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Review

Animal models of absence epilepsies: What do they model and do sex and sex hormones matter?

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ABSTRACT

While epidemiological data suggest a female prevalence in human childhood- and adolescence-onset typical absence epilepsy syndromes, the sex difference is less clear in adult-onset syndromes. In addition, although there are more females than males diagnosed with typical absence epilepsy syndromes, there is a paucity of studies on sex differences in seizure frequency and semiology in patients diagnosed with any absence epilepsy syndrome. Moreover, it is unknown if there are sex differences in the prevalence or expression of atypical absence epilepsy syndromes. Surprisingly, most studies of animal models of absence epilepsy either did not investigate sex differences, or failed to find sex-dependent effects. However, various rodent models for atypical syndromes such as the AY9944 model (prepubertal females show a higher incidence than prepubertal males), BN model (also with a higher prevalence in males) and the Gabra1 deletion mouse in the C57BL/6J strain offer unique possibilities for the investigation of the mechanisms involved in sex differences. Although the mechanistic bases for the sex differences in humans or these three models are not yet known, studies of the effects of sex hormones on seizures have offered some possibilities. The sex hormones progesterone, estradiol and testosterone exert diametrically opposite effects in genetic absence epilepsy and pharmacologically