required for formation of adult NSCs	Mouse	SGZ	Han, Y. G. *et al*. (2008)
Notch	Required for NSC self-renewal, maintenance	Mouse	SVZ	Chojanacki, A. *et al*. (2003); Imayoshi, I. *et al*. (2010)
		Mouse	SGZ	Breuning, J. J. *et al*. (2007); Ables, J. L. *et al*. (2010); Ehm, O. *et al*. (2010)
	Required for dendritic arborization	Mouse	SGZ	Breuning, J. J. *et al*. (2007)
	Increases SVZ neurogenesis	Rat	SVZ	Wang X. *et al*. (2009)
	Required for maturation of neurons	Mouse	SVZ	Fujimoto, M. *et al*. (2009)
BMP	Decreases neurogenesis; Promotes glia differentiation; Promotes neuroblasts survival	Mouse	SVZ	Lim, D. A. *et al*. (2000)
	Blocking BMP *via* Noggin is required for NSC self-renewal	Mouse	SGZ	Bonaguidi, M. A. *et al*. (2008)
	Blocking BMP *via* Noggin increases neurogenesis	Mouse	SGZ	Guo, W. *et al*. (2011)
Neurotrophins				
BDNF	Required for survival of newborn neurons	Mouse	SGZ/SVZ	Linnarsson, S. *et al*. (2000); Bergami, M. *et al*. (2008)
	Increases neurogenesis	Rat	neurogenic and non-neurogenic niches	Benraiss *et al*. (2001); Pencea *et al*. (2001)
		Rat	SGZ	Katoh-Semba, R. *et al*. (2002); Scharfman, H. *et al*. (2005)
	No effect in neurogenesis in mice; Decreases neurogenesis in rats	Rat/Mouse	SVZ	Galvao, R. P. *et al*. (2008)
	Required for progenitor proliferation	Mouse	SGZ	Li, Y. *et al*. (2008)
	Required for dendritic arborization and functional integration of newborn neurons	Mouse	SGZ	Bergami, M. *et al*. (2008)
NT-3	Required for neuronal differentiation	Mouse	SGZ	Shimazu, K. *et al*. (2006)
NGF	Promotes survival of neurons	Rat	SGZ	Frielingsdorf, H. *et al*. (2007)

(Table 3) contd….

Molecules	Effect on Neurogenesis	Species	Region	Refs.
Growth factors				
FGF-2	Increases neurogenesis; Enhances dendritic growth	Rat	SGZ	Rai, K. S. *et al*. (2007)
	Required for progenitor proliferation	Mouse	SGZ	Zhao, M. *et al*. (2007)
IGF-1	Increases neurogenesis	Rat	SGZ	Aberg M. A. *et al*. (2000); Lichtenwalner R. J. *et al*. (2001)
	Instructs multipotent progenitors to become oligodendrocytes	Rat	SGZ	Heish, J. *et al*. (2004)
	Required for migration from SVZ to OB	Mouse	SVZ	Hurtado-Chong, A. *et al*. (2009)
VEGF	Increases neurogenesis	Rat	SGZ/SVZ	Jin, K. *et al*. (2002)
	Required for progenitor proliferation	Rat	SGZ	Warner-Schmidt, J. L. (2007)
Neurotransmitters				
Glutamate	Reduces neurogenesis	Rat	SGZ	Cameron, H. A. (1995)
	Increases neurogenesis	Rat	SGZ	Bai, F. *et al*. (2003)
	Required for survival of new neurons	Mouse	SGZ	Tashiro, A. *et al*. (2006)
	Required for migrating neuroblasts survival	Mouse	SVZ	Platel, J. C. *et al*. (2010)
GABA	Reduces the speed of migrating neuroblasts	Mouse	SVZ	Bolteus A. J. *et al*. (2004)
	Reduces neurogenesis	Mouse	SVZ	Liu, X. *et al*. (2005)
	Required for synaptic integration and dendritic development of new neurons	Mouse	SGZ	Ge, S. *et al*. (2006)
	Required for NSC maintenance	Mouse	SGZ	Song J, *et al*. (2012)
	Promotes survival of newborn progenitors	Mouse	SGZ	Song J, *et al*. (2013)
Dopamine	Required for progenitor proliferation	Mouse	SGZ/SVZ	Hoglinger, G. U. *et al*. (2004); Baker, S. A. *et al*. (2004)
	Increases neurogenesis	Rat	SVZ	Van Kampen, J. M. *et al* (2004)
	Required for progenitor proliferation in GCL; Deafferentation increases neurogenesis in the glomerular layer	Rat	SVZ	Winner, B. *et al*. (2006)
Inflammatory cytokines	Decreases neurogenesis	Rat	SGZ	Ekdahl C.T. *et al*. (2003)
	Decreases neurogenesis	Rat	SGZ	Monje, M. L. *et al*. (2003)
	Decreases neurogenesis	Mouse	SGZ	Iosif, R. E. *et al*. (2006)
	Decreases neurogenesis; Promotes astroglial differentiation	Mouse	SGZ	Zonis, S. *et al*. (2013)

