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Review article

Differential effects of antiseizure medications on neurogenesis: Evidence from cells to animals

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ABSTRACT

Neurogenesis, the process of generating functionally integrated neurons from neural stem and progenitor cells, is involved in brain development during embryonic stages but continues throughout life. Adult neurogenesis plays essential roles in many brain functions such as cognition, brain plasticity, and repair. Abnormalities in neurogenesis have been described in many neuropsychiatric and neurological disorders, including epilepsy.

While sharing a common property of suppressing seizures, accumulating evidence has shown that some antiseizure medications (ASM) exhibit neuroprotective potential in the non-epileptic models including Parkinson's disease, Alzheimer's disease, cerebral ischemia, or traumatic brain injury. ASM are a heterogeneous group of medications with different mechanisms of actions. Therefore, it remains to be revealed whether neurogenesis is a class effect or related to them all. In this comprehensive literature study, we reviewed the literature data on the influence of ASM on the neurogenesis process during brain development and also in the adult brain under physiological or pathological conditions. Meanwhile, we discussed the underlying mechanisms associated with the neurogenic effects of ASM by linking the reported *in vivo* and *in vitro* studies. PubMed, Web of Science, and Google Scholar databases were searched until the end of February 2023. A total of 83 studies were used finally.

ASM can modulate neurogenesis through the increase or decrease of proliferation, survival, and differentiation of the quiescent NSC pool. The present article indicated that the neurogenic potential of ASM depends on the administered dose, treatment period, temporal administration of the drug, and normal or disease context.

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1. Introduction

Neurogenesis is the formation of new neurons from neural stem cells (NSC) and their progenitors, whereas gliogenesis refers to producing supporting cells by generating oligodendrocytes and astrocytes [1]. Neurogenesis includes multistep processes, consisting of NSC self-renewal, proliferation, differentiation, maturation, and migration into the brain circuit [1,2]. In mammals, "embryonic neurogenesis" starts in the early stages of development in the telencephalon and peaks at first postnatal ages. In the developing brain, the central nervous system (CNS) initiates from neuroepithelial cells, placed in entire areas of the neural tube. At first, neuroepithelial cells proliferate symmetrically and then transit to apical radial glial-like cells, which directly or indirectly differentiate into neuronal cells (Fig. 1) [3]. In adults, neurogenesis persists in specific brain regions named neurogenic niches, such as the subgranular zone (SGZ) area of the hippocampal dentate gyrus (DG), and the part of lateral ventricles named subventricular zone (SVZ), as well as the olfactory bulb (OB) [4,5]. Neurogenesis is important for establishing the neuronal network that underlies complex behaviors, such as memory formation and the learning process, and is carefully regulated by different intrinsic factors and extracellular signaling pathways like brain-derived neurotrophic factor (BDNF), epidermal growth factor (EGF), fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), bone morphogenetic proteins (BMP), mammalian target of rapamycin (mTOR), wnt/β-catenin cascade, *etc* [6,7].

Both physiological and pathophysiological stimulus may affect the adult hippocampal neurogenesis process. On the other hand, alterations in brain neurogenesis may link to the pathogenesis of many neurologic, neurodegenerative, and neuropsychiatric disorders such as Alzheimer's disease [8,9], stress/anxiety and depression [10], schizophrenia [11], Parkinson's disease [12], stroke [13], epilepsy and age-related cognitive dysfunction [14].

Different studies have shown that the decrease in neurogenesis might be reversed by antidepressants, antipsychotics, and/or increasing physical exercise.

Epilepsy is one of the most common serious neurological condition characterized by an enduring predisposition to epileptic seizures [15]. It is approximated that about 10% of people will experience a seizure during their life [16,17].

Antiseizure medications (ASM) are the mainstay of symptomatic epilepsy management. ASM have different pharmacologic profiles, including mechanism of action, pharmacokinetic properties, propensity for drug-drug interactions, side effect profiles and toxicities, clinical efficacy, and therapeutic spectrum (narrow *vs.* broad). According to the timeframe in which ASM have been developed, they are classified into three generations [18,19]. The First-generation or older ASM mostly have cyclic ureide-based structures, such as ethosuximide (succinimides), phenytoin (hydantoins), phenobarbital and primidone (barbiturates), and trimethadione (oxazolidinediones). Benzodiazepines, carbamazepine, and valproate were also usually considered as the first generation ASM. They were introduced between 1960 and 1975 and exhibited different chemical structures and superior tolerability to the cyclic ureides. The newer, second and third-generation ASM, namely (based on the year of FDA approval) vigabatrin, zonisamide, oxcarbazepine, lamotrigine, gabapentin, felbamate, topiramate, tiagabine, levetiracetam, pregabalin, rufinamide, stiripentol, lacosamide, eslicarbazepine acetate, clobazam, ezogabine, perampanel, brivaracetam, cannabidiol and cenobamate have been approved since the late of 1980s. These medications have favorable pharmacokinetic properties and drug interactions, and even better tolerability and

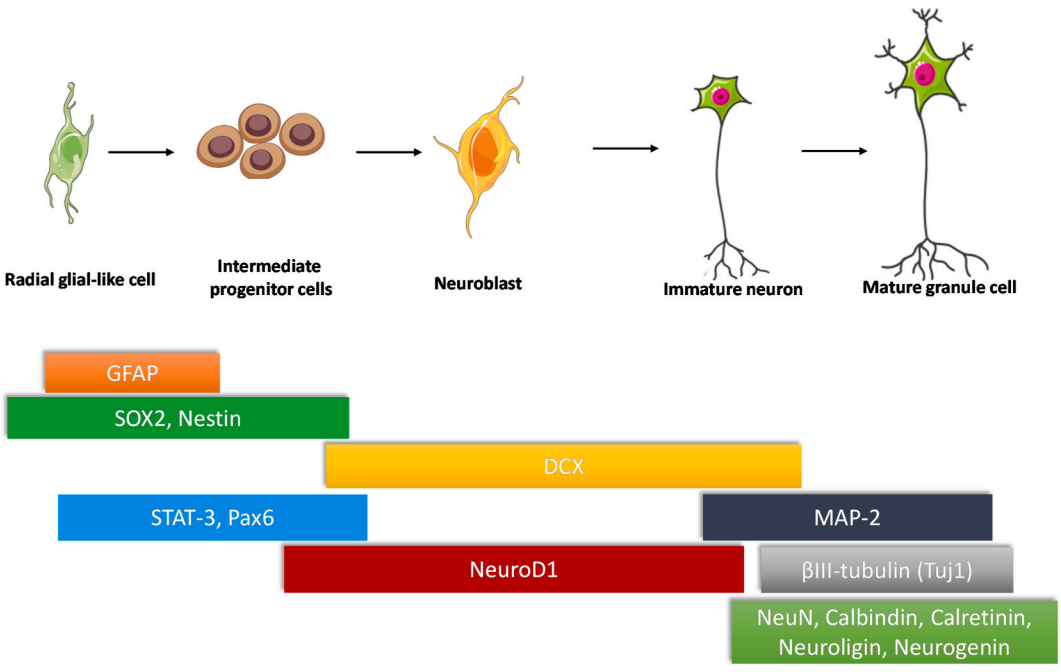

Fig. 1. An overview of hippocampal neurogenesis in mammals.
The stage-specific protein expressions are shown in the colored horizontal panels adjacent to the specific cell-stages.

toxicity profiles, in respect to the older ASM [20,21].

In addition to antiseizure activity, accumulating evidences have shown that some ASM exhibit neuroprotective potential in the non-epileptic models including Parkinson's disease, Alzheimer's disease, cerebral ischemia, or traumatic brain injury. Moreover, several studies suggest that ASM can modulate neurogenesis through the modification of proliferation, survival, and differentiation of the quiescent NSC pool [22–26].

ASM are a heterogeneous group of compounds, therefore, it remains to be revealed whether neurogenesis is a class effect or related to them all. In the present review, we searched the available literature on the ability of ASM to affect embryonic and adult neurogenesis and explored the underlying mechanisms.

2. Methods

2.1. Search strategy

A bibliographic search was performed to extract original articles combining drug names (e.g., valproate) and using relevant keywords such as 'antiseizure medications', 'epilepsy', 'neural progenitor cell', 'neural stem cell', 'neural precursor cell', 'neurogenesis', 'differentiation', 'proliferation', 'developing brain', 'subventricular zone', 'dentate gyrus'. PubMed, Web of Science, Scopus, and ScienceDirect were used as electronic databases. No time limitation was used in the current review and both *in vitro* and *in vivo* research were included. We discussed each medicine based on the classification of ASM generations. The first generation of ASM included in this review were carbamazepine, ethosuximide, phenobarbital, phenytoin, and valproate. Gabapentin, levetiracetam, lamotrigine, lacosamide, oxcarbazepine, pregabalin, perampanel, rufinamide, topiramate, and zonisamide were considered as the second- and third-generations ASM in this article [18].

