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Rodent models: Where it all started with these “truths”

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1. Introduction

In the field of developmental epilepsy, researchers have utilized animal models, mostly rodents, to better understand the pathophysiology of epilepsy in the immature brain. Based on the findings from these models, certain ‘truths’ were thought to be operant and have been taught for many years (Table 1). In this paper, we will discuss whether these “truths” remain valid given the information we know today.

2. The immature CNS is more prone to seizures than the mature CNS

The incidence of epilepsy is higher early in life with a second peak occurring in individuals over the age of 65 [1]. However, one must consider newborns and infants are more often exposed to potentially epileptogenic insults such as hypoxemia ischemia than adults [2] or

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may carry genetic variants that predispose to early onset seizures and epilepsies [3]. This may in part explain the higher incidence of epilepsy in this age group.

3. Excitation develops before inhibition

One common hypothesis for the mechanism of increased epileptogenicity in the immature brain is that there is late development of inhibition and precocious development of excitatory neurotransmission. This is presumed due to the depolarizing 'excitatory effect' of GABA in the immature brain. The available data now suggests this might not be applicable to all regions of the brain [4–6] due to specific patterns of balance between excitation and inhibition during different periods of development. In the mature brain, there is a higher extracellular Cl^- concentration, relative to the intracellular Cl^- concentration, due to a higher expression and/or activity of K^+/Cl^- cotransporters, which export Cl^- (e.g., KCC2), compared with $\text{Na}^+/\text{K}^+/\text{Cl}^-$ cotransporters that import Cl^- (e.g., NKCC1). Activation of GABA_A receptors (GABA_ARs) induces hyperpolarization due to an influx of Cl^- following the electrochemical gradient. Hyperpolarization is associated with inhibition, due to decreased firing, and therefore GABA is considered an inhibitory neurotransmitter in the mature brain [7].

The presumed 'excitatory' effect of the GABA_ARs in the immature brain is also not clear. In the immature brain, there is less KCC2 [8] compared with NKCC1 [9], so the intracellular Cl^- concentration is higher compared to that in mature cells. Activation of GABA_ARs in immature neurons induces efflux of Cl^- , following the Cl^- electrochemical gradient, and triggers small depolarization. However, depolarization does not necessarily imply excitation as action potentials are not always triggered by such small depolarization [4,10].

There is evidence to indicate that the maturation of GABA_AR signaling in terms of the depolarizing effects varies by sex and location in the brain [4–6]. In the substantia nigra pars reticulata (SNr) for example, the switch from depolarizing to hyperpolarizing GABA effects occurs at 17 days of life in the male rat whereas it occurs much earlier, at 10 days of life, in the female rat. In the hippocampus, this transition occurs even earlier in both sexes with the female again maturing sooner than the male [7,11,12]. Although in these two locations, females tend to exhibit earlier maturation patterns than males, the opposite has been shown to occur in the cerebellum [13].

4. Seizure patterns are unique for the developing brain

Seizures appear to be less coordinated with often multifocal manifestations in younger age groups compared to older age groups, as shown in the kindling models of epilepsy [14]. The clinical seizures in neonates may have less coordinated motor manifestations than older children or adults. This may be due to the incomplete myelin maturation. The developing brain appears to be more susceptible to multi-focal seizures and recurrent seizures including status epilepticus, than the mature brain, even when exposed to a lesser or similar epileptic stimuli [15].

5. Spasms are an age specific seizure pattern

Epileptic spasms were thought to be an age-specific seizure pattern. Now it is known that spasms can be observed in many age groups. The International League Against Epilepsy (ILAE) has suggested using the more general term ‘epileptic spasms’ which includes infantile spasms [16]. In the new classification of seizures, the term ‘epileptic spasm’ is included in focal, generalized or unknown onset [17]. What does appear to be age dependent is the development of West syndrome, which consists of the triad of epileptic spasms, arrest of psychomotor development and the electroencephalographic pattern of hypsarrhythmia. Galanopoulou and Scantlebury created a model of spasms [18] by unilateral injections of doxorubicin intracerebroventricularly and lipopolysaccharide in the cortex of rat pups at postnatal day 3 (PN3) followed by an intraperitoneal injection of p-chlorophenylalanine at PN5. Spasms were seen at PN4 and lasted until PN11–12. The rats with spasms also demonstrated a cognitive decline, learning and memory deficits and autistic-like behavior compared to controls. This was not replicated when injecting rats at PN15. This age specific model of spasms may provide novel insights to pathological processes underlying West syndrome due to structural and metabolic etiologies and maybe new treatments [18].

