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Review

Sex-specific consequences of early life seizures

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ABSTRACT

Seizures are very common in the early periods of life and are often associated with poor neurologic outcome in humans. Animal studies have provided evidence that early life seizures may disrupt neuronal differentiation and connectivity, signaling pathways, and the function of various neuronal networks. There is growing experimental evidence that many signaling pathways, like $GABA_A$ receptor signaling, the cellular physiology and differentiation, or the functional maturation of certain brain regions, including those involved in seizure control, mature differently in males and females. However, most experimental studies of early life seizures have not directly investigated the importance of sex on the consequences of early life seizures. The sexual dimorphism of the developing brain raises the question that early seizures could have distinct effects in immature females and males that are subjected to seizures. We will first discuss the evidence for sex-specific features of the developing brain that could be involved in modifying the susceptibility and consequences of early life seizures. We will then review how sex-related biological factors could modify the age-specific consequences of induced seizures in the immature animals. These include signaling pathways (e.g., $GABA_A$ receptors), steroid hormones, growth factors. Overall, there are very few studies that have specifically addressed seizure outcomes in developing animals as a function of sex. The available literature indicates that a variety of outcomes (histopathological, behavioral, molecular, epileptogenesis) may be affected in a sex-, age-, region-specific manner after seizures during development. Obtaining a better understanding for the gender-related mechanisms underlying epileptogenesis and seizure comorbidities will be necessary to develop better gender and age appropriate therapies.

Contents

Introduction . . . 154
Why look for sex-specific effects of seizures? . . . 154
GABA signaling . . . 155
Glutamatergic receptors . . . 155
Catecholaminergic system . . . 158
Cholinergic system . . . 159
Signaling pathways involved in epileptogenesis . . . 159
Morphological differences . . . 159
Age-specific effects of early life seizures . . . 159
Sex-specific consequences of early life seizures . . . 160
GABA signaling . . . 160
Neurogenesis . . . 162
Histological changes . . . 162
Behavioral tests . . . 162
Seizure susceptibility, mortality, epileptogenesis in induced models of seizures . . . 162

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Conclusions . . . 162
Acknowledgments . . . 163
References . . . 163

Introduction

Early life seizures are among the most common clinical signs of brain dysfunction. They can be caused by genetic abnormalities or acquired insults such as perinatal asphyxia, traumatic brain injury, intracranial hemorrhage, central nervous system infection, malformations of cortical development, metabolic disturbances or just fever (Annegers et al., 1995; Chapman et al., 2012; Huang et al., 1998; Jensen, 2009; Sillanpaa et al., 2008; Tekgul et al., 2006; Verity et al., 1985). In humans, early onset seizures including neonatal seizures not associated with acute metabolic derangements, and particularly status epilepticus (SE), have been linked to poor neurologic outcome and increased risk of subsequent neurodevelopmental dysfunction and epilepsy (Brunquell et al., 2002; Holmes, 2009; Ronen et al., 2007; Sheppard and Lippe, 2012). Animal studies have corroborated these observations showing that the immature brain is more prone to seizures but more resilient to seizure-induced histopathological injury to the hippocampus or epileptogenesis compared with the adult brain (Albala et al., 1984; Friedman and Hu, 2014; Galanopoulou, 2008a; Galanopoulou and Moshe, 2009; Galanopoulou et al., 2002; Holmes, 2005; Nardou et al., 2013; Sperber et al., 1991). Early life seizures may, under certain circumstances, adversely alter the developing brain and disrupt neuronal differentiation, signaling and connectivity, and ultimately the function of specific neuronal networks (Auvin et al., 2012; Ben-Ari and Holmes, 2006; Sankar and Rho, 2007; Scantlebury et al., 2007). Among the factors contributing to the different effects of early life seizures are the incomplete maturation of the operant neurotransmitter systems and networks, metabolic factors, or interactions with environmental or systemic factors. In experimental studies, the consequences of early life seizures are strongly age- and model-dependent.