immature and mature granule neurons in β-catenin cKO mice [110].

Recent studies on epileptic animal models and human data highlight the importance of the Wnt/β-catenin signaling pathway in epilepsy. Elevated expression of Wnt signaling was relevant to the increased neurogenesis and neuronal death commonly observed after various seizures [125, 136-139]. In a study by Qu and colleagues, knocking down β-catenin was found to attenuate aberrant neurogenesis induced by KA injection *via* Wnt signaling [138]. Unfortunately, the effect on seizures or epileptogenesis was not reported. Other studies have been conducted to investigate the role of the Wnt signaling pathway in epilepsy. After the conditional deletion of β-catenin in the dorsal telencephalon using the cre-loxP system, β-catenin knockout mice exhibited increased seizure susceptibility and an increased number of seizures compared with wildtype (WT) mice [140]. Instead, Yang and colleagues found confusing results that both deletion and overexpression of β-catenin had a notable impact on seizure susceptibility after pentylenetetrazole (PTZ) seizures [141]. However, whether the role of the Wnt signaling pathway in epilepsy specifically depended on adult neurogenesis is still unknown and requires further investigation.

4.4. BDNF

BDNF has been shown to play an active role in regulating neurogenesis. For example, Linnarsson and colleagues demonstrated that BDNF was required for the survival of the continuously regenerating populations of neurons in the adult DG and SVZ based on the discovery that the number of new cells was decreased in heterozygote BDNF knockout mice [142]. On the other hand, the use of riluzole to increase BDNF in the hippocampus or chronic BDNF infusion directly into the adult DG both increased proliferation of granule precursor cells [126, 128]. Conditional loss of TrkB in BDNF/TrkB signaling in newly-generated neurons was also reported to be required for neurogenesis in the adult DG [143]. Another study, however, indicated that survival, dendritic arborization, and functional integration of newborn neurons depended on the BDNF/TrkB signaling pathway [144].

In the chronic phase of epilepsy, BDNF decreased coinciding with the decrease of neurogenesis [127]. In addition, emerging evidence suggests that activation of BDNF and its tropomyosin receptor kinase B (TrkB) occurred in both animal models and patients with epilepsy [145, 146]. Moreover, augmentation of BDNF-TrkB signaling by direct infusion or transgenic overexpression of BDNF resulted in increased seizure susceptibility [147, 148], while conditional knockout or chemical-genetic inhibition of TrkB protected against epileptogenesis [149, 150]. However, whether there is a causal relationship between the anti-epileptogenesis effect of BDNF and its broad regulation of neurogenesis is still an unanswered question.

