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Epileptogenesis in neonatal brain

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SUMMARY

Epilepsy is a chronic neurological disorder affecting 65 million people worldwide. The etiologies of seizures can often be identified as genetic, metabolic, structural, immunologic or infectious, but in many cases the cause is unknown with the current diagnostic tools. Epileptogenesis is a process during which genetic or other acquired etiologies/insults lead to functional, structural, or network reorganization changes in the brain that may lead to the development of, or progression of, spontaneous seizures. During development, there are continuous changes in the structure, function, and network operation that also show sex specificity, which may alter the mechanisms underlying the generation of seizures (ictogenesis) and epileptogenesis. Understanding the mechanisms of early life epileptogenesis will enable the development of rationally designed age- and sex-appropriate therapies that would improve the overall quality of patients' lives. Here, we discuss some of these processes that may affect seizure generation and epileptogenesis in the neonatal brain.

Keywords

Seizure; Epilepsy; Rodent; Status epilepticus; Genetic; Kindling

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Conflict of interest statement

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1. Introduction

Epilepsy is defined as an ongoing process resulting in the generation of epileptic seizures. A Task Force commissioned by the International League Against Epilepsy (ILAE) proposed that the diagnosis of epilepsy can be made if a person has “1. At least two unprovoked (or reflex) seizures occurring more than 24 h apart; 2. One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; 3. Diagnosis of an epilepsy syndrome” [1]. There is a recently published position paper of specific classification of the types of epilepsies by the ILAE Classification Task Force of the Commission for Classification and Terminology that is very useful for clinicians and scientists. According to this reorganized classification, epilepsies can be taxonomized with the help of the seizure types as focal, generalized, generalized and focal, and unknown [2]. Epilepsy is associated with neurobiologic changes that may be akin to the different types of epilepsies, and which may exhibit cognitive impairment as well as psychological comorbidities [3]. Most importantly, the updated classification emphasizes the need to identify, if possible, the cause of the epilepsy, which could be genetic, metabolic, structural, immunologic or infectious, and to recognize specific syndromes.

Epileptogenesis refers to the development and extension of tissue that has the ability to cause recurrent unprovoked seizures leading to the development of an epileptic situation and/or the progression after this situation is established [4]. The incidence of seizures and epilepsies is high during the neonatal and infantile periods [5]. Early life seizures, as well as their etiologies, can affect the maturation of the developing brain, neurogenesis, neuronal circuitry and network activity. Under certain conditions, seizures may also produce cell injury and/or cell loss, metabolic and genetic changes, and lead to epileptogenesis with age-dependent effects.

A wide range of seizure types and epilepsies may occur during the neonatal and infantile period in humans. Seizures in the neonatal period are most often associated with acute illnesses such as hypoxia, hypoxia/ischemia, perinatal stroke, and a variety of metabolic disturbances that do not always lead to epilepsy (see articles in this issue by Soul and by Pisani and Sagnoli) [6]. During infancy and early childhood, fever can also trigger seizures [7]. Often the etiology of epilepsy is genetic, structural, or metabolic. Metabolic disorders associated with epilepsy are often due to inborn errors of metabolism. Genetic etiologies can be either benign seizure syndromes (e.g., self-limited neonatal seizures) or more severe epilepsy syndromes (e.g., Ohtahara syndrome, early myoclonic encephalopathy) with the understanding that a genetic mutation may have various clinical phenotypes [from benign to intractable epilepsies such as those associated with the potassium voltage-gated channel, KQT-like subfamily, member 2 (KCNQ2) mutations], and the same apparent clinical phenotype may be associated with a variety of genetic alterations (as is the case with the Ohtahara syndrome; see articles in this issue by Axen and Olsen and by Cornet et al.). In several cases, neonatal epilepsies show a more chronic and evolving phenotype through advancing age, as they evolve into different types of epilepsy syndromes, such as West syndrome (with the characteristic seizure type being infantile spasms), also suggesting that they may share common epileptogenic pathways.

As discussed below, the stages of human development cannot be accurately defined by specific ages in a developing rodent, since various processes mature at different rates. Animal models of epilepsies may also differ in their phenotype (e.g., age of seizure onset or presence, types of seizures, comorbid conditions) from human equivalent epilepsies due to species differences. Here, we consider aspects of neonatal epileptogenesis based on what is known from the clinical arena and we also discuss data from animal models that investigate epileptogenic mechanisms relevant to neonatal or neonatal/infantile epilepsies, including the maturational factors that contribute to seizure susceptibility, and the developmental changes that take place in neurotransmitter systems.

2. How to interpret brain developmental stages in rodents and compare them with humans?

Rodents are often used in studies of seizures and epilepsies and have offered significant insights into the pathophysiology of these conditions, despite the existence of noteworthy anatomical, genetic, biological, lifestyle, epigenetic and other species differences with humans. There have been several studies comparing the developmental stages between rodents and humans so that an analogy and extrapolation of the findings from animal studies to humans could be established. A way of comparing the maturation stage of developing pups is by looking at the maturation of the hypothalamus–pituitary–gonadal axis along with the species- and sex-specific changes occurring during development at the reproductive system [8,9]. In this scheme, the neonatal stage in rodents corresponds to postnatal (PN) day 0–6, infancy around PN7–21, the juvenile age at PN21–32 in females and PN21–35 in males, early puberty occurs around PN32–36 in females and PN35–45 in males, and finally adulthood begins at PN60 in both sexes (reviewed in [8]). However, in cross-species comparisons of brain growth, DNA, cholesterol and water content, it is proposed that PN8–10 rodent pups could be compared to full-term human newborns. The first postnatal week for rodents would correspond to premature newborns at the third trimester of human gestation (reviewed in [8]). Thus, because different developmental processes mature along different time lines and rates in humans and rodents, a unified simplistic approach may not be feasible. For example, rodent pups open their eyes around PN13–15, whereas eye-opening in human newborns happens almost immediately after birth. Moreover, rodents gradually develop their ability to ambulate and can explore the environment around the third week of life. On the contrary, humans are born with eyes open and ambulate typically after the first year of life [10]. Hence, it is of utmost importance to consider the species-specific maturation rates of the developmental processes that are pertinent to the systems and functions studied in each experimental project when trying to extrapolate findings across species, but also to acknowledge the limitations of such comparisons (Tables 1 and 2).