2.2. Study selection

Non-English articles and dissertations were neglected for inclusion. In the primary search, 214 studies were included. Next, duplicate researches were deleted. Screening of the remaining articles was performed by reading the titles, abstracts, or full texts according to the eligibility criteria. A total of 83 articles were included in the reviewing process. The search strategy used for the present article follows the PRISMA 2009 checklist and is listed in Fig. 2.

3. Epilepsy and neurogenesis

Status epilepticus, induced either by electrical stimulation of amygdala or hippocampus or a chemoconvulsant)such as kainic acid, or pilocarpine (, has been usually used to model human temporal lobe epilepsy (TLE) [27]. In the acute animal models of status epilepticus, hippocampal neurogenesis was dramatically increased. However, epilepsy-induced new neurons had abnormal morphology (e.g., altered dendrites, axonal sprouting), aberrant differentiation, and ectopic integration into DG [28].

Unlike acute stages, chronic TLE is associated with a decrease in neurogenesis [29,30]. It is believed that abnormal hippocampal neurogenesis could contribute to the comorbidities associated with chronic epilepsy including cognitive, behavioral, and emotional difficulties [31]. By intraperitoneal injection of bromodeoxyuridine (BrdU), it was found that the proliferation of hippocampal NSC has been significantly decreased in the animal models of TLE. Furthermore, chronic epilepsy considerably reduced the hippocampal

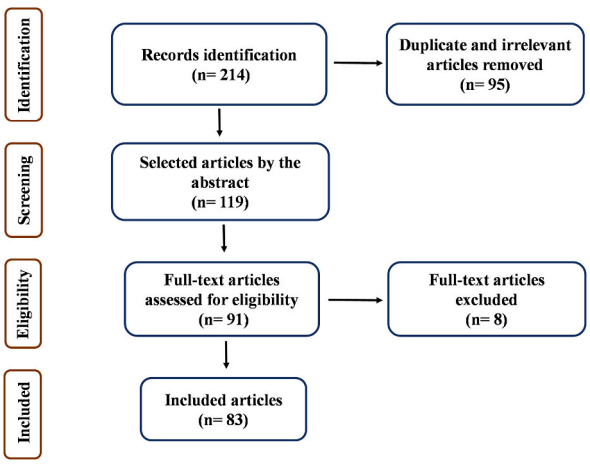

Fig. 2. The flow diagram of the search strategy.The literature search identified 214 publications initially. Then, the duplicate, irrelevant, non-English, review papers, the dissertations and the abstracts were excluded during screening and eligibility processes. A total of 83 articles were included in the current review.

expressions of doublecortin (DCX^+), βIII-tubulin$^+$, and $NeuN^+$ neuronal markers, as compared to the age-matched healthy animals. In addition, during TLE the differentiation of newly born cells into glia was increased [32]. It is hypothesized that during chronic epilepsy the factors that support neuronal differentiation are dramatically decreased. It may consist of a reduction in the levels of BDNF, neurotrophin-3 (NT-3), nerve growth factor (NGF), Wnt proteins, insulin-like growth factor (IGF)-1, FGF-2, and reelin in the chronically epileptic brain [33]. Changes in neuronal homeostasis during epilepsy can lead to microglia activation, upregulation of the levels of proinflammatory mediators like tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1β, transforming growth factor-beta (TGF-β), overactivation of N-methyl-D-aspartate (NMDA) receptors, and reduction of ϒ-aminobutyric acid (GABA)-mediated neurotransmission, which impairs neurogenesis and synaptic plasticity [34]. Moreover, the process of epilepsy development, known as epileptogenesis, is associated with changes in the expression of a myriad of genes, probably via disruption in histone acetylation. Histone modification is critical for the modulation of neurobiological functions including neurogenesis and synaptogenesis, neural network function, and synaptic plasticity [35].

4. The first-generation ASM and neurogenesis

4.1. Carbamazepine

Carbamazepine (CBZ) is a voltage-dependent sodium channels blocker and is usually prescribed for the treatment of generalized- and focal-onset seizures. In addition, CBZ is one of the ASM used for managing pregnant women suffering from epilepsy [36,37]. It has been proved that CBZ accumulation in the fetal tissues may result in congenital malformations and behavioral dysfunctions. It is hypothesized that neuronal apoptosis and alterations of neurogenesis are responsible for CBZ-induced cognitive deficits in the offsprings. A recent study by Gonzalez-Maciel showed that oral maternal exposure to 100 mg/kg/day of CBZ, before and during the neurogenesis period at embryonic days 7–15, increased neuronal apoptosis and decreased DCX^+ expressing immature neural cells in the SGZ of offsprings [38].

In zebrafish embryos, exposure to 1–5 μg/L of CBZ significantly overexpressed the mRNA levels of neurogenesis-related genes, *neurogenin 1 (Ngn1)* and *NeuroD,* and also astrocyte differentiation gene, *Gfap*. It has been well documented that overexpressions of *Ngn1* and *NeuroD* are related to ectopic abnormal neurogenesis [39]. It was also revealed that CBZ exposure disturbed the larvae's normal growth and accelerated motor behaviors, which may be linked to the impact of CBZ on neurogenesis [39]. Similarly, treatment of human embryonic stem cells (hESC) with CBZ (3–30 μM) for either 1 or 7 days, significantly disrupted neural differentiation with a concomitant decrease in the expressions of neurogenesis-related genes including *βIII-tubulin*, *Ngn1*, *Reelin*, and microtubule-associated protein *(MAP-2)* [40]. It was also found that CBZ may affect embryonic brain development and neurogenesis via down-regulation of Tcf/Lef transcription factors in the Wnt/β-catenin signaling pathway and inhibition of TGF-β signaling [40].

In the same way, 10 days of treatment with CBZ at 200–1000 μM, notably reduced cell viability and neurosphere size of human NSC, *in vitro* [41]. Also, exposure to 375 μM of CBZ decreased astrocyte and neuronal differentiation, which is confirmed by low expression levels of GFAP and βIII-tubulin proteins [41]. Cao et al. also showed that treatment with 100 μM of CBZ disrupted neurogenesis in TERA2.cl.SP12 human stem cells [42].

While CBZ could significantly decrease neurogenesis in both developmental and adult stages in cultured NSC, postnatal exposure to CBZ had no obvious effects on neurogenesis. Chen et al. reported that chronic oral administration of CBZ (120 mg/kg) during 7–28 postnatal days, did not significantly modify hippocampal cell survival and proliferation, and neuronal differentiation (percent of DCX^+ cells) [43].

4.2. Ethosuximide

Ethosuximide (ESM) was approved for the treatment of absence seizures by inhibition of T-type calcium current in thalamic neurons [44,45]. ESM has been shown to promote neurogenesis in developing brains. It was reported that 100 μM of ESM increased hippocampal NSC population and neurosphere formation at embryonic day 12. It enhanced the percentage of $BrdU^+/DCX^+$ and $BrdU^+/NeuN^+$ neuronal cells, while no important alterations were detected in the number of glial cells (S100-β^+ cells) and oligodendrocytes ($CNPase^+$ cells). On the other hand, ESM at 200, and 400 μM showed toxic effects on embryonic NSC [26].

Furthermore, it was reported that ESM (1 μM, 6 days) promoted NSC proliferation (by increased $BrdU^+$ cells) and neurogenesis (by enhanced βIII-tubulin$^+$, MAP-$2^{+,}$ and $GABA^+$ neurons) in the stem cells isolated from the forebrain cortex of 3-day-old rats [46].

Szewczyk et al. showed that long-term exposure to ESM (20 mg/kg, 10 days) did not induce any cognitive deficits in the pilocarpine (300 mg/kg, i.p) mouse model of status epilepticus. Moreover, ESM had no negative effects on neurogenesis and the level of $BrdU^+/NeuN^+$ cells in the pilocarpine-treated mice [47].

Andres-Mach et al. confirmed that intraperitoneal treatment with ESM (10 mg/kg, 10 days) did not impair cognition and cell proliferation (the number of $BrdU^+$ cells), but significantly reduced $GFAP^+$ cells in the dentate SGZ of 6-week-old C57BL/6 mice [48].