4.5. Neurotransmitters

Neurotransmitters are small diffusible molecules that act as the basis of chemical communication between neurons. Glutamate is the predominant excitatory neurotransmitter in the adult mammalian brain and plays important role in numerous complex processes. Both electrophysiological and immunohistochemical evidence suggests glutamate receptors are expressed on neural progenitor cells in adult neurogenic niches. In the adult DG, NMDA receptors were shown to regulate the survival of new neurons during a short, critical period soon after birth [151]. Single cell knock-out of the NMDA receptor resulted in apoptosis of migrating neuroblasts, indicating that glutamate mediated the survival and functional integration of neuroblasts *via* NMDA signaling [152]. In addition, AMPA receptors also take part in regulation of adult neurogenesis. Chronic administration of an AMPA receptor potentiator significantly increased cell proliferation in the hippocampus, which was the first *in vivo* study investigating the role of AMPA receptors in neurogenesis [153].

GABA is the key inhibitory neurotransmitter in the adult brain. Intriguingly, similar to its double-edged role in epilepsy [154, 155], it exerts a dual role on immature GCs: initially depolarizing and subsequently hyperpolarizing, depending on the level of intracellular chloride [156]. In the SVZ, nonsynaptic GABA released from neuroblasts reduced the proliferation of GFAP-expressing progenitors, which provides a negative feedback mechanism for controlling the proliferation of progenitors [132]. Furthermore, the speed of neuroblast migration in RMS was studied in acute sagittal brain slices, and the results suggested GABA reduced the speed of cell migration through $GABA_A$ receptor activation [131]. GABA was also shown to be required for synaptic integration and dendritic development of newborn neurons [156]. In addition, Ge and colleagues demonstrated that parvalbumin (PV^+) interneuron released GABA acted through the gamma2 subunit containing $GABA_A$ receptors to maintain adult NSC quiescence and inhibit symmetric self-renewal and astrocyte fate choice [157]. Their subsequent study indicated that activation of PV^+ interneurons promoted survival and development of newborn progenitors [158].

Although these above-mentioned neurotransmitter pathways are commonly accepted to be involved in seizure susceptibility and epileptogenesis, whether they act through modulation of adult neurogenesis remains to be further investigated. Neurotransmitters like GABA can exert diverse functions based on the level of subtypes of GABAergic neurons and microcircuits or circuits, such as feed-back circuits, feed-forward circuits, and disinhibition circuits [159]. Thus, further studies are needed to dissect the roles of neurotransmitters and their specific effects on adult neurogenesis at the microcircuit and circuit level, which may be of great benefit for anti-epileptogenic therapeutics.

4.6. Inflammatory cytokines

A great deal of work has been devoted to dissecting the role of cytokines in the direct or indirect regulation of neurogenesis. First of all, neural progenitors constitutively express receptors for pro-inflammatory cytokines [160]. Despite controversies resulting from the use of different experimental models, most *in vitro* experiments showed that pro-inflammatory cytokines generally suppressed proliferation both through direct and indirect mechanisms [133, 161]. For example, interleukin (IL)-6 markedly induced expression of p21 in hippocampus-derived neuronal progenitor cells and arrested proliferation of progenitors of neuronal lineage, while astroglial cells continued to proliferate [161]. Using animal models with loss of tumor necrosis factor receptor (TNF-R1 and TNF-R2), it was also revealed that both under basal conditions and after SE, cell proliferation in the DG was elevated in TNF-R1(-/-) and TNF-R1/R2(-/-) mice [162]. In addition to experiments with single cytokine exposure, administration of lipopolysaccharide (LPS), a method commonly used to stimulate the innate inflammatory response, was reported to disrupt progenitor proliferation, decrease differentiation into neurons, and reduce survival of neuroblasts [134, 135, 163]. Experiments with intraventricular LPS injections demonstrated that cytokines and activated microglia were, to a large extent, responsible for the decrease in neurogenesis [163, 164].