3. Maturation factors modifying seizure susceptibility

A wide variety of genetic and non-genetic causes have been implicated in the pathogenesis of seizures [2]. An increasing number of genetic variations and defects are being linked to epilepsy syndromes [11–13]. Structural abnormalities, trauma, stroke, infectious diseases and tumors usually lead to cell loss and network impairment that play crucial roles in

epileptogenesis along with cortical dysplasia and autoimmune disorders [11]. The increased incidence of seizures and epilepsy during the neonatal and infantile periods highlights the relevance of age-specific, developmental factors that increase susceptibility to seizures and epilepsy in addition to the high incidence of insults such as hypoxia–ischemia. These factors include age-specific, developmental differences in neuronal network properties and function, ion homeostasis, synaptic density, myelination, and glial development, in patterns of expression and signaling of common neurotransmitters and signaling pathways in the brain, in susceptibility to injury and ability to regenerate, or other biological factors.

3.1. Developmental changes in neurotransmitter systems

3.1.1. GABA signaling—The neurotransmitter γ -aminobutyric acid (GABA) is synthesized by glutamic acid decarboxylase (GAD) isoforms GAD65 and GAD67 in the brain, and is found in most regions of the central nervous system. In mature neurons, GABA is important for effecting inhibition [14]. GABA signaling participates in a wide spectrum of functions by controlling neuronal communication, mostly affecting neuronal inhibition, with a few exceptions that will be discussed later. As a result, many antiseizure drugs target GABA receptors (e.g. phenobarbital and midazolam). GABA receptors include the ionotropic GABA_A and GABA_C receptors (often classified together since they are both Cl[−] channels) and metabotropic GABA_B receptors. GABA_A and GABA_C receptors (GABA_AR, GABA_CR) are pentameric receptors composed of five subunits that comprise a Cl[−] channel. Activation of these GABA_AR and GABA_CR has hyperpolarizing effects due to influx of Cl[−] (reviewed in [8,14]). However, in many immature neurons, the GABA_AR and GABA_CR responses may be depolarizing due to an excess of intracellular Cl[−] that results in an efflux of Cl[−] when such receptors are activated. This elevated intracellular Cl[−] is due to a relative dominance of cation chloride cotransporters (CCCs) that transport Cl[−] intracellularly [e.g., sodium-potassium-chloride cotransporters (NKCCs)] as opposed to CCCs, such as potassium chloride cotransporters (KCCs), which reduce intracellular Cl[−] concentration (15).

A developmental increase in KCC2 has been noted, for example, in several brain regions, and sex differences in CCCs have been reported in sexually dimorphic areas [8,15]. For example, higher KCC2 mRNA expression has been shown in the substantia nigra pars reticulata (SNR) in female than in male PN15 and PN30 rats [15]. Increase of KCC2 mRNA expression in both sexes during development has also been reported for other brain structures. Further, KCC3 mutations have been linked to Andermann syndrome, which may also manifest epileptic seizures [16].

The early developmental depolarizing GABA effects are not necessarily excitatory; action potentials are rarely triggered, perhaps due to shunting of the membrane [14]. Nonetheless, these depolarizing potentials are important for normal brain development, exerting neurotrophic effects and influencing synaptogenesis (reviewed in [8,14,17]). This transition of GABA_AR signaling from depolarizing to hyperpolarizing occurs at different timepoints in different regions of the brain with sex-specific differences [18]. For instance, in the GABAergic neurons of the SNR of the male rat, this switch takes place around the 17th day of life, but in females somewhat earlier, around the 10th day of life [19]. Earlier appearance

of hyperpolarizing GABA_A receptor responses in females than in males also occurs in the CA1 pyramidal neurons of the hippocampus and substantia nigra pars compacta (reviewed in [8]).

Genetic defects linked to loss of function of GABA_A receptor subunits have been linked to early-life epilepsy [16]. Known genetic defects of GABA_A receptors have been mainly associated with childhood absence epilepsy (CAE), genetic epilepsy with febrile seizures plus (GEFS+) and autosomal dominant juvenile myoclonic epilepsy (JME) [16]. In addition, defects of *GABRA1* gene (coding for GABA_A receptor subunit α_1), one of the isoforms of GABA_A receptor subunit, are linked to infantile spasms; *GABRB1* gene defects are also connected to the etiopathogenesis of infantile spasms, whereas *GABRB3* gene mutations are associated with both infantile spasms and Lennox–Gastaut syndrome [20,21]. Deletions of chromosomal loci with genes of GABAergic receptor subunits have also been associated with conditions characterized by seizure manifestations, such as the Angelman syndrome [16]. Seizures may also disrupt GABA_A receptor signaling by altering the subunit composition of its receptors or causing abnormal reversal of the polarity of GABA_AR currents in an age-, sex-, region-, and timing-specific manner [8,15].

3.1.2. Glutamate signaling—Glutamate is the main excitatory amino acid neurotransmitter in neurons, and its receptors fall into the following classes: ionotropic glutamate receptors (iGluRs) and metabotropic glutamate receptors (mGluRs). iGluRs are ligand-gated ion channels that allow the flux of sodium, potassium and calcium ions [22]. The main iGluR subtypes are *N*-methyl-D-aspartate receptors (NMDARs), α -amino-3-hydroxy-5-methyl-4-isoxazole propionate receptors (AMPA), and kainate receptors. Each subtype consists of several subunits.

In the immature brain, increased levels of the NR2B, NR2A and NR3A subunits have been observed in neuronal NMDARs [22]. The increased expression of these subunits results in elevated levels of NMDAR-mediated calcium influx as well as lower threshold for seizures and excitotoxic hypoxic–ischemic injury [22]. As for AMPARs, there is an increased prevalence of GluR2 subunit-deficient receptors in the developing rodent brain, and therefore such receptors are calcium impermeable. AMPARs are also relatively lacking GluR2 in the developing human brain, mainly during the term and early postnatal period in cortical neurons [22]. As in GABA_AR signaling, there are sex- and age- specific differences affecting the expression of certain subunits, such as NR2A and NR2B of NMDARs and GluR1 of AMPARs in the hippocampus of rat pups [8]. Developmental changes in glutamate receptors are not uniform [17]. Region-specific changes appear in the expression of NMDARs in the hippocampus and cortex of rats during different developmental stages (reviewed in [23]).