Incidence studies have indicated a higher incidence of acute symptomatic seizures (excluding febrile seizures) in males than in females, including in pediatric populations (Annegers et al., 1995). The age-specific incidence of acquired (nongenetic) epilepsy, in general, is only mildly higher in males than in females (Hauser et al., 1993; Kotsopoulos et al., 2002) without statistically significant sex differences (Perucca et al., 2014–in this issue). However interesting sex-specific differences emerge when specific seizure syndromes or epilepsies are considered. Females appear to have greater risk for generalized-onset epilepsy in general (Hauser et al., 1993), childhood absence, or photosensitive seizures of genetic or unknown etiology (Asadi-Pooya et al., 2012; Nicolson et al., 2004; Taylor et al., 2004, 2013), or febrile status epilepticus (Hesdorffer et al., 2013). In contrast, mild male predominance has been shown in Landau–Kleffner syndrome, West and Lennox Gastaut syndromes, and severe myoclonic epilepsy of infancy (Aicardi and Chevrie, 1970; Galanopoulou et al., 2000; Tsai et al., 2013; Widdess-Walsh et al., 2013). Regarding the consequences of seizures, clinical and epidemiological studies indicate sex-differences in the natural course of epilepsy in adults. However, very few conclusive clinical studies exist on sex-specific outcomes in very young individuals with seizures or epilepsies, due to experimental limitations.

Despite the obvious phenotypic differences between males and females, most of the preclinical studies on the consequences of early life seizures have been performed either only in male animals or the sex distribution of the subjects has not been reported. Increasing evidence supports that the sexual dimorphism of the brain starts very early in life, differentially affecting molecular signaling pathways, physiologic functions or morphologic attributes, including of brain regions classically involved in seizure expression and control. If the male and female brains operate differently, it would be expected that early seizures should have sex-specific effects. Indeed, few studies have started evaluating the sex-specific effects of early life seizures on neurogenesis, GABAergic or other signaling pathways, behavioral tests, or subsequent injury (Castelhano et al., 2010; Desgent et al., 2012; Galanopoulou, 2008a; Lemmens et al., 2005). It is less clear whether these changes lead to distinct long-term epilepsy or functional outcomes. In this review, we will discuss the animal studies on the sex-specific acute and long-term consequences of early life seizures and will discuss the underlying pathophysiologic mechanisms.

Why look for sex-specific effects of seizures?

Brain maturation is a long process of evolving changes in neurogenesis and migration, gliogenesis, cellular differentiation, synaptogenesis, myelination and synaptic pruning, all of which can be affected by the ongoing developmental processes that occur in systems outside the CNS. It is controlled by species-specific, genetic or non-genetic biological, environmental or epigenetic factors, many of which influence differently males and females. In humans, brain maturation begins about 3 weeks after conception and continues until about 30 years of life (Kolb et al., 2013). To facilitate the comparison between humans and rodents, Table 1 outlines the chronology of developmental stages in male and female rats. Postnatal (PN) 8–10 rodents have been suggested to be developmentally equivalent to human newborn babies, because the

Table 1
Developmental stages in rats, based on hypothalamus–pituitary–gonadal maturation.

Stage	Females		Males	
	PN	Features	PN	Features
Neonatal	0–6		0–6	
Infantile	7–21		7–21	
Juvenile	21–32		21–35	
Early pubertal	32–36	Anestrus to early proestrus; pulsatile gonadotropin release in sleep only	35–45	Pulsatile gonadotropin release in sleep only
Puberty	34–38	1st proestrus, first estrus; 1st surge of gonadotropins and vaginal opening	45–60	Gonadotropin release also in wakefulness; maximal testicular response to gonadotropins; increase in Leydig cells and steroidogenesis
Adult	>60		>60	

The table is based on reference Ojeda et al. (1980). Please note that these age groups have been defined based on the endocrine changes occurring during maturation and not brain maturation. In general, PN8–10 rats are considered equivalent to full-term newborn humans, based on gross brain growth and its DNA, cholesterol and water contents that resemble those of a human full-term neonate (Dobbing and Sands, 1979; Gottlieb et al., 1977).