Inflammatory pathways have also been commonly accepted to be involved in seizure susceptibility and epileptogenesis [165-169]. Transient increases in IL-1β after prolonged febrile seizures promoted adult epileptogenesis [170, 171]. Roseti *et al*. (2015) found that pathophysiological concentrations of IL-1β decreased the GABA amplitude by up to 30% in specimens from patients with TLE and led to seizure

generation due to neuronal hyper-excitability, suggesting an epileptogenesis role for IL-1β [172]. Besides, toll-like receptors (TLRs) were also associated with epileptogenesis. In a pilocarpine model of SE, deletion of TLR3 decreased epileptogenesis while reducing levels of cytokines IL-1β and microglial activity [173]. Antagonists or knockout of high mobility group box 1 (HMGB1)-TLR4 signaling in an animal model also decreased acute and chronic seizure recurrence [174-177]. However, whether these inflammatory pathways act through modulation of adult neurogenesis remains to be investigated.

Several signaling molecules associated with adult neurogenesis have been found to produce notable changes in epilepsy, suggesting that these signaling pathways take part in certain phases of epileptogenesis by mediating neurogenesis to a certain degree. Considering the close relationship among epilepsy, neurogenesis, and its regulation pathways, it is natural for us to take advantage of these pathways to target neurogenesis as one of the future directions of pharmacological intervention for epileptogenesis. However, small molecules targeting these pathways and epileptogenesis have yet to be clearly identified. Meanwhile, whether small molecule modulation of these pathways to mediate aberrant neurogenesis will ultimately be therapeutically beneficial for epileptogenesis still remains to be determined. Furthermore, it is important to consider the broader effect of small molecules on other functions, since the signaling pathways we mentioned above are also critical for many normal processes.

5. PERSPECTIVES

Despite a relatively comprehensive understanding of changes to adult neurogenesis and preliminary evidence for its role in epileptogenesis, there are still a number of research directions that require significant investigation. Further studies in these directions with more advanced technologies may help adult-born GCs to be better applied to future epilepsy therapy.

5.1. Direction 1: Adult Neurogenesis and its Underlying Neural Circuit Mechanisms in Different Types of Epilepsies

Epileptogenesis is known to be associated with an extensive set of brain changes that play either causal or resultant roles, including cell loss, inflammation, neurogenesis, and mossy fiber sprouting. Although neurogenesis may play important causal roles in epilepsy, its role may vary from essential in some models to irrelevant in others. The mechanisms underlying seizures among different animals may also differ. Determining which models require neurogenesis and whether and how these models are related to human epilepsy is of great importance.

Meanwhile, newborn DGCs may be heterogeneous in different types of epilepsies or even one epilepsy with different stages. Consistent with this idea, various roles for adult-born GCs were presented in different experimental paradigms [66, 67, 70, 72, 76]. Also, as was described by Cho *et al*. (2015), although the single round of GCV treatment before acute SE led to a reduction of SRS, no significant reduction was observed after more complete ablation of neurogenesis was achieved by two rounds of GCV [72]. One possible explanation is that populations of newborn neurons with the ability to suppress chronic seizures were ablated by two rounds of GCV treatment. If the epileptic DG contains both pathological and protective newborn DGCs, which integrate into different circuits, the net effect of early ablation techniques that act on the entire population may vary depending on the relative ratio of pathological and protective newborn DGCs. However, more suitable tools are urgently required to dissect the sole contribution of different DGCs and provide direct evidence for the existence of both pathological and protective DGCs. Advances may come from providing direct evidence for the role played by hilar ectopic DGCs and HBDs. Their morphological and electrophysiological properties generally suggest that they are pro-epileptic because they may integrate into the existing circuit with more excitatory projections received and sent compared with normotopic DGCs [178-181]. Existing contradictory studies used various approaches to ablate neurogenesis effectively. The approaches used to ablate neurogenesis may exert different effects on hilar ectopic DGCs and HBDs, which may also help to clarify the existing contradictory findings.