3.1.3. Channel expression—Ion channels may also influence neuronal activity and have therefore been implicated in epileptogenesis. The changes that occur during development affecting channel expression and regulation seem to be sex and age specific [15]. Hyperpolarization-activated cyclic nucleotide-gated (HCN) channels, members of the potassium channel family, participate in resting membrane potential and excitability of dendrites. It has been shown that hippocampal HCN channel expression changes after

experimental prolonged hyperthermia-induced seizures. These changes are characterized by a depolarization shift of HCN channel activation and a slowing of the activation and deactivation kinetics of somatic and dendritic channels, leading to hippocampal hyperexcitability [23].

Mutations in genes *KCNQ2* and *KCNQ3*, encoding voltage-gated potassium (Kv) channels Kv7.2 and Kv7.3, respectively, are linked to self-limited familial neonatal epilepsy and involved in the promotion of constant action potential firing, which is controlled by KCNQ2/3 channels [23]. The age-specific expression of seizures in this syndrome has been attributed either to interactions with the depolarizing GABA_AR effects, or to age-specific KCNQ isoforms or alternative splicing (reviewed in [23]). Additionally, voltage-gated sodium channel dysfunctions that mainly lead to hyperexcitability have been involved in some early-life epilepsy syndromes, including Dravet syndrome or severe myoclonic epilepsy of infancy (SMEI) and generalized epilepsy with febrile seizures plus syndrome (GEFS+) [16,22]. Table 3 lists some of the genes that have been identified in epilepsy and which are associated either with neonatal or with infantile seizures and epilepsies. Since channel expression and regulation mature during network development, any disturbance at that point could cause network abnormalities and probably affect later life also.

3.2. Network maturation during brain development

3.2.1. Sex and hormonal milieu influence the function of seizure controlling networks—It has been shown that sex hormones contribute to the organization of sexual dimorphic features as they determine the anatomical and functional differences of certain brain regions in the male and the female brain [8,30]. These differences between the two sexes should be taken into consideration while examining the development and the function of brain structures, such as the substantia nigra pars reticulata (SNR). Through the exposure of rodents to flurothyl-induced seizures (a model of generalized clonic and tonic-clonic seizures), SNR has been determined as a brain structure that controls the seizure activity, in a region-, age-, and sex-specific manner [30]. The SNR contains two distinct regions: the anterior SNR (SNRa) and the posterior SNR (SNRp). In adulthood, in response to GABA-mimetic drugs, the SNRa mediates anticonvulsant effects while in males only, the SNRp mediates proconvulsant effects; there is no such proconvulsant region in females. During maturation, the functional differentiation between SNRa and SNRp appears after PN25 in both sexes, and earlier in females (PN25) than in males (PN30) [30]. Even prior to this age, the effects of GABA agonists are sex specific. Prior to PN25, males have only a GABA-agonist-mediated sensitive proconvulsant SNR region, whereas in females similar treatments do not alter seizure control. Further studies also showed that, in rodents, the sex- and age-related maturation of the GABAergic system as well as the seizure-controlling function of the SNR are also determined by the gonadal hormones and their metabolites [8,30]. In males, neonatal castration shifts the SNR phenotype to the female one [30]. SNR also contributes in processing information. The mechanism used for these functions is known as “dynamic gating”. According to this mechanism, the SNR functions as an inhibitor of the excitation through the basal ganglia and prefrontal cortex, with the help of GABAergic projection neurons [7,8,14]. All these functions served by SNR may be affected by epileptogenic processes in the developing brain.

4. Epileptogenesis due to structural/metabolic etiologies

Kindling in immature rats has been a highly advantageous animal model of epileptogenesis. The first protocol of amygdala kindling in infantile rats (PN15–18) was published in 1981 [31]. The establishment of this method has been very useful for the assessment of proneness to the development of seizures, and once kindling is induced it lasts until adulthood [32,33]. These kindling experiments in immature rats have demonstrated the age-related differences in behavioral expressions of seizures and a modified seizure scoring scale has been developed to describe their progression in infantile pups (PN15–18) [33]. More importantly, the kindling studies demonstrated that baby rats have shorter refractory periods (i.e., periods when stimulations may not provoke seizures) and therefore can be kindled with short stimulation intervals that cannot induce kindling in adults; this may explain why pups experience seizure clusters and status epilepticus [7]. Furthermore, the immature brain is more prone to develop multifocal seizures with concurrent, alternating stimulations whereas in the adult brain only one seizure-onset focus is dominant. Alternating stimulations accelerate kindling in PN15 pups, resulting in severe seizure phenotypes that are rare in adults. Interestingly metabolic studies using the 2-deoxyglucose technique show that the SNR is not metabolically active during seizures in pups, whereas it has increased uptake in adult rats [34]. Similar age-dependent findings were observed in models of status epilepticus (SE) [35]. As PN15 or younger rat pups are more vulnerable to the development of SE than adult rats [7], these data suggest that “adult” homeostatic mechanisms involved in the control and cessation of seizures such as the SNR-based circuits do not function properly early in life and become effective with maturation earlier in females than in males.

Models of SE have yielded insight to the sequelae of prolonged seizures, such as those induced by the administration of kainic acid and lithium-pilocarpine. There are two critical features of these models. The first is that SE-induced injury in hippocampal and limbic structures does not occur in the first two weeks of life, and increases with age after PN21, although genetic background or strain may influence the degree of SE-induced injury [7]. The second important characteristic of SE models is that spontaneous recurrent seizures (SRS) more frequently manifest in animals with identifiable brain injury. In the study by Nehlig’s group, after the induction of SE in PN21 Sprague–Dawley rats, MRI changes were observed just 6 h later in entorhinal and piriform cortices of the animals that developed epilepsy (reviewed in [7]).