Also, Tiwari et al. demonstrated that ESM improved hippocampal neurogenesis in the amyloid-β model of AD rats. Both acute (3 days) or sub-acute (2 weeks) treatment with 125 mg/kg of ESM induced hippocampal neurogenesis by increased expressions of DCX and NeuN molecules, without any significant changes in the astroglial markers [26]. On the contrary, succinimide (an inactive analog of ESM), at the dose of 125 mg/kg did not have any significant influence on both embryonic and adult neurogenesis [26].

Another study also highlighted ESM-stimulated neuronal differentiation of stem cells derived from rat skeletal muscle (rMDSCs) [49]. The study also found that treatment with 4 mM of ESM in combination with 25 ng/ml of bFGF for 8 days, differentiated a greater proportion of rMDSCs into the neural-like cells expressing NeuN and βIII-tubulin, rather than oligodendrocyte marker, Olig2 [49].

In the same way, ESM notably increased the hippocampal mRNA expression levels of genes involved in neurogenesis including *Nestin*, *DCX*, *βIII-tubulin*, *Ngn1*, *neuroligin*, *Stat-3*, *Pax-6*, and *NeuroD1* in AD-like model rats [26]. It was suggested that ESM-induced neurogenesis was mediated via up-regulation of phosphoinositide 3-kinases (PI3K)/protein kinase B (Akt)/Wnt/β-catenin signaling cascade, as it was significantly blocked in the presence of 100 nM of Wnt antagonist (Dkk-1) and 10 nM of PI3K/Akt inhibitor (LY294002) [26,50].

4.3. Phenytoin

Phenytoin (PHT) or diphenylhydantoin has been developed since 1930 for the treatment of focal- and generalized-onset seizures. The mechanisms contributing to the antiseizure activity of PHT include inhibition of voltage-dependent sodium channels, inhibition of calcium-calmodulin protein phosphorylation, suppression of ionotropic glutamate receptors, and enhancement of GABAergic transmission [51].

High concentration of PHT (250–660 μM, 10 days) significantly reduced cell viability, neurosphere size, cell migration, GFAP, and βIII-tubulin levels in human cultured NSC [41].

Maternal exposure to PHT may lead to fetal hydantoin syndrome, and mental and physical defects, in the developing brains. Oral treatment by PHT (35 mg/kg) during postnatal days 2–4 or days 5–14 significantly decreased the population of mature neuronal cells (calbindin$^+$ cells) in the DG and reduced the dendritic development of Purkinje cells in the cerebellum of C57BL/6 mice [52,53]. Moreover, PHT disrupted the migration of mice cerebellar granule cells, detected by BrdU labeling [53]. Newborn mice exposed to PHT during infancy also showed spatial learning and memory deficits [52].

PHT administration (10 mg/kg for 30 days, orally) caused significant phosphorylation of EGF and FGF receptors in the SVZ of adult male mice brains. PHT also enhanced the population of neural progenitors and neuroblasts (BrdU$^+$/SOX2$^+$ and BrdU$^+$/DCX$^+$ cells) in the SVZ. It also expanded the number of Olig2$^+$ cells around the lateral ventricles. Although PHT significantly decreased the proportion of mature neurons (NG2$^+$ glia and NeuN$^+$ cells) but promoted the percent of mature oligodendrocyte RIP$^+$ cells in the OB [54]. The same investigators also showed that PHT (10 mg/kg, 30 days) dose-dependently promoted the proliferation of NSC in the SVZ and SGZ areas of the adult mice brain [55].

4.4. Phenobarbital

Phenobarbital (PB) belongs to the barbiturate family which improves the effect of GABA. PB's clinical utility in the management of seizures is limited because of its sedating effects [56]. Animal studies suggest that short- and long-term treatment of PB suppressed neurogenesis in the neonates [57,58]. Administration of 50 mg/kg of PB to newborn rats during the postnatal days 4–6 resulted in a great reduction of proliferative capacity and also decreased neurogenesis by reduced expressions of DCX, calretinin, and NeuN neuronal markers in the DG. PB decreased the levels of neurotrophins and neuronal transcription factors including NGF, BDNF, NT-3, and Pax6, Prox1, Sox2, Tbr1/2 [57,58]. The addition of caffeine (10 mg/kg) could restore PB-induced neurogenesis impairment [57]. Moreover, chronic intraperitoneal treatment with 40 mg/kg of PB starts at postnatal day 7 until 3- or 4-week-old, reduced DCX$^+$ neurons, and decreased the percentage of BrdU$^+$-labeled cells in rats. It also declined BDNF and NT-3 mRNA expressions in the neonatal rat brain, without any changes in mossy fiber sprouting [43,59]. It seems that the effect of PB on infants' neurogenesis is not transient and even at 6-month-old, these rodents had fewer neural cells in the DG and also showed impaired memory and learning tasks [60]. However, administration of 30–60 mg/kg PB at postnatal day 12, did not change hippocampal neurogenesis in a neonatal stroke mice model [61].

In an *in vitro* model of neurogenesis using human stem cells (TERA2.cl.SP12) which subsequently give rise to neurons, PB at 100–1000 μM alleviated the viability of stem cells [42]. Moreover, 10 days of treatment with a high concentration of PB (>1000 μM) markedly declined the viability, migration, astrocyte, or neuronal differentiations in isolated human NSC [41].

4.5. Valproic acid

Valproic acid (VPA) is a broad-spectrum ASM with mood-stabilizing properties. VPA exerts its antiseizure effects by suppressing voltage-dependent sodium channels, facilitating GABAergic transmission, and inhibiting T-type calcium channels [62]. It has been also well documented that VPA modulates DNA transcription through inhibition of histone deacetylase (HDAC), mTOR, BDNF, and glial cell line-derived neurotrophic factor (GDNF) signalings [63,64].

Maternal VPA use is clinically restricted because of the risk of fetal valproate syndrome in developing embryos. In particular, prenatal exposure to high levels of VPA, particularly during neural tube closure, is associated with unusual brain formation, developmental neurotoxicity, and behavioral abnormalities in rodents. In accordance, maternal exposure to VPA is an established experimental model of autism spectrum disorder (ASD), as well as neural tube deficits [65].

It is well recognized that VPA exposure during pregnancy altered the expressions of multiple proteins related to glutamatergic and GABAergic neurotransmissions. Synaptic plasticity enhancement mediated by NMDA receptors and disruption of the normal excitatory-inhibitory shift of GABAergic currents leads to irregular signaling pathways, synaptic impairments, and neurogenesis deficits, leading to ASD [66,67].

It was found that maternal exposure to VPA (200–300 mg/kg, i.p., twice on gestational days 26 and 29 could lead to prominent neurogenesis impairments and autistic-like behaviors in monkey offsprings. Both male and female neonates showed a decrease in the number of NeuN$^+$ neurons and reduced the Ki-67$^+$ progenitors in the cerebellar external granular cell layer [68].

Prenatal exposure to 500 mg/kg VPA at embryonic day 12.5 also impaired neurogenesis and cognitive functions in 5-week-old mice offspring. Postnatal intracerebral transplantation of bone marrow-isolated mesenchymal stem cells increased DCX^+ neurons in the DG and restored the deficits in cognitive and social behaviors also induced by VPA [69].

In the DG, GABAergic interneurons play an important role in neurogenesis regulation by expressing reelin, an extracellular matrix glycoprotein, and calcium-binding proteins like parvalbumin, which modulate the migration of progenitor cells. Oral exposure to 667–2000 ppm of VPA during development (from embryonic day 6 until postnatal day 21) significantly reduced the subpopulation of $reelin^+$, $GAD67^+$, and $parvalbumin^+$ GABAergic interneurons with the reduced expression of the associated genes in the DG of offspring [70]. It was also found that the percentage of $PCNA^+$ proliferating cells and $NeuN^+$ mature neurons increased in the adult stage of animals exposed to 2000 ppm of VPA during infancy [70].

VPA also inhibited neurogenesis in P19 mouse embryonal carcinoma cells. The neurogenesis was improved by inducing the nuclear factor erythroid-related factor (NRF2) antioxidant response, which combated cellular redox disruption [71].

Sahakyan et al. reported the negative influence of VPA on neurogenesis in human amniotic fluid stem cells isolated from myelomeningocele, a severe form of neural tube imperfection. They showed that VPA (1 mM) reduced the percentage of $SOX2^+$, $Nestin^+$, $\beta III\text{-}tubulin^+$, and $brain\ lipid\text{-}binding\ protein^+$ radial glial cells in the isolated neural progenitor cells [72].