Furthermore, the contribution of newborn neurons to epileptogenesis may follow complex temporal dynamics. Rabies virus-mediated mapping studies revealed that DGCs born 7 days before or 3 days after SE showed significant increases in the connectivity ratio of excitatory-to-inhibitory connections, while the connectivity ratio of DGCs born 21 days before or 14 days after SE was not altered [64]. However, studies to determine the functional contributions of DGCs born at different timepoints relative to SE induction are still lacking. Newborn DGCs generated prior to, immediately after SE, or at chronic stages of epilepsy may play different roles based on different morphology and connection properties. Meanwhile, the morphological and physiological phenotypes of adult-born cells change markedly while they mature and young adult-born DGCs (~ 4-weeks-old) were reported to influence hippocampal function and behavior in a different manner compared with mature ones (>8 weeks-old) [182-185]. For example, Gu and colleagues [184] found that reversibly silencing ~4-weeks-old cells after training significantly disrupted retrieval of hippocampal memory, as compared to other ages. These functional distinctions may be attributed to the different integration patterns of mature DGCs from young adult-born DGCs. In summary, understanding the specific roles of heterogeneous adult-born DGCs and their integration patterns may be critical for optimizing the intervention timepoints and providing precise pharmacological candidates for preventing epileptogenesis.

5.2. Direction 2

Adult neurogenesis as a potential target for comorbidities of epilepsies including cognitive deficit and depression.

The patients with epilepsy are often at an increased risk for depression, anxiety, sleep disturbances, and cognitive impairment [186-189]. Recently, it has been increasingly recognized that the expression of comorbid conditions may precede seizures and that these conditions are not uniformly resolved even if seizures are fully controlled. In addition,

AEDs may also cause cognitive and psychiatric disturbances. Thus, to improve the quality of life for many patients with epilepsy, a desirable "cure" must involve more than stopping or preventing seizures, but also must ameliorate the accompanying comorbidities [190, 191].

Newborn DGCs have long been considered to be critical in several hippocampus-dependent functions. The first evidence comes from correlational studies linking the levels of neurogenesis with performance in classical behavioral tasks probing the function of the hippocampal formation, such as the Morris water maze [192]. Environmental conditions and strategies that target cell death of adult-born neurons or other approaches that can increase neurogenesis were shown to enhance hippocampus-dependent learning and memory, indicating a possible functional link between neurogenesis and learning memory performance [11, 12, 193, 194]. Likewise, a number of negative factors, including stress and aging, showed an association between decreased levels of neurogenesis with reduced hippocampus-dependent memory performance [20, 192].

At present, no single AED seems to treat accompanying cognitive deficits. However, as is the case for adult neurogenesis under normal conditions, adult neurogenesis may be promising in treating epilepsy while improving epilepsy-associated cognitive decline. Consistent with this idea, existing studies have already made some progress: genetic ablation of neurogenesis prior to SE was shown to reduce chronic seizure frequency and normalize epilepsy-associated cognitive deficits [72]. Additionally, a widely prescribed drug for epilepsy, valproic acid, was found to potently suppress seizure induced neurogenesis through modulation of Wnt signaling and restored hippocampal-dependent memory function [195]. Inflammatory cytokines such as IL-1 might affect cognitive function by neurogenesis and LTP [196], while they were also shown to be associated with epilepsy both in animal models and clinical patients [170, 171, 197-199].