Perinatal hypoxia–ischemia and traumatic brain injury are common external insults that can result in both acute symptomatic seizures during the neonatal period and epilepsy (chronic unprovoked seizures) later in life [22]. Contributing factors may include the developmental changes in excitatory and inhibitory neurotransmission discussed earlier. Hypoxia with [36,37] or without [37,38] ischemia in PN7–10 rats has been used to study the development of epilepsy. PN60–180 rats with prior exposure to hypoxia at PN10 experience seizures consisting of behavioral arrests with runs of spike-wave discharges (~7 Hz) [38]. As histological studies have not revealed neuronal injury, it has been proposed that alterations in synaptic plasticity and connectivity after hypoxic-induced seizures at PN10 may trigger epileptogenesis, in the absence of demonstrable lesions (reviewed in [38]). In contrast, in the model of combined unilateral carotid occlusion followed by hypoxia at PN7, focal-onset

motor seizures occur in adulthood, often in clusters, with an increase in seizure frequency and severity with time [36,37]. A combined study of continuous video-electroencephalographic (EEG) monitoring followed by detailed histological analysis demonstrated that spontaneous seizures occur only in rats with ischemic lesions and not in rats exposed to hypoxia only [36,37].

Infantile spasms typically manifest during the first year of human life, yet they also follow potentially epileptogenic perinatal insults, such as ischemia, hypoxia–ischemia, and inflammation, which are critical for epileptogenesis. The multiple-hit rat model of infantile spasms created by our laboratory recapitulates infantile spasms due to structural lesions [10,21]. According to this model, PN3 Sprague–Dawley male rats are stereotactically injected with right intracerebroventricular (i.c.v.) infusions of doxorubicin and right parietal cortical lipopolysaccharide infusions, followed by intraperitoneal injections of the serotonin depletor *p*-chlorophenylalanine at PN5. Pups develop clusters of flexion and extension spasms with electrodecremental responses between PN4 and 13, whereas other types of seizures start manifesting at PN9 [10]. Although DLP induction occurs during the neonatal rodent age (PN3–5), spasms – a classical motor seizure – occur between PN4 and PN13 which is the period when the motor system and ambulatory ability develop in rat pups, being equivalent to the infantile stage of motor development in humans. The multiple-hit rat model of infantile spasms also manifests sociability deficits as well as visuospatial learning deficits that are partially reversible with certain treatments [39].

One such therapy involves modification of the mechanistic target of rapamycin (mTOR) pathway, a regulator of metabolism and physiology, cell proliferation, and cell size regulation. Overactivation of mTOR signaling has been implicated in tuberous sclerosis complex (TSC), a genetic disorder that often manifests with epileptic spasms. Dysregulation of the mTOR pathway has been found in cortical malformations and dysplasias that are also considered etiologies of infantile spasms [40]. For these reasons, we used the multiple-hit rat model of infantile spasms to investigate the effects of the mTOR inhibitor rapamycin after the onset of the spasms. A three-day pulse treatment of high doses of rapamycin between PN4 and PN6 stopped spasms and improved the rats' performance in the Barnes maze test [39]. The same treatment prevented the overactivation of the mTOR pathway that was observed in the cortex of the pups with spasms, suggesting the involvement of mTOR pathway in infantile spasms of non-genetic etiology [39].

The tetrodotoxin (TTX) model is another chronic model of epileptic spasms in rats. In this model, right cerebral cortical or hippocampal infusions of this sodium channel blocker are administered to Wistar rats starting at PN10–12 for four weeks [21]. Spasms first appear at PN21 and continue until adulthood. The TTX model has been very useful in monitoring EEG patterns with multiple electrodes, with the presence of patterns resembling hypsarrhythmia or hemihypsarrhythmia in adult rats [21].

Table 4 lists the frequently occurring non-genetic insults in neonates and animal models relevant to neonatal seizures or epilepsies.

5. Genetic epilepsies with neonatal or neonatal/infantile onset

Genetic components have been involved in several early-life epilepsies. Yet, the number of animal models based on genetic defects investigating neonatal epileptogenesis is limited. Whereas there is a wide variety of genetic mouse models for epilepsy, epilepsy is typically studied in older animals, mainly due to species or technical limitations in performing video-EEG recording in neonatal mice pups. Table 5 lists several genetic human syndromes and equivalent models with neonatal/infantile-onset epilepsy.

5.1. Mutations may produce either self-limited or severe epilepsies

Genetic variants may also have different effects if they affect different cell types. Self-limited familial neonatal epilepsy is characterized by seizures in an otherwise healthy infant observed between the 2nd and 8th days of life (see articles in this issue by Cornet et al. and by Vanhatalo) [25]. It is an autosomal dominant disorder associated with potassium channel mutations in KCNQ2 or KCNQ3 genes. However, in other infants, KCNQ2 variants may lead to an early-onset epileptic encephalopathy (KCNQ2 encephalopathy), which resembles Ohtahara syndrome. The KCNQ2 gene is located on chromosome 20q13.3 and encodes four α -subunits of the potassium channel, which can interact with the α -subunits produced from the member 3 (KCNQ3) gene, located on chromosome 8q24, and form a functional potassium channel. Mutations in KCNQ3 have also been implicated in self-limited familial neonatal epilepsy. Voltage-gated sodium channels (VGSCs) play a leading role in neuronal excitability of all brain regions as well as in the initiation and propagation of action potentials. Loss-of-function mutations of the sodium channel 1A (*SCN1A*) gene, causing changes in channel activity, have been implicated in Dravet syndrome and GEFS+. Dravet syndrome is an infantile-onset drug-refractory epilepsy, manifested by cognitive and motor impairments and increased mortality risk. Similar to the human data and depending on the genetic defect, animal models may demonstrate different phenotypic and pathologic features. As discussed earlier, mutations that differentially affect various cell types may have an impact on the expression of seizures during development. As distinct neuronal cell types mature in different ways and at different tempos, the effects on network function may be variable and more studies are necessary to investigate the influence of mutations.

6. Effects of drugs on brain development

Antiseizure drugs (ASDs) that are used in the treatment of neonatal seizures may have adverse effects on brain development, often accelerating programmed cell death. For example, phenytoin and phenobarbital may lead to neuronal cell apoptosis in immature rodents at around PN7 whereas levetiracetam or topiramate do not [47]; however, the long-term effects of this exclusively time-sensitive (around PN7) acceleration of what is assumed to be a normal process are not clear. Furthermore, in these studies the animals were not experiencing seizures at the time the drug was administered [48]. A recent study in PN7 rats induced to SE with very high doses of lithium and pilocarpine suggested that phenobarbital and midazolam given after the onset of clonic SE may lead to neuronal injury in different brain areas [49], but, in other models of SE at this age, cell death was not observed [8,9,19,48]. Such studies, however, raise the concern that drug development for neonatal and

pediatric seizures needs to be conducted in age-specific models to evaluate for both efficacy and safety.