In adult male Sprague-Dawley rats who were treated with VPA (300 mg/kg twice daily for 14–28 days), neurogenesis disruption (by decreasing the proliferative $BrdU^+$ and immature DCX^+ cells) was detected in the SGZ of the DG [73]. Treatment with melatonin (8 mg/kg/day for 14 days) suppressed the VPA-induced neurogenesis deficits by increasing cell proliferation, improving survival, and enhancing the number of immature neurons in the SGZ [73]. Researchers believed that MT2 melatonin receptor activation enhances neurogenesis by upregulating neurodevelopmental gene/protein expression in ischemic-stroke mice [74].

Male Wistar rats who received 300 mg/kg of VPA twice a day for 10 days showed cognitive deficits and neurogenesis impairments in the SGZ of the DG. Discontinuing VPA treatment resulted in recovered memory, enhanced cell proliferation, and increased expression levels of BDNF and Notch1 [75].

In keeping with these observations, oral administration of VPA (900 mg/kg, 28 days) in postpubertal rats (5-week-old animals) diminished the percentage of DCX^+ and $NeuN^+$ granule cells but amplified astrocyte subpopulation ($GFAP^+$ cells) in the hippocampus [76].

VPA infusion (0.25 mg/μl, 2 weeks) significantly diminished the population of $Pax6^+/NeuN^+$ cells in the midbrain of adult transgenic NesCreERT2/R26eYFP mice, probably via HDAC inhibitory action [77].

However, Chen et al. did not find any negative effects of valproate (250 mg/kg, orally for 28 days) on cell survival and neurogenesis in the dorsal hippocampus of the immature brain (Postnatal day 7) [43].

In contrast to the above-mentioned studies, numerous studies also indicated that VPA may promote neurogenesis. Daily administration of VPA (100–200 mg/kg/day, i.p.) from gestational day 12.5 until birth, enhanced hippocampal $BrdU^+$ and DCX^+ cells in the offsprings, however, the memory function remained intact [78].

It was also established that treatment of NSC, isolated from rat's ganglionic eminence, with 0.5 mM VPA for 6 days amplified the number of $\beta III\text{-}tubulin^+$/BrdU-labeled neurons, but decreased the generation of astrocytes [79]. The effect was related to the robust rise of cyclin D2 and prostaglandin E2 synthase and suppression of Bad expression [79]. VPA also stimulated neuronal differentiation in non-transformed human fetal forebrain stem cell cultures [79]. Most of the newly generated neurons were phenotypically GABAergic, as presented by the increased expression of the GAD65/67 GABA synthesis enzyme [79].

In neuron-glia cultures isolated from the midbrain of Fisher rats at the embryonic days 13–14, VPA at 0.6 mM for 48 h prolonged the survival of DA neurons following lipopolysaccharide (LPS) or 1-methyl-4-phenylpyridinium (MPP^+) insults. The underlying mechanisms associated with the beneficial effects of VPA were up-regulation of GDNF and BDNF expressions in the astrocytes and the suppression of pro-inflammatory factors released from microglia [80,81]. On the contrary, the previous experimental evidence has demonstrated that VPA (100 mg/kg) reduced the expressions of BDNF and NT-3 mRNA in the developing rat brain, but increased cell neurogenesis [59].

Hsieh et al. also reported that adult rat exposure to VPA (300 mg/kg, i.p., for 14 days twice daily) induced neuronal differentiation by overexpression of *NeuroD* in the hippocampal neuronal progenitor cells, in association with inhibition of HDAC [82].

The neurogenesis-enhancing effect of VPA has also been confirmed in the APP/PS1/Nestin-GFP triple transgenic mouse model of AD. As described by Zeng et al., intraperitoneal injection of 30 mg/kg/day VPA for 4 weeks considerably improved cognitive impairment and promoted NSC proliferation, differentiation, and neuronal maturation by enhancement of $BrdU^+$, $Nestin^+$, $NeuN^+$, and $GFAP^+$ cells in DG and SVZ [83,84].

VPA treatment (150 mg/kg, i.v.) reduced brain edema and lesions and significantly up-regulated the genes involved in neurogenesis such as *NeuroD*, in the Swine model of traumatic brain injury and hemorrhagic shock [85].

Treatment with VPA (100 mg/kg) 24 h after middle cerebral artery occlusion for 7 days significantly reduced ischemic cell damage, increased survival, and generation of oligodendrocytes, and also improved the percentage of $BrdU^+/DCX^+$ new neurons in the SVZ and striatal ischemic boundary zone of rats. Moreover, acetylation of histone H4 in the neuroblasts of the ischemic region increased, which may be related to the neurogenic influence of VPA [86].

VPA treatment (10 mg/kg) in combination with arachidonyl-2′-chloroethylamide (ACEA, a cannabinoid CB1 receptor agonist) for 10 days also stimulated proliferation ($Ki\text{-}67^+$ and $BrdU^+$ cells) and differentiation ($NeuN^+$ and $GFAP^+$ cells) of neural progenitors in the dentate SGZ of C57BL/6 mice [87]. In the same way, treatment with VPA (150 mg/kg/day) for 4 weeks promoted the number of $NeuN^+$ neurons and increased the survival of dopaminergic neurons derived from murine-induced pluripotent stem cells, which were transplanted in the striatum of male intact rats [88].

Additionally, VPA exposure (30 mg/kg, i.p., for 4 weeks) improved neurogenesis and the pathological alterations of AD via

suppression of glycogen synthase kinase-3β (GSK-3β) and activation of the Wnt/β-catenin signaling pathway [83]. Moreover, VPA at 50–150 μg/ml produced neurotrophic effects and promoted neurite growth in the human neuroblastoma SH-SY5Y cells, through the extracellular signal-regulated kinase (ERK) pathway [89]. This mechanistic finding was entirely similar to an *in vivo* study in male C57BL/6 mice described that VPA-supplemented chow (20 g/kg for 4 weeks) promoted neurogenesis, as demonstrated by double stainings of BrdU with Nestin, Tuj1, and NeuN, concomitant with the stimulation of ERK signaling pathway [22].

5. The second- and third-generations ASM and neurogenesis

5.1. Gabapentin

Gabapentin (GBP) is a gabapentinoid agent with a similar chemical structure to GABA but its function is not related to GABA synthesis or action [90]. The mechanism of the antiseizure activity of GBP is not totally known, but it binds to auxiliary $\alpha_2\delta_{1/2}$ subunit of voltage-gated calcium channels (VGCCs) and inhibits inward calcium current [91].

GBP (50 mg/kg) exposure during embryonic days 1–5 or 6–15 had no neurotoxic or apoptotic effects in Wistar albino male rats [92]. It was shown that exposure of rat cortical stem cells isolated at embryonic day 14 to GBP (16 μg/ml) for 7 days, notably enhanced the number of MAP-2^+ cells, without any significant changes in $GFAP^+$ astrocytes progenitors, indicating that gabapentin promoted neural differentiation [93]. In the same way, GBP (1 nM) remarkably improved neuronal differentiation of adult mouse hippocampal NSC by a rise in MAP-2 expression [25]. The underlying mechanism behind the neurogenic effect of GBP was binding to the VGCCs and inhibition of the excitatory transmission in the presynaptic area [90]. Using $\alpha_2\delta$ subunit antagonists (L-isoleucine and L-(+)-α-phenylglycine), the promoting effect of GBP on neurogenesis was blocked [25].

5.2. Lacosamide

Lacosamide (LCM) is an amino acid derivative approved to treat focal and primary generalized tonic-clonic seizures, as mono- or adjunctive-therapy. Unlike other sodium current blocking agents, LCM optionally increases slow inactivation, without interaction with the fast inactivation gating [94]. Szewczyk and co-workers evaluated the impact of 10 mg/kg of LCM for 10 days on hippocampal neurogenesis and also learning and memory processes after status epilepticus caused by pilocarpine in C57BL/6 mice [47]. It was found that the long-term administration of LCM notably decreased the total number of newborn neurons by a reduction in $BrdU^{+/}NeuN^+$ co-labeled cells in the dentate SGZ. However, LCM had no negative influence on cognitive functions after status epilepticus. Results from MRI spectroscopy also did not show any important alterations in the level of selected neurometabolites essential for the appropriate course of the neurogenesis process [47]. In the same way, treatment with 10 mg/kg of LCM for 10 days, significantly reduced the percentage of $BrdU^+$ cells, $NeuN^+/BrdU^+$ cells, and $GFAP^+/NeuN^+$ cells in the dentate SGZ of treated mice. The study showed that LCM, compared to control, significantly decreased the neurogenesis process and impaired cognition in mice [48]. Shishmanova-Doseva et al. also showed that long-term administration of LCM induced learning and memory impairment in rats via the suppression of the BDNF signaling pathway in a dose-dependent manner [95]. On the other hand, it was shown that LCM (30 mg/kg) improved cognition in Wistar rats, maybe due to HDAC inhibitory effect in the cerebral cortex [96].