In addition, a substantial number of psychiatric diseases (*e.g.* depression and anxiety) were also found to be closely related to neurogenesis. Newborn neurons may be critically involved in the disease process of depression and represent a potential treatment target owing to the fact that a number of clinically used antidepressants, such as fluoxetine, strongly enhance neurogenesis [21, 200]. Furthermore, direct evidence for the role played by neurogenesis in depression was provided by taking advantage of transgenic and radiation methods to specifically alter adult neurogenesis [24, 201]. Hippocampal IL-1β may be a factor contributing to depression in TLE. Induction of IL-1β expression in rats with chronic TLE may ultimately lead to epilepsy-associated depressive-like behavior. Pharmacological blockade of hippocampal IL-1R exerts an antidepressant effect in the post-SE model, suggesting its potential use for treating depression and epilepsy. In addition, using chemical-genetic approaches to selectively inhibit activation of TrkB, a receptor for BDNF, can prevent the development of TLE and ameliorates comorbid anxiety-like behavior and destruction of hippocampal neurons [149].

Taken together, further studies are urgently needed to clarify the functional characteristics of neurogenesis in different comorbidities of epilepsies and their underlying mechanisms.

5.3. Direction 3: Druggable Signaling that Drives Abnormal Adult Neurogenesis and its Underlying Neural Circuit in Epileptogenesis

Although numerous signaling pathways are critically involved in various aspects of physiological neurogenesis, studies addressing whether and how components of these pathways may directly or indirectly mediate different aspects of epileptogenesis are relatively limited; a focus on seizure-induced neurogenesis, seizure susceptibility, and the development of epilepsy with respect to these pathways is urgently needed. In addition, several studies examined neurogenesis in both the acute and chronic periods following seizures, but many studies investigating protein levels did not correlate with these time periods. Therefore, it is difficult to decide what role a certain signaling pathway may have in regulating neurogenesis at different time periods following seizures. Based on the dissection of contributions of adult-born DGCs born at different timepoints and different ages, investigations for optimization of when modulation of this pathway may be most beneficial and appropriate as a therapeutic target is of great importance. In addition, when manipulating signaling pathways, it is critical to assess the effects of manipulation on other downstream functions. With recent advances in single-cell sequencing technology, the possibility exists of distinguishing aberrant and normal neurogenesis. This would provide a more explicit understanding of the heterogeneity of adult neurogenesis. In this way, we may find more specific and more efficient targets for epileptogenesis.

In addition, based on the classic view that epilepsy is caused by an imbalance of "excitatory-inhibition", searching for methods to instruct adult-born DGCs to preferentially differentiate into GABAergic interneurons (fate change) may be of great potential in preventing epileptogenesis. Results from research taking advantage of an induced pluripotent stem cell (iPSCs) model suggest this possibility for dysregulation of GABA/Glutamate differentiation [202]. Encouragingly, some *in vitro* studies also show promising results by taking advantage of a cocktail of small molecules (*e.g.* lineage-specific transcription factors) that can change the cellular environment and achieve specific fate decisions [203-205]. The fate choice of neural progenitors *in vivo* can be dictated by the environment of the neurogenic niche; however, with regard to searching for appropriate molecules to control the fate of aberrant newborn DGCs during epilepsy, significant research is still required to fully understand this process. Meanwhile, whether it is possible to reduce ectopic hilar DGCs by urging DGCs to integrate into normal rather than pro-epileptic circuits may also be of great value. Future studies using new technologies like optogenetics and single-cell sequencing are expected to alter fate commitment, as well as the integration patterns of adult DGCs.

CONCLUSION

In this review, we outlined the connection between epilepsy and various aspects of neurogenesis (proliferation, survival, migration and integration) from the perspective of the

neurogenesis playing a role in epileptogenesis. Besides, interventions of neurogenesis with pharmacological and genetic methods and their consequences were summarized. However, the complex association between neurogenesis and epileptogenesis presents a great obstacle for researchers and hinders the outcome of potential therapies. The functional implications of neurogenesis haven't yet been fully elucidated. In addition, numerous signaling pathways that can regulate neurogenesis and are critically involved in epileptogenesis were also presented. Future investigations may revolutionize the therapies of epilepsy by preventing or controlling epilepsy, as well as ameliorating comorbidities.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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