7. Conclusions

With the possible lifelong impact of neonatal seizures, it is important to identify risk factors and biomarkers to predict outcomes as a function of underlying etiologies as well as seizure burden. Some early-life seizure animal models yield evidence for the possible consequences of neonatal seizures, including epileptogenesis, the developmental alterations of neurotransmitters, changes in network maturation, and sex and hormonal differences that affect brain development during the epileptogenic process. The development of new animal models may broaden our horizons through inclusion of genetic components and a better understanding of the brain region-specific molecular pathways at specific ages. Any new data will need to be carefully compared and synthesized to understand the spectrum of induced alterations including the circumstances under which detrimental effects of seizures and their treatments occur and how to prevent them.

Practice points

- Neonatal seizures and epilepsies have distinct seizure phenotypes and etiologies.
- Antiseizure drugs may have age-, gender-, and region-specific short- and long-term effects in newborns.
- The immaturity of endogenous brain networks and signaling pathways may contribute to the age, gender, region-specific vulnerability of newborns to seizures.

Research directions

- Extrapolation of findings from animal models to humans should consider possible species and model differences and the different maturational trajectories of relevant neurobiological processes.
- The development of better treatments for neonatal seizures and epilepsies would benefit from the use of age- and sex-appropriate seizure and epilepsy models.
- Improved technologies for the recording of neonatal seizures in newborn pups would enhance efforts to validate and study animal models of neonatal seizures and epilepsies.

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References

1. Fisher RS, Acevedo C, Arzimanoglou A, et al. ILAE official report: a practical clinical definition of epilepsy. *Epilepsia*. 2014; 55:475–82. [PubMed: 24730690]
2. Scheffer IE, French J, Hirsch E, et al. Classification of the epilepsies: New concepts for discussion and debate – Special report of the ILAE Classification Task Force of the Commission for Classification and Terminology. *Epilepsia Open*. 2016; 1:37–44. [PubMed: 29588927]
3. Fisher RS, van Emde Boas W, Blume W, et al. Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). *Epilepsia*. 2005; 46:470–2. [PubMed: 15816939]
4. Pitkanen A, Nehlig A, Brooks-Kayal AR, et al. Issues related to development of antiepileptogenic therapies. *Epilepsia*. 2013; 54(Suppl 4):35–43.
5. Hauser WA, Annegers JF, Kurland LT. Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935–1984. *Epilepsia*. 1993; 34:453–68. [PubMed: 8504780]
6. Baram TZ, Jensen FE, Brooks-Kayal A. Does acquired epileptogenesis in the immature brain require neuronal death. *Epilepsy Curr*. 2011; 11:21–6. [PubMed: 21461261]
7. Spicciarich MC, Moshé SL. Translational studies of infantile epileptic encephalopathies. 2017 In press.
8. Akman O, Moshe SL, Galanopoulou AS. Sex-specific consequences of early life seizures. *Neurobiol Dis*. 2014; 72(Pt B):153–66. [PubMed: 24874547]
9. Galanopoulou AS, Moshe SL. In search of epilepsy biomarkers in the immature brain: goals, challenges and strategies. *Biomarkers Med*. 2011; 5:615–28.
10. Scantlebury MH, Galanopoulou AS, Chudomelova L, Raffo E, Betancourth D, Moshe SL. A model of symptomatic infantile spasms syndrome. *Neurobiol Dis*. 2010; 37:604–12. [PubMed: 19945533]
11. Pitkanen A, Engel J Jr. Past and present definitions of epileptogenesis and its biomarkers. *Neurotherapeutics*. 2014; 11:231–41. [PubMed: 24492975]
12. Epi4K C, Epilepsy Phenome/Genome Project. De novo mutations in epileptic encephalopathies. *Nature*. 2013; 501(7466):217–21. [PubMed: 23934111]
13. Paciorkowski AR, Thio LL, Rosenfeld JA, et al. Copy number variants and infantile spasms: evidence for abnormalities in ventral forebrain development and pathways of synaptic function. *Eur J Hum Genet*. 2011; 19:1238–45. [PubMed: 21694734]
14. Briggs SW, Galanopoulou AS. Altered GABA signaling in early life epilepsies. *Neural Plast*. 2011; 2011:527605. [PubMed: 21826277]
15. Galanopoulou AS. Sexually dimorphic expression of KCC2 and GABA function. *Epilepsy Res*. 2008; 80:99–113. [PubMed: 18524541]
16. Galanopoulou AS. Mutations affecting GABAergic signaling in seizures and epilepsy. *Pflügers Archiv*. 2010; 460:505–23. [PubMed: 20352446]
17. Insel TR, Miller LP, Gelhard RE. The ontogeny of excitatory amino acid receptors in rat forebrain – I. N-methyl-D-aspartate and quisqualate receptors. *Neuroscience*. 1990; 35:31–43. [PubMed: 1972786]
18. Galanopoulou AS. Dissociated gender-specific effects of recurrent seizures on GABA signaling in CA1 pyramidal neurons: role of GABA(A) receptors. *J Neurosci*. 2008; 28:1557–67. [PubMed: 18272677]
19. Kyzozis A, Chudomel O, Moshe SL, Galanopoulou AS. Sex-dependent maturation of GABAA receptor-mediated synaptic events in rat substantia nigra reticulata. *Neurosci Lett*. 2006; 398:1–5. [PubMed: 16540244]