As reported by Licko et al. 24-day treatment with low-dose (10 mg/kg) and high-dose (30 mg/kg) of LCM significantly diminished the status epilepticus-associated aberrant neurogenesis in rats' hippocampus by suppression of abnormal rises in the number of $NeuN^+/BrdU^+$ cells. In addition, high-dose of LCM inhibited the status epilepticus-associated long-term changes in the population of DCX-labeled neuronal progenitor cells [24].

5.3. Lamotrigine

Lamotrigine (LTG) is a broad-spectrum drug that is used alone or in combination with other ASM to treat focal and generalized-onset seizures [97]. It inhibits sodium currents by selective binding to the inactivated states of sodium channels and suppresses the release of the excitatory amino acids, aspartate and glutamate [98]. According to Chen et al. although LTG (20 mg/kg) had no obvious effects on the DG neurogenesis in normal rats, significantly reduced aberrant neurogenesis in the DG of rats with temporal lobe epilepsy (TLE) induced by lithium-pilocarpine [99].

It was revealed that long-term (21 days) administration of LTG increased hippocampal cell neurogenesis in the neonatal rat brain, but reciprocally reduced the mRNA levels of BDNF and NT-3, only at high dose (80 mg/kg) [58].

5.4. Levetiracetam

Levetiracetam (LEV) is a broad-spectrum ASM that is approved to treat focal and generalized-onset seizures [100]. The underlying mechanism of LEV is not entirely obvious; however binding to the neuronal synaptic vesicle glycoprotein (SV2A) is considered as the main responsible for its action [101,102].

LEV has been shown to affect both embryonic and adult neurogenesis. An *in vitro* study on rat fetal NSC isolated at gestational day 14.5, LEV (50 μM) enhanced proliferation, and increased neuronal differentiation, as revealed by enhanced expression levels of DCX and NeuN. It decreased the percentage of the $GFAP^+$ and $Olig2^+$ cells. The addition of MK801 (NMDA receptor antagonist) to LEV treatment significantly diminished LEV-induced neurogenesis but enhanced the astroglial differentiation. Co-treatment with saclofen ($GABA_B$ receptor antagonist) did not significantly impair LEV-induced neurogenesis [103].

Like embryonic evidence, multiple recent studies have shown that LEV enhanced adult neurogenesis. It was demonstrated that LEV (i.p, 10 mg/kg) with ACEA treatment for 10 days, significantly increased proliferating Ki-67$^+$ cells in male C57BL/6 mice [104]. Based on the study results, the percentage of newborn neurons (NeuN$^+$ cells) increased in the animals who received LEV in combination with ACEA, while LEV *per se* significantly reduced the neurogenesis. Moreover, the astrocytes population (GFAP$^+$ cells) was considerably reduced after exposure to LEV or LEV + ACEA [48,104].

Zhang and colleagues established the potential role of the Wnt/β-catenin signaling in LEV subchronic (7 days) or chronic (35 days) effects on hippocampal neurogenesis in adult C57BL/6 mice [105]. Chronic LEV treatment (130 and 260 mg/kg, orally) promoted the proliferation of NSC, intermediate progenitors, and neuroblasts and differentiation of newborn immature neurons, while subchronic treatment significantly suppressed neurogenesis. Furthermore, chronic LEV administration increased the levels of Wnt 3a, and β-catenin while decreasing the expression of GSK-3β, and Axin2. Subchronic exposure to LEV downregulated the Wnt/β-catenin pathway activity [105].

The study by Yan et al. emphasized the impact of LEV (300 and 600 mg/kg, 4 weeks) on neurogenesis in adult male mice. It was estimated that the underlying molecular mechanism is PI3K/Akt cascade, which was confirmed by increased levels of PI3K and phosphorylated Akt in the hippocampus of treated animals. Additional research on PC12 cells also indicated that 10–100 μM of LEV upregulated the PI3K/Akt signaling pathway which was blocked by the pharmacological inhibitor of PI3K (LY294002). In the presence of LY294002, additional treatment with 100 μM of LEV activated this cascade again [106]. The above researches suggested that, under physiological conditions, LEV promoted neurogenesis *in vitro* and *in vivo*.

Sugaya et al. suggested that LEV (320 μM) for 25 days exert the antiepileptogenic activity in the status epilepticus evoked by kainic acid, through inhibition of neuronal proliferation and atypical migration of new neurons from the dentate SGZ to the hilus [107].

5.5. Oxcarbazepine

Oxcarbazepine (OxCBZ) is an analog of CBZ and is used in focal-onset seizures as an alternative for CBZ. It acts through the inhibition of voltage-dependent sodium channels. Besides, it increases potassium outward current and inhibits glutamatergic transmission, and modulates the functions of calcium currents [108].

Prenatal exposure to 100 mg/kg/day of OxCBZ, before and during the neurogenesis period at embryonic days 7–15, increased neuronal apoptosis and decreased DCX expressing immature neurons in the SGZ of rat offsprings [38]. Similarly, it was shown that OxCBZ (100 mg/kg) exposure during the preimplantation-implantation period (embryonic days 1–5) or organogenesis period (embryonic days 6–15) induced neuronal apoptosis in Wistar albino male rats [92].

On the contrary to the embryonic findings, Ahn et al. reported that OxCBZ exerted neuroprotection against transient global cerebral ischemia in the gerbils' hippocampus. Pre (30 min before ischemia) and post (5 days after ischemia) injection of 200 mg/kg of OxCBZ intraperitoneally (but not 100 mg/kg) enhanced the number of NeuN$^+$ cells and decreased the GFAP$^+$ population in the CA1 area of gerbils' hippocampus [109].

5.6. Perampanel

Perampanel (PER) is a non-competitive antagonist of AMPA receptor, used to control focal and generalized seizures as adjunctive therapy. In the long-term (5 weeks) pilocarpine-induced status epilepticus, PER (8 mg/kg, i.v, 60 min after the initiation of status epilepticus) prevented deficits in spatial and recognition memories, neuronal loss, and severe astrogliosis in the rat hippocampal CA1 and CA3 areas. PER also slightly increased NeuN$^+$ cells, but significantly reduced GFAP$^+$ astrocytes [110].

In a more recent investigation, PER showed neuroprotective effects and inhibited cell apoptosis after acute traumatic injury in primary cultured cortical neurons. It was suggested that PER-induced neuroprotection is mediated by the activation of Akt and inactivation of the GSK-3β signaling pathway. Pharmacological inhibition of Akt by LY294002 partially antagonizes the protective potential of PER [111].

5.7. Pregabalin

Pregabalin (PGB) modulates calcium currents, as like as GBP [112,113]. PGB (0.1–10 nM) concentration-dependently increased the numbers of newborn neurons differentiated from adult hippocampal progenitors [25]. In an *in vivo* study, intraperitoneal injection of 10 mg/kg of PGB for 21 days, led to increased hippocampal neurogenesis in adult mice, as revealed by enhancement of BrdU$^+$/NeuN$^+$/GFAP$^-$ cells proportion and no changes on BrdU$^+$/NeuN$^-$/GFAP$^+$ cells [25]. It was noted that the $\alpha_2\delta_1$ subunit of VGCCs mediated the neurogenic effects of PGB in hippocampal NSC, *in vitro* [25]. The inhibition of the nuclear factor-κB (NF-κB) signaling pathway (as the downstream of $\alpha_2\delta_1$ subunit activation) significantly prevented the neurogenesis stimulated by PGB [25,91].

5.8. Rufinamide

Rufinamide (RUF) regulates sodium channels activity, in particular, prolongs the inactivation condition of the sodium channels. It is approved for the management of generalized seizures associated with Lennox-Gastaut syndrome [114].

It was established that RUF treatment (3 mg/kg for 4 weeks) considerably promoted cognitive behavior and increased neurogenesis in the DG of aged gerbils. RUF also amplified the population of Ki-67$^+$, DCX$^+$, and BrdU$^+$/NeuN$^+$ co-labeled cells, and also the expressions of IGF-1, its receptor (IGF-1R), and p-CREB, with no changes in BDNF or its receptor [115]. It was concluded that RUF,

through up-regulation of IGF-1, IGF-1R, and p-CREB, stimulated neurogenesis in the hippocampus of the aged gerbils [115].

5.9. Topiramate

Topiramate (TPM) is a weak carbonic anhydrase inhibitor used to treat focal and primary generalized tonic-clonic seizures [116]. TPM inhibits the voltage-dependent sodium channels by stabilizing the inactivated condition and decreases the L-type high-voltage-activated calcium current. It also stimulates $GABA_A$ receptors and antagonizes AMPA and kainate currents [117].

Chronic administration of 40 mg/kg TPM (orally, from postnatal day 7 for 28 days) had no negative influences on the proliferation of $BrdU^+$ cells and the expression patterns of NeuN, DCX, or GFAP markers [43]. On the contrary, TPM decreased BDNF and NT-3 mRNA expressions in developing rat brains [59].

In the temporal lobe epilepsy model, TPM (80 mg/kg, orally) promoted ectopic neurogenesis by increasing the percentage of newborn neurons (DCX^+) in the DG, without any negative impact on hippocampal neurogenesis in healthy rats [99].

In D-galactose-induced aging mice, oral administration of 50 mg/kg of TPM for 4 weeks ameliorated neuroblast damage and promoted neuroblast proliferated Ki-67^+ cells and immature DCX^+ cells in the DG, via increasing superoxide dismutase and catalase activities [118].

5.10. Zonisamide

Zonisamide (ZNS) is a sulfonamide agent which be useful for focal and generalized seizures. ZNS has voltage-dependent sodium and T-type calcium channels blocking activities [119].

Recently, Takahashi et al. showed that ZNS increased the survival of mouse- or human-induced pluripotent stem cell-derived dopaminergic neurons after transplantation in the rat striatum [88,119].

6. Discussion

Neurons were for a long time thought to renew themselves. In the 1960s the phenomenon of neurogenesis was discovered, but it was not until 1998 that neurogenesis was demonstrated in humans [120]. Neurogenesis is one of the main mechanisms of brain plasticity and repair. The new neurons would either integrate into existing neuronal circuits or generate trophic factors or other signaling molecules that can act in a paracrine manner. Neurogenesis is commonly enhanced in epilepsy, but the number of neurons are normally balanced by cell death to not result in overgrowth. The incorporation of new neurons into existing circuits is also challenging because the inappropriate incorporation of new neurons might be implicated in epileptogenesis. Studies have indicated that adult-generated granule cells in the DG exert anticonvulsive effects in healthy brains, while they develop abnormal morphological and physiological properties during epilepsy development [121].

Most studies on adult neurogenesis were performed in rodents, particularly in mice, because modern gene manipulation techniques were available to explore the many aspects of neurogenesis. However, due to the rare availability of optimum human brain tissue and also methodological challenges (such as lack of noninvasive and safe investigatory methods for conducting high-quality in-vivo

Table 1
Antiseizure medications increase neurogenesis.

ASM	Model	Administration	Effect	Ref
Gabapentin	NPC isolated from adult hippocampal of mouse	1 nM	**Promotes neurogenesis** Increase the MAP2 expression	[87]
	Cortical stem cells isolated from rat fetus	16 μg/ml, from ED 14, 7 days	**Promotes neurogenesis** increases the $MAP2^+$ cells	[93]
Levetiracetam	C57BL/6 mice	10 mg/kg, i.p., 10 days with ACEA 10 mg/kg	**Increases neurogenesis** Increased Ki-67^+, $NeuN^+$ cells	[104]
	ICR mice	300–600 mg/kg, i.p., 4weeks	**Enhances neurogenesis** Increases the $BrdU^+$, $NeuN^+$ cells, Up-regulation of PI3K/Akt signaling	[106]
	C57BL/6 mice	130 and 260 mg/kg, p.o., 35 days	**Increases neurogenesis** Increases the Ki-67^+, Nestin$^+$/$MCM2^+$, Tbr2^+/$MCM2^+$, DCX+/MCM2+ cells, Up-regulation of Wnt/β-catenin signaling pathway	[105]
	NSC isolated from rat fetal ganglionic eminence	50 μM, ED 14.5, 6 days	**Enhances neurogenesis** Increases DCX^+ and $NeuN^+$ cells, Decreases the $GFAP^+$ and Olig2^+ cells	[103]
Pregabalin	NPC isolated from male mouse hippocampus	10 mg/kg, 21 days	**Promotes neurogenesis** Increases in proportions of $BrdU^+$/$NeuN^+$/$GFAP^-$ neurons	[25]
	Adult hippocampal NPC	0.1–10 nM	**Promotes neurogenesis** Increased newborn neurons	[25]
Zonisamide	mouse- or human-induced pluripotent SC-derived dopaminergic neurons transplanted in rats	30–60 mg/kg, 30 days	**Increases neurogenesis**	[119]

studies), designing a robust study on neurogenesis in humans is a challenge. The use of relatively safe neuroimaging approaches, combined with novel techniques in stem cell biology such as induced pluripotent cells might be a solution [122].

As reviewed here, ASM may increase (Table 1), decrease (Table 2), or exert dual effects (Table 3) on neurogenesis. The dosing schedule, temporal administration of the drug, the studied brain region or specific molecular markers, and normal or disease context may affect neurogenesis (Tables 1–4).

The dosing schedule may affect the responses of NSC to ASM. For example, oral administration of 900 mg/kg of VPA for 28 days diminished the percentage of DCX^+ and $NeuN^+$ granule cells in the hippocampus, but VPA at the dose of 250 mg/kg with the same protocol exerts no substantial effects on the hippocampal neurogenesis. In the same way, LEV treatment for 35 days could promote the proliferation of NSC and neuroblasts, and differentiation of newborn neurons, while 7 days of treatment significantly suppressed neurogenesis.

It seems that the investigated brain region is another important factor related to the controversial neurogenic capacity of ASM. In mammals, neurogenic niches (SGZ of the hippocampal DG, and the SVZ of lateral ventricles) exhibit many similarities but also some differences. SVZ NSC produce olfactory bulb interneurons and corpus callosum oligodendrocytes, whereas SGZ NSC generates dentate granule neurons and astrocytes. Notably, NSC derived from both niches generate all three neural lineages once propagated in culture with high concentrations of growth factors, therefore, the *in vivo* niche may limit adult NSC potential [123–125]. It was shown that PHT significantly decreased the population of mature neuronal cells in the DG but increased SVZ NSC. Moreover, some researchers used DCX as a young neuronal marker, however, others believed that DCX is not specific for newborn neurons, and may also expressed by non-neuronal glial cells [126].

While ASM may decrease aberrant neurogenesis in the status epilepticus, they may promote neurogenesis in different neurological and neuropsychiatric disorders (Table 4). LEV and LTG may show promise, as the drugs enhance neurogenesis in normal or developing brains, whereas suppress seizure-induced ectopic neurogenesis.

Based on the current data, while the first-generation or older ASM mostly decreased neurogenesis, ESM enhanced neurogenesis. In addition, some newer ASM including LCM, LTG, and OxCBZ, reduced neurogenesis significantly in different studies.

As previously mentioned, ASM are a heterogeneous group of medications with various mechanism of action. ASM that inhibits Na^+ voltage channels such as CBZ, PTH, LTG, OxCBZ, and LCM may decrease neurogenesis. There is conflicting results about VPA which may be related to other mechanism of action.

The molecular mechanisms underlying the changes in neurogenesis mediated by ASM might be related to the regulation of neurotransmitters, ion channels, trophic factors (such as BDNF, GDNF), and wnt/β-catenin, PI3K/Akt, or Ras-MAPK signaling pathways (Fig. 3).

The biggest limitation that may probably occur in the present review like others, is related to database searching for selecting articles such as missing some relevant studies, exclusion of non-English language studies, and time constraints. Because of the lack of clinical data about the role of ASM in human neurogenesis, the present research is focused on preclinical researches. It is recommended to study neurogenesis *ex vivo* in biopsied tissues or postmortem brain samples from ASM-treated epileptic patients, with incorporations of BrdU or ^{14}C into the DNA or detection of neuronal markers. Future studies are also needed to identify the impact of ASM on human neurogenesis using magnetic resonance imaging (MRI) or proton magnetic resonance spectroscopy (H-MRS) based methods.

7. Conclusion

In this review, we have summarized current pieces of literature on the relevance of exposure to ASM in normal (Tables 1–3) and also in the neuropathological states accompanied by neurogenesis deficits, such as status epilepticus, Alzheimer's disease, Parkinson's disease, *etc* (Table 4).

Table 2
Antiseizure medications decrease neurogenesis.

ASM	Model	Administration	Effect	Ref
Phenobarbital	Sprague-Dawley rat offspring	40 mg/kg, i.p., from PND 7 3–4 weeks	**Decreases neurogenesis** Reduction in BDNF and NT-3 mRNA expression	[43]
	Human stem cells (TERA2.cl.SP12)	100–1000 μM	**Decreases neurogenesis** Reduces viability and proportion of SC subsequently differentiated into neurons	[42]
	Neonatal Wistar rats	50 mg/kg, i.p. throughout PND 4-6	**Decreases neurogenesis** Reduction in DCX^+, $calretinin^+$, $NeuN^+$ cells in the DG, Decreases the expression of *Pax6, Sox2, Tbr1/2, Prox1, NGF, BDNF, NT-3*	[57]
Lacosamide	C57BL/6J mice Hippocampus	10 mg/kg, i.p., 10 days	**Decreases neurogenesis** Reduction in $BrdU^+/NeuN^+$ cells in SGZ	[47]
	C57BL/6J mice	10 mg/kg, i.p., 10 days	**Decreases neurogenesis** Reduces $NeuN^+/BrdU^+$, $GFAP^+/NeuN^+$ cells in the SGZ	[48]
Oxcarbazepine	Wistar rat offspring	Maternal exposure to 100 mg/kg, ED 7-15	**Decreases neurogenesis** Decreased DCX^+ cells in the SGZ	[38]
	Wistar albino male rats	Maternal exposure to 100 mg/kg, ED 1–5 or 6-15	**Decreases neurogenesis**	[92]

Table 3
Antiseizure medications with dual effects on neurogenesis.

ASM	Model	Administration	Effect	Ref
Carbamazepine	Zebrafish embryo	1–5 μg/L, 24h	**Enhances neurogenesis** Up-regulation in the expressions of *NeuroD and Ngn1 and GFAP*	[39]
	Human embryonic stem cell (H9 hESC)	0.033–0.33 mM, 1–7 days	**Decreases neurogenesis** Reduction in the *βIII-tubulin*, *Ngn1*, *reelin*, *MAPt*, and *MAP-2 expression* Down-regulation of Wnt/β-catenin pathway	[40]
	Wistar rats offspring	Maternal exposure to 100 mg/kg, p.o., ED 7-15	**Decreases neurogenesis** Increases DCX^+ cells in the SGZ	[38]
	Sprague-Dawley rat offspring	120 mg/kg, p.o., PND 7-28	**No effect on neurogenesis** No alteration DCX^+ cells in the hippocampus	[43]
Ethosuximide	Rat skeletal muscle stem cells (rMDSCs)	4 μM, 8 days	**Enhances neurogenesis** Increase the percentage of $NeuN^+$ and $TuJ1^+$ cells	[49]
	Forebrain cortex NSC isolated from 3-day-old rats	0.1 and 1 μM, 6 days	**Enhances neurogenesis** Increase $BrdU^+$, $βIII\text{-}tubulin^+$, and $MAP2^+$ cells	[46]
	NSC isolated from rat hippocampus at ED 12	50, 100, 150 μM	**Enhances neurogenesis** Increase $BrdU^+$, $Nestin^+$, $NeuN^+$, and DCX^+ cells in the DG and SVZ Up-regulation of Wnt/β-catenin pathway	[26]
	6 weeks old C57BL/6 mice	10 mg/kg, i.p., 10 days	**Decreases neurogenesis** Reduction in $GFAP^+/NeuN^+$ cells in the SGZ	[48]
Phenytoin	C57BL/6 mice	35 mg/kg, p.o., PND 5-14	**Decreases neurogenesis** Reduction in $calbindin^+$ cells in the DG, Reduced the dendritic development of Purkinje cells in the cerebellum	[52]
	Jcl:ICR mice	10,17.5,25, 35 mg/kg, p.o., PND 2-4	**Decreases neurogenesis** Reduction in cerebellar granule cells migration by BrdU labeling	[53]
	BALB/c postnatal mice	10 mg/kg, p.o., 30 days	**Enhances neurogenesis** Increases $BrdU^+/SOX2^+$ and $BrdU^+/DCX^+$ cells in the SVZ Decreases $NG2^+$ glia and $NeuN^+$ cells, Promoted RIP^+ cells in the OB	[54]
	Balb/C mice	10 mg/kg, p.o., 30 days	**Enhances neurogenesis** Increases $BrdU^+$ cells in the SGZ	[55]
Valproic acid	Monkey offspring	Maternal exposure to 200–300 mg/kg, i.p., ED 26 and 29)	**Decreases neurogenesis** Reduced $NeuN^+$ and $Ki\text{-}67^+$ cells in the cerebellar external granular layer	[68]
	5-week-old rats	900 mg/kg, p.o., 28 days	**Decreases neurogenesis** Decreases the DCX^+ and $NeuN^+$ cells but increases $GFAP^+$ in the SGZ	[76]
	Wistar rats offspring	100–200 mg/kg, i.p., ED 12.5 until birth	**Enhances neurogenesis** Increase $BrdU^+/DCX^+$ cells in the SGZ and DG	[78]
	Sprague-Dawley rats	300 mg/kg, i.p., 14 days	**Decreases neurogenesis** Decrease the $Ki\text{-}67^+$, $BrdU^+$ and DCX^+ cells in the SGZ	[73]
	Rat lateral ganglionic eminence-isolated cells	0.5 μM	**Enhances neurogenesis** Increases BrdU and $βIII\text{-}tubulin^+$ cells but decreased astrocytes, Up-regulation of cyclin D2 and prostaglandin E2 synthase	[79]
	Neuron-glia cocultures isolated from midbrain of Fisher rats	0.6 mM, 48h	**Enhances neurogenesis** Increases survival of DA neurons following LPS or MPP + insult Up-regulating of GDNF and BDNF expressions	[81]
	Sprague-Dawley rat offspring	250 mg/kg, p.o., PND 7, 28 days	**No negative effects on neurogenesis**	[43]
	Wistar rats	300 mg/kg, i.p., 10 days	**Inhibits neurogenesis** Reduces $Ki\text{-}67^+$ cells, Decreases expression of Notch1 and BDNF in SGZ	[75]
	Wistar rats	300 mg/kg, i.p., 14 days	**Enhances neurogenesis** Overexpression of *NeuroD*	[82]
	Adult transgenic NesCreERT2/R26eYFP mice	0.25 mg/μl, infusion, 2 weeks	**Decreases neurogenesis** Reduces the $Pax6^+/NeuN^+$ cells in the midbrain	[77]
	Rat offspring	667–2000 ppm, p.o., ED6-PND21	**Decreases in neurogenesis** Reduction in $reelin^+$, $GAD67^+$, $parvalbumin^+$ neurons in DG Increases $PCNA^+$, $NeuN^+$ neurons in adult stage	[70]

(*continued on next page*)

Table 3 (*continued*)

ASM	Model	Administration	Effect	Ref
	5-old weeks mice offspring	Prenatal exposure to 500 mg/kg, ED 12.5	**Decreases neurogenesis** Decreases DCX^+ cells in the DG	[69]
	C57BL/6 mice	10 mg/kg, i.p., 10 days + ACEA 10 mg/kg	**Enhances neurogenesis** Increases $BrdU^+$, Ki-67^+, $NeuN^+$, $GFAP^+$ cells in SGZ	[87]
	Murine induced pluripotent SC-derived dopaminergic neurons transplanted in rats	150 mg/kg, i.p., 4 weeks	**Enhances neurogenesis** Increases $NeuN^+$ cells in the striatum	[88]
	C57BL/6 mice	20 g/kg, p.o., 4 weeks	**Enhances neurogenesis** Increases $BrdU^+$, $Nestin^+$, $Tuj1^+$, $NeuN^+$ cells Activation of ERK signaling pathway	[22]
Lamotrigine	Wistar rats	20 mg/kg, p.o., twice daily	**No effects on neurogenesis**	[99]
	Developing rat brain	80 mg/kg, 21 days	**Enhances neurogenesis**	[58]
Topiramate	Sprague-Dawley rat offspring	40 mg/kg, p.o., PND 7 for 28 days	**No effect on neurogenesis** Any negative effect on $BrdU^+$, DCX^+, $NeuN^+$ cells	[43]
	Wistar rats	80 mg/kg, p.o., twice daily	**No effects on neurogenesis**	[99]

Table 4
Effects of antiseizure medications on neurogenesis in animal models of neurological diseases.

Disease	ASM	Model	Administration	Effects	Ref
Status epilepticus (SE)	**Ethosuximide**	Pilocarpine mouse model of SE	20 mg/kg, i.p., 10 days	**No disturbs neurogenesis** No negative effects on the $BrdU^+/NeuN^+$ cells	[47]
	Lacosamide	SE model in Sprague-Dawley rats	30 mg/kg, i.p., 24 days	**Decreases aberrant neurogenesis** Suppression of abnormal $BrdU^+/NeuN^+$ cells	[24]
	Lamotrigine	lithium-pilocarpine rat model of TLE	20 mg/kg, p.o., twice daily	**Decreases aberrant neurogenesis** Reduces the $BrdU^+$ cells in the DG	[99]
	Levetiracetam	Kainate model of seizure in rats	320 μM, icv, 25 days	**Decreases aberrant neurogenesis** Reduces the BrdU+/DCX + cells in SGZ	[107]
	Perampanel	Pilocarpine induced- SE in rat	8 mg/kg, i.v, before SE	**Aberrant neurogenesis** Increases $NeuN^+$ cells, Reduced $GFAP^+$ astrocytes	[110]
	Topiramate	lithium-pilocarpine rat model of TLE	80 mg/kg, p.o., twice daily	**Promotes ectopic neurogenesis** increases the $NeuN^+$ cells in the DG	[99]
Cerebral ischemia	**Phenobarbital**	Neonatal stroke model in CD1 mice	30–60 mg/kg, i.p., PND 12	**No alters in neurogenesis**	[61]
	Valproic acid	Middle cerebral artery occlusion in rats	100 mg/kg, i.p, 7 days	**Increases neurogenesis** Increases DCX^+ and $BrdU^+$ cells in the SVZ and ischemic boundary zone	[86]
	Oxcarbazepine	Transient global cerebral ischemia in gerbils' hippocampus	200 mg/kg, i.p.	**Enhances neurogenesis** Increases $NeuN^+$ cells, Decreased $GFAP^+$ population in the CA1 region	[109]
Traumatic brain injury	**Valproic acid**	TBI and hemorrhagic shock in Yorkshire swine	150 mg/kg, infusion	**Increases neurogenesis** Down-regulation of apoptosis, glial cell proliferation Up-regulation of *NeuroD*	[85]
Alzheime's disease	**Ethosuximide**	Amyloid-β model of AD rats	125 mg/kg, i.p., 3 days or 2 weeks	**Enhances neurogenesis** Increases DCX^+ and $NeuN^+$ cells	[26]
	Valproic acid	APP/PS1/Nestin-GFP triple transgenic mouse model of AD	30 mg/kg, i.p., 4 weeks	**Promotes neurogenesis** Increases $BrdU^+$ cells, nestin-GFP^+, DCX^+, $NeuN^+$ cells in DG and SVZ Up-regulation of Wnt/β-Catenin signaling pathway	[83, 84]
	Rufinamide	Aged Gerbils (24-months old)	1–3 mg/kg, i.p., 4 weeks	**Enhances neurogenesis** Increases Ki-67^+, DCX^+, $BrdU^+/NeuN^+$ cells in DG Increase expression of IGF- 1R and p-CREB	[115]
	Topiramate	Aged mice (D-galactose)	50 mg/kg, p.o., 4 weeks	**Promotes neurogenesis** increases the Ki-67^+ and DCX^+ cells in the DG	[118]

ASM could modulate different stages of neurogenesis (NSC proliferation, survival, neuronal differentiation, maturation, and neurite outgrowth). The neurogenic capacity of ASM also depends on the administered dose, treatment period, temporal administration of the drug, the studied brain region or specific molecular markers, and normal or disease context. The molecular mechanisms underlying the changes in neurogenesis mediated by ASM might be related to the regulation of neurotransmitters, ion channels, trophic factors (such as BDNF, GDNF), and wnt/β-catenin, PI3K/Akt, or Ras-MAPK signaling pathways.

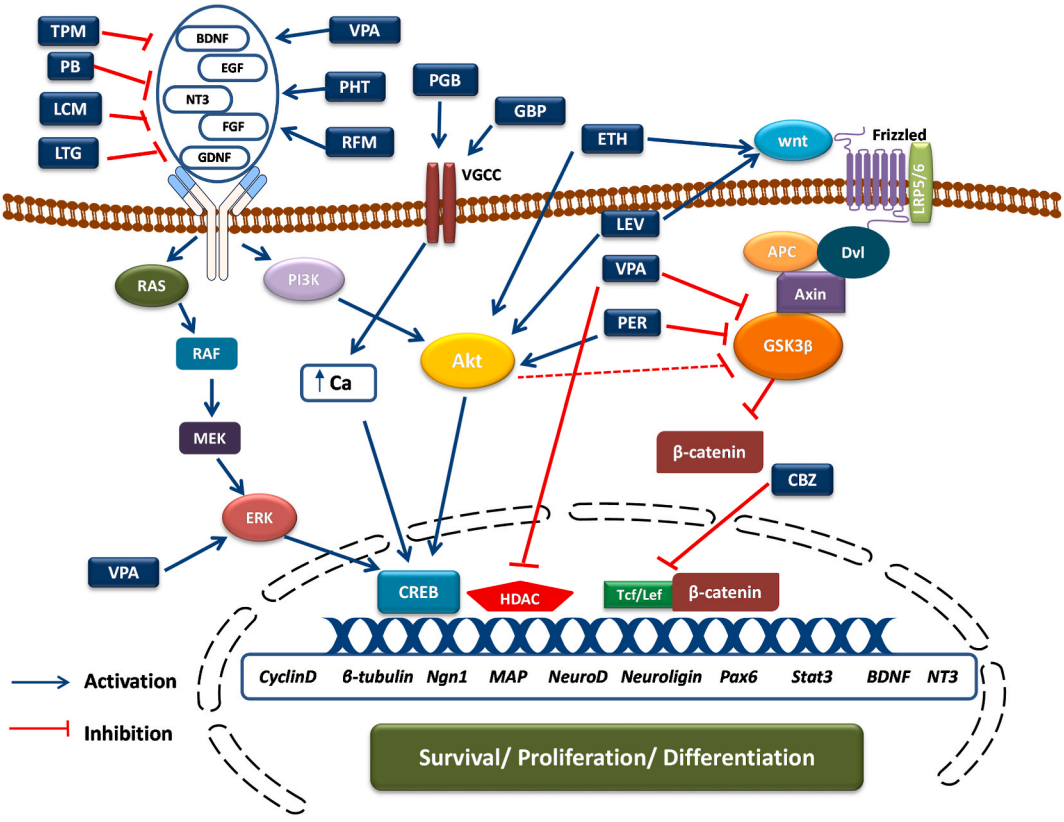

Fig. 3. Schematic representation of major signaling pathways involved in neurogenesis affected by antiseizure medications (ASM). CBZ: Carbamazepine; ESM: Ethosuximide; GBP: Gabapentine; LCM: Lacosamide; LTG: Lamotrigine; LEV: Levetiracetam; OxCBZ: Oxcarbazepine; PER: Perampanel; PGB: Pergabaline; PB: Phenobarbital; PHT: Phenytoin; RUF: Rufinamide; TPM: Topiramate; VPA: Valproic acid; ZNS: Zonisamide; APC: Adenomtous Polyposis Coli; Akt: Protein kinase B; Dvl: Dishevelled; TCF/LEF (T-cell factor/lymphoid enhancer factor); GSK-3β:glycogen synthase kinase 3β; HDAC:Histone deacetylase; LRP5/6:lipoprotein receptor-related protein; BDNF: Brain-derived neurotrophic factor; NGF: Nerve growth factor; NT-3: Neurotrophin-3; CREB: cAMP response element-binding protein; EGF: Epidermal growth factor; FGF: Fibroblast growth factor; PI3K: Phosphoinositide 3-kinases; Ngn1: Neurogenin 1; MEK: Mitogen-activated protein kinase/ERK kinase; ERK: Extracellular-signal-regulated kinase.

The majority of data about the neurogenic potential of ASM presented here comes from researches on laboratory mice and rats or zebrafish. However, neurogenesis may vary among different species in its features, dynamics, and regulation [127]. Therefore, the predictive validity of these animal models to conclude the modulatory effects of ASM on neurogenesis in the human brain is questionable. While it might not prevent us from making conclusions about the significance of ASM on neurogenesis or even prevent us from generalizing to human, it certainly does not help us achieve these outcomes.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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