6. Mechanisms involved in the control of seizures are age dependent

The SNr is a powerful system with an important role in the control of seizures and also in processing information via a “dynamic gating” mechanism [19]. The SNr is tonically active and serves as an inhibitor of the excitatory pathway through the basal ganglia and prefrontal cortex via the GABAergic projections [20]. Its effects over seizure control are age dependent [15,19,21] and sex-specific [22,23]. In adult male rats, the focal administration of GABA_Aergic agonists bilaterally to the anterior region of SNr produces an anticonvulsant effect, while there is a proconvulsant effect if this is done in the posterior regions of the SNr [20,24]. In the adult female rats, the GABA_Aergic stimulus only produce anticonvulsant effects by affecting the anterior SNr. GABA_Aergic agonists’ infusions in the posterior SNr of female rats have no effect on seizure control [22,23].

In male rats younger than 25 days, GABA_Aergic stimuli produce proconvulsant effects regardless of the region in which it is administered in the SNr. The change in function of the anterior and posterior regions occurs during puberty [22]. Sex-specific studies have shown that micro infusions in the SNr initially have no effect on seizures in the infant female rats. The GABA-sensitive anticonvulsant region emerges at 25 days of age. Castration of neonatal male rats changes the ability of the SNr to control seizures, conferring features of the female phenotype with extinction of the posterior SNr mediated proconvulsant effects and the earlier emergence of the anterior SNr anticonvulsant region [23].

7. Early in life, seizures and especially status epilepticus can cause more pronounced brain injury and mesial temporal lobe sclerosis than seizures later in life

The effects of seizures, including status epilepticus, early in life and its relationship to the development of mesial temporal sclerosis have been a topic of discussion and research for many years [25–29]. The two most common models of status epilepticus involve the use of either kainic acid [30] or lithium pilocarpine [30,31]. Both agents produce brain injury in adult rats [32] which leads to spontaneous seizures [33,34]. Status epilepticus can be induced in rat pups with lower doses of pro-convulsant agents in both models [33,34]. Limbic injury including hippocampal injury is not often induced in rats less than PN21 with the intensity of neuronal loss increasing with the age of the animal at the time the convulsant was injected [30,35,36]. In some models using different strains of rats, cell loss and apoptosis was observed in the hippocampus around PN 10–12, suggesting of a genetic predisposition but, again, this injury was much less pronounced than that seen in older animals [37–41]. The Consequences of Febrile Status Epilepticus in Children (FEBSTAT) study showed only about ten percent of children with status epilepticus had some evidence of acute hippocampal injury on imaging [42]. Longer follow-up is ongoing to see the percentage who develop mesial temporal sclerosis.

8. Conventional antiseizure drugs (ASD) are not effective in infants and children and especially in the neonatal period

A study by Painter in the late 90s showed that less than 50% of neonates responded to phenytoin or phenobarbital [43]. In a recent prospective cohort of 534 neonates with acute symptomatic seizures, 66% had an incomplete response to the initial loading dose of ASD [44]. Both studies reinforced the notion that conventional ASD are not as effective in the neonatal period. However, the etiology of the seizures seems to play a key role in predicting the response to treatment. It has now been shown that status epilepticus in comatose patients in older age groups is as difficult or harder to control than neonatal seizures even with the new available drugs [45,46]. In rat models of status epilepticus, Hasson [47] et al. showed that high doses of diazepam or pentobarbital were effective in stopping 1 h long status epilepticus in 15 or 21 day old rats. Neither drug was effective at stopping status epilepticus in 9-day old animals. This may suggest that the treatment protocols conventionally used to stop ongoing status epilepticus may be suboptimal, age-specific protocols may be required to maximize their efficacy, and, also, new treatments should be pursued.