20. EuroEPINOMICS-RES Consortium, Epilepsy Phenome/Genome Project, Epi4K C. De novo mutations in synaptic transmission genes including DNMT1 cause epileptic encephalopathies. *Am J Hum Genet.* 2014; 95:360–70. [PubMed: 25262651]
21. Galanopoulou AS, Moshe SL. Pathogenesis and new candidate treatments for infantile spasms and early life epileptic encephalopathies: a view from preclinical studies. *Neurobiol Dis.* 2015; 79:135–49. [PubMed: 25968935]
22. Rakhade SN, Jensen FE. Epileptogenesis in the immature brain: emerging mechanisms. *Nat Rev Neurol.* 2009; 5:380–91. [PubMed: 19578345]
23. Bender RA, Baram TZ. HCN channels in developing neuronal networks. *Prog Neurobiol.* 2008; 86:129–40. [PubMed: 18834920]
24. Siekierska A, Isrie M, Liu Y, et al. Gain-of-function FHF1 mutation causes early-onset epileptic encephalopathy with cerebellar atrophy. *Neurology.* 2016; 86:2162–70. [PubMed: 27164707]
25. Uchida T, Lossin C, Ihara Y, et al. Abnormal gamma-aminobutyric acid neurotransmission in a Kcnq2 model of early onset epilepsy. *Epilepsia.* 2017; 58:1430–9. [PubMed: 28575529]
26. Allen NM, Mannion M, Conroy J, et al. The variable phenotypes of KCNQ-related epilepsy. *Epilepsia.* 2014; 55:e99–105. [PubMed: 25052858]
27. Shellhaas RA, Wusthoff CJ, Tsuchida TN, et al. Profile of neonatal epilepsies: characteristics of a prospective US cohort. *Neurology.* 2017; 89:893–9. [PubMed: 28733343]
28. Gursoy S, Ercal D. Diagnostic approach to genetic causes of early-onset epileptic encephalopathy. *J Child Neurol.* 2016; 31:523–32. [PubMed: 26271793]
29. Steinlein OK. Mechanisms underlying epilepsies associated with sodium channel mutations. *Prog Brain Res.* 2014; 213:97–111. [PubMed: 25194485]
30. Giorgi FS, Galanopoulou AS, Moshe SL. Sex dimorphism in seizure-controlling networks. *Neurobiol Dis.* 2014; 72(Pt B):144–52. [PubMed: 24851800]
31. Moshe SL, Sharpless NS, Kaplan J. Kindling in developing rats: variability of afterdischarge thresholds with age. *Brain Res.* 1981; 211:190–5. [PubMed: 7225835]
32. Moshe SL, Albala BJ. Kindling in developing rats: persistence of seizures into adulthood. *Brain Res.* 1982; 256:67–71. [PubMed: 7093730]
33. Goddard GV, McIntyre DC, Leech CK. A permanent change in brain function resulting from daily electrical stimulation. *Exp Neurol.* 1969; 25:295–330. [PubMed: 4981856]
34. Handforth A, Ackermann RF. Mapping of limbic seizure progressions utilizing the electrogenic status epilepticus model and the 14C-2-deoxyglucose method. *Brain Res Rev.* 1995; 20:1–23. [PubMed: 7711764]
35. Albala BJ, Moshe SL, Okada R. Kainic-acid-induced seizures: a developmental study. *Brain Res.* 1984; 315:139–48. [PubMed: 6722574]
36. Kadam SD, Dudek FE. Neuropathological features of a rat model for perinatal hypoxic–ischemic encephalopathy with associated epilepsy. *J Comp Neurol.* 2007; 505:716–37. [PubMed: 17948865]
37. Kadam SD, White AM, Staley KJ, Dudek FE. Continuous electroencephalographic monitoring with radio-telemetry in a rat model of perinatal hypoxia–ischemia reveals progressive post-stroke epilepsy. *J Neurosci.* 2010; 30:404–15. [PubMed: 20053921]
38. Sun, H., Jensen, FE. Modeling hypoxia-induced seizures and hypoxic encephalopathy in developing brain. In: Pitkänen, A., Buckmaster, PS., Galanopoulou, AS., Moshé, SL., editors. *Models of seizures and epilepsy.* 2nd. New York: Academic Press; 2017. p. 697–711.
39. Raffo E, Coppola A, Ono T, Briggs SW, Galanopoulou AS. A pulse rapamycin therapy for infantile spasms and associated cognitive decline. *Neurobiol Dis.* 2011; 43:322–9. [PubMed: 21504792]
40. Galanopoulou AS. Basic mechanisms of catastrophic epilepsy – overview from animal models. *Brain Dev.* 2013; 35:748–56. [PubMed: 23312951]
41. Bastar, J., Spampinato, JG., Kadam, SD., et al. Perinatal hypoxic–ischemic encephalopathy: a model of stroke-induced pediatric epilepsy. In: Pitkänen, A., Buckmaster, PS., Galanopoulou, AS., Moshé, SL., editors. *Models of seizures and epilepsy.* 2nd. New York: Academic Press; 2017. p. 713–25.

42. Scantlebury MH, Ouellet PL, Psarropoulou C, Carmant L. Freeze lesion-induced focal cortical dysplasia predisposes to atypical hyperthermic seizures in the immature rat. *Epilepsia*. 2004; 45:592–600. [PubMed: 15144423]
43. Singh NA, Otto JF, Dahle EJ, et al. Mouse models of human KCNQ2 and KCNQ3 mutations for benign familial neonatal convulsions show seizures and neuronal plasticity without synaptic reorganization. *J Physiol*. 2008; 586:3405–23. [PubMed: 18483067]
44. Chiu C, Reid CA, Tan HO, et al. Developmental impact of a familial GABAA receptor epilepsy mutation. *Ann Neurol*. 2008; 64:284–93. [PubMed: 18825662]
45. Jeong, A., Wong, M. Tuberous sclerosis and other mTORopathies. In: Pitkänen, A. Buckmaster, PS. Galanopoulou, AS., Moshé, SL., editors. *Models of seizures and epilepsy*. 2nd. New York: Academic Press; 2017. p. 797-810.
46. Katsarou A-M, Moshé SL, Galanopoulou AS. Interneuronopathies and their role in early life epilepsies and neurodevelopmental disorders. *Epilepsia Open*. 2017; 2:284–306. [PubMed: 29062978]
47. Ikonomidou C. Prenatal effects of antiepileptic drugs. *Epilepsy Curr*. 2010; 10:42–6. [PubMed: 20231922]
48. Hasson H, Kim M, Moshé SL. Effective treatments of prolonged status epilepticus in developing rats. *Epilepsy Behav*. 2008; 13:62–9. [PubMed: 18337179]
49. Torolira D, Suchomelova L, Wasterlain CG, Niquet J. Phenobarbital and midazolam increase neonatal seizure-associated neuronal injury. *Ann Neurol*. 2017; 82:115–20. [PubMed: 28556259]

Table 1

Developmental stages in rodents based on maturation of hypothalamo-pituitary-gonadal axis (reviewed in [8]).

Stage	Female (PN)	Male (PN)
Neonatal	0–6	0–6
Infantile	7–21	7–21
Juvenile	21–32	21–35
Early pubertal	32–36	35–45
Puberty	34–38	45–60
Adult	>60	>60

PN, postnatal day.

Table 2

Species equivalency for developmental milestones (reviewed in [9]).

Milestones	Rodents	Humans
Duration of gestation	23 days	40 weeks
Full-term neonate ^a	PN8–13	39–40 weeks
Eye opening	PN13–15	Right after birth (~26 weeks)
Weaning from mother/end of breastfeeding	PN21	6 th month or later
Ambulation	2 weeks	>1 st year of life
Life expectancy	2 years	~80 years in USA

PN, postnatal day.

^a Estimates of the equivalency with full-term human neonates were done based on measurements of the brain growth spurt in newborn rodents (reviewed in [8] and [9]). Other biological processes may mature at different rates.

Table 3

Selected genes associated with neonatal and/or infantile seizures/epilepsies.

Genes	Neonatal seizures/epilepsies	Infantile seizures/epilepsies/pathology	References
ARX		XLAG ISSX Interneuronopathy Cortical atrophy Abnormal WM	Reviewed in [21]
CDKL5		ISSX Rett syndrome Cortical atrophy Abnormal WM	Reviewed in [21]
DCX		IS Lennox-Gastaut syndrome Lissencephaly	Reviewed in [21]
DNM1		IS Lennox-Gastaut syndrome	Reviewed in [21]
FHF1 (FGF12)		Early-onset epileptic encephalopathy	[24]
FHF2		GEFS+	[24]
FLNA		IS Lennox-Gastaut syndrome	Reviewed in [21]
GABRA1		IS	Reviewed in [21]
GABRB3		IS Lennox-Gastaut syndrome	Reviewed in [21]
GABRB2		IS	Reviewed in [21]
KCNQ2	Self-limited familial neonatal epilepsy	Self-limited familial neonatal-infantile epilepsy	[25,26,27]
KCNQ3	Self-limited familial neonatal epilepsy	Self-limited familial neonatal-infantile epilepsy	[26,27]
PAFAH1B1/LIS 1		IS Lennox-Gastaut syndrome Choreiform movements Lissencephaly	Reviewed in [21]
PCDH19		PCDH19 epilepsy or EIEE, mainly affecting females	Reviewed in [28]
SCN1A		Febrile seizures GEFS+ Dravet syndrome SMEB West syndrome (IS) Doose syndrome (myoclonic astatic epilepsy) ICEGTC Rasmussens's encephalitis Lennox-Gastaut syndrome	Reviewed in [29]
SCN2A	Self-limited familial neonatal epilepsy Neonatal epileptic encephalopathy	Self-limited familial neonatal-infantile epilepsy EIEE	Reviewed in [27,29]
SCN8A		Infantile epileptic encephalopathy	Reviewed in [29]
SCN1B		GEFS+	Reviewed in [29]
SEMA5B		IS	Reviewed in [21]
SPTAN1		EIEE ISSX Cortical atrophy, cerebellar atrophy, abnormal WM, thin corpus callosum	Reviewed in [21]
STXBP1 (MUNC18-1)		EIEE IS Atrophy, abnormal WM	Reviewed in [21]

Genes	Neonatal seizures/epilepsies	Infantile seizures/epilepsies/pathology	References
TSC1, TSC2		TSC IS Epilepsy Tubers	Reviewed in [21]

ARX, Aristaless-related homeobox gene; CDKL5, cyclin-dependent kinase-like 5; DCX, doublecortin; DNM1, dynamin 1; EIEE, early infantile epileptic encephalopathy; FHF1, fibroblast growth factor homologous factor 1; FHF2, fibroblast growth factor homologous factor 2; FGF12, fibroblast growth factor 12; FLNA, filamin A; GABRA1, GABA_A receptor subunit; GABRB3, GABA_A receptor subunit; GABRB2, GABA_B receptor subunit; GEFS+, generalized epilepsy with febrile seizures plus; ICEGTC, intractable childhood epilepsy with generalized tonic-clonic seizures; IS, infantile spasms; ISSX, X-linked IS syndrome; KCNQ2, potassium voltage-gated channel, KQT-like subfamily, member 2; KCNQ3, potassium voltage-gated channel, KQT-like subfamily, member 3; PCDH19, protocadherin 19; SCN1A, sodium channel, voltage-gated, type I, α -subunit; SCN2A, sodium channel, voltage-gated, type 2, α -subunit; SCN8A, sodium channel, voltage-gated, type 8, α -subunit; SCN1B, sodium channel, voltage-gated, type I, β -subunit; SEMA5B; semaphoring 5B; SMEB, borderline severe myoclonic epilepsy; SPTAN1, spectrin α , non-erythrocytic 1; STXBP1, syntaxin binding protein 1; TSC, tuberous sclerosis; WM, white matter; XLAG, X-linked lissencephaly with ambiguous genitalia.

Frequently occurring non-genetic insults in neonates and animal models relevant to neonatal seizures or epilepsies.

Table 4

Neonatal insults	Existing animal model	Species/age at induction	Relevant seizure/epilepsy	Mechanism of animal models	Epilepsy	Insights into early life epileptogenesis	References
Perinatal hypoxia	Hypoxia-induced neonatal seizure models	Long-Evans rats (PN10–12); Sprague-Dawley rats (PN7–10); Wistar rats (PN10); C57BL/6 mice (PN6–8)	Hypoxic seizures (PN10); recurrent spontaneous seizures (spike and wave activity on EEG), behavioral arrest and facial automatisms later in life	Exposure to graded global hypoxia (7–4% O ₂) in an air tight chamber	Hypoxic encephalopathy; recurrent spontaneous non-convulsive seizures later in life (spike-wave discharges)	[38]	
Perinatal stroke	Hypoxia-ischemia induced seizure models	Sprague-Dawley rats (PN7–10); Wistar rats (PN7); C57BL/6 mice (PN7)	Tonic seizures; tonic-clonic seizures during and immediately after the HI episode (PN7); Cognitive and behavioral deficits	Unilateral carotid ligation and exposure to hypoxia by replacing air with either nitrous oxide or nitrogen; oxygen and glucose deprivation responsible for brain damage	PHIE→S RS in later life and epileptic state (probably due to cerebral infarct); acquired pediatric epilepsy	Changes in network excitability [38,41]	
Neonatal freeze/hyperthermia	Animal model of a typical hyperthermic seizures	Sprague-Dawley rats; PN1 (induction of freeze lesion), PN10 (HSs)	Stereotypical behavioral seizures; JMC; HLC; GCs	Induction of freeze lesion at right sensorimotor cortex at PN1; HSs at PN10	Atypical febrile seizures in early childhood; MTLE in adult life	Temporal lobe developmental manifestations (focal cortical dysplasia, microdysgenesis) [42]	
Structural lesions leading to IS	Multiple-hit rat model of IS	Sprague-Dawley rats; PN3 (doxorubicin/lipopolysaccharide), PN5 (PCPA)	Spasms (PN4–13). Other seizures after PN9. Spontaneous motor seizures in adulthood	Right intracerebral doxorubicin/lipopolysaccharide (PN3), PCPA (PN5)	Subsequent epilepsy after PN9 and in adulthood; regression, impaired learning and sociability	Acquired interneuronopathy due to structural lesion	
Tetrodotoxin induced epileptic spasms	Tetrodotoxin model of epileptic spasms	Sprague-Dawley rats; PN10–12	Spasms after PN21 through adulthood	TTX infusions in the right hippocampus or central cortex of PN10–12 rats	Subsequent epilepsy	Reviewed in [40]	

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GCs, generalized convulsions; EEG, electroencephalography; HI, hypoxia-ischemia; HLC, hindlimb clonus; HSs, hyperthermic-induced seizures; IS, infantile spasms; JMC, jaw myoclonus; MTLE, mesial temporal lobe epilepsy; MTS, mesial temporal sclerosis; PCPA, *p*-chlorophenylalanine; PHIE, perinatal hypoxic-ischemic encephalopathy; PN, postnatal; TTX, tetrodotoxin.

Table 5

Genetic human syndromes and equivalent models with neonatal/infantile-onset epilepsy.

Human syndrome	Model name	Species/strain	Gene defect	Phenotype (seizures and other important features)	References
Neonatal onset					
Self-limited familial neonatal epilepsy	KCNQ2 and KCNQ3 mouse models of benign familial neonatal convulsions	Mice	<i>Kcnq2</i> -A306T KI (exon 6 point mutation). <i>Kcnq3</i> -G311V KI (exon 5 point mutation)	Both <i>Kcnq2</i> -A306T and <i>Kcnq3</i> -G311V KI homozygous mice manifested early generalized tonic-clonic, after PN21 (both strains) but as early as 2nd week of life in <i>Kcnq3</i> -G311V KI (video-monitoring). Video-EEG studies in adulthood confirmed SRS of probably limbic origin in both strains.	Reviewed in [43]
Neonatal/infantile onset					
Generalized epilepsy with febrile seizures plus (GEFS+)	Model of GABA _A $\gamma 2$ (R43Q) gene mutation	Mice	<i>Gabrg-2</i> ^{R/Q} KI	Spontaneous 6–8 Hz SWDs. Behavioral arrest; hyperexcitability with enhanced susceptibility to proconvulsant challenges	[44]
TSC	Infantile/juvenile model of TSC	<i>Tsc</i> ^{+/–} mice		Seizures at PN9–18 only. No neuropathological abnormalities; social impairment; cognitive deficits	[45]
Animal models of Dravet syndrome or GEFS+					
Dravet	<i>Scn1a</i> CKO	Mice	Exon 25 deletion	Spontaneous seizures (stage 3–5, Racine scale). Premature death after seizures (PN18–22). Thermal-induced seizures (PN16)	Reviewed in [46]
Dravet	<i>Scn1a</i> CKO	Mice	Conditional deletion of exon 7; deletion in global inhibitory neurons	Heterozygous develop spontaneous seizures (PN16) with occasional subsequent death. Homozygous (PN10–15): hypoactivity, jerks; death by PN15	Reviewed in [46]
Dravet	<i>Scn1a</i> CKO	Mice	Conditional deletion of exon 7; deletion in forebrain excitatory neurons and haploinsufficiency in inhibitory neurons	Ameliorates seizure related sudden death	Reviewed in [46]
Dravet	<i>Scn1a</i> CKO	Mice	Conditional deletion of exon 7; deletion in PRV interneurons	Homozygous: spontaneous seizures (PN14); death by PN30 Heterozygous: spontaneous seizures, and death after PN16. Ataxia (PN10)	Reviewed in [46]
Dravet	<i>Scn1a</i> KI, R1407X	Mice	Human R1407X nonsense mutation	Heterozygous: Low threshold in PTZ seizures; hyperactivity, stereotypies, social interaction deficits, impaired context-dependent spatial memory, aversion to novel odors; deficits in sociability and fear memory rescued by low-dose clonazepam. Heterozygous and homozygous: spontaneous seizures (1 month old)	Reviewed in [46]
GEFS+	<i>Scn1a</i> KI, R1648H	Mice	Human R1648H mutation	Homozygous: spontaneous generalized seizures (jump, jerks, head nodding, clonus, hindlimb extension). Lower threshold to hyperthermic or flurothyl seizures. Premature death (PN16–26).	Reviewed in [46]

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Human syndrome	Model name	Species/strain	Gene defect	Phenotype (seizures and other important features)	References
Rodent models of IS	<i>Arx</i> (GCG)10+7	Mice	pA1, 8GCG triplet insertion	Heterozygous: less severe phenotype than homozygous Spasms PN7–11. Seizures with arrest; limbic, GTC. Interictal spikes. Low anxiety, impaired associative learning and social interactions	Reviewed in [46]
	<i>Apc</i> cKO	Mice	CKO deletion of <i>Apc</i> gene in excitatory cortical and striatal inhibitory neurons	Flexion-extension spasms (PN5–14). Learning and memory deficits, impaired sociability, stereotypes in adults	Reviewed in [46]

APC, adenomatous polyposis coli; ARX, Aristaeless-related homeobox gene; cKO, conditional knockout; EEG, electroencephalogram; GABA A $\gamma 2$, γ -aminobutyric acid receptor, type A, $\gamma 2$ -subunit; DBA, Dilute Brown Non-Agouti; GTC, generalized tonic-clonic; IS, infantile spasms; KI, knockout; PN, postnatal; PTZ, pentylenetetrazole; Scn1a, sodium channel, voltage-gated, type I, α -subunit; SRS, spontaneous recurrent seizures; TSC, tuberous sclerosis.