9. There are unique age specific treatments and treatment related issues

A recent study showed that giving ANA12, a small-molecule selective tyrosine receptor kinase B antagonist, reversed postischemia KCC2 downregulation and significantly rescued phenobarbital resistant seizures in 7 and 10 day old rats [48]. Female rats were also noted to be better responders than male rats. A similar approach was done with bumetanide, used as a NKCC1 inhibitor in a rat model of hypoxic ischemic neonatal seizures [49]. Bumetanide in combination with phenobarbital was more effective than phenobarbital alone for the

treatment of seizures [49]. A small European open-label phase 1/2 trial using bumetanide as an add-on therapy given to neonates who did not respond to phenobarbital was stopped prematurely after 14 babies were enrolled due to hearing loss of three out of eleven survivors [50]. A larger double blind randomized-controlled trial is underway, with results expected shortly [51].

Galanopoulou has established an approach using pharmacokinetics in rats to develop therapy screening programs at different ages and syndromes. Using this method, she has shown the effectiveness of several drugs for the treatment of infantile spasms, including rapamycin as well as a vigabatrin analog (CPP-115), paving the way for possible human trials. Adaptation of doses is often needed to select the best effective and tolerated treatments for specific age groups but also epilepsy syndromes. Furthermore, the treatment protocols may need to be tailored for the syndromes they target [18,52]. This approach has enabled the development of epilepsy syndrome-specific platforms for the treatment of pediatric epilepsies.

Many fear that drugs given early in life are associated with accelerated apoptosis. A study in neonatal rats [53] revealed impaired striatal-mediated behavior on day of life 25 after exposure to phenobarbital. There was also absent inhibitory and excitatory synaptic connectivity in rats exposed at day of life 7 to a single dose of phenobarbital, phenytoin, or lamotrigine compared to controls [53]. It was recently proposed that midazolam or phenobarbital given in PN7 rats with lithium-pilocarpine status epilepticus increased neuronal injury in certain limbic, cortical or basal ganglia regions [54]. However further studies are needed to confirm or contest these findings using dose-response experiments and video-EEG monitoring to ascertain their effects on seizures, in models of early life seizures. There is no clear evidence in humans at this point that the drugs induce apoptosis when given to treat ongoing seizures.

10. Conclusions

In this review, we tried to address truths that we thought were written in stone. Table 2 shows the assumptions that were then and now and we provide data to suggest that there should be reconsidered and readdressed as more information becomes available.

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Table 1

The ‘Truths’.

The immature CNS is more prone to seizures than the mature CNS
Excitation develops before inhibition
Seizure patterns are unique for the developing brain
Spasms are an age specific seizure pattern
Mechanisms involved in the control of seizures are age dependent
Early in life seizures, and especially status epilepticus can cause more pronounced brain injury and mesial temporal lobe sclerosis than seizures later in life
Conventional antiseizure drugs (ASD) are not effective in infants and children especially in the neonatal period
There are unique age specific treatments and treatment related issues

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Table 2

The immature CNS is more prone to seizures than the mature CNS

Then	Now
The immature CNS is more prone to seizures than the mature CNS	Probably etiology dependent and/or due to age-specific signaling or brain circuitry factors
Excitation develops before inhibition	Not a rule; site-dependent
Seizure patterns are unique for the developing brain	Related to connectivity and myelination
Spasms are an age-specific seizure pattern	West syndrome is age specific; spasm as a seizure type can occur in any age
Mechanisms involved in the control of seizures are age-dependent	Yes, on many occasions; there may be gender effects
Early in life seizures and, especially, status epilepticus cause more pronounced brain injury and mesial temporal sclerosis	Overstated; injury may occur in genetically predisposed individuals
Conventional ASD are not effective in infants and children	Not correct; effects may be dose dependent
There are unique age specific treatments and treatment related issues	Yes, for certain conditions; But there are syndrome specific considerations such as West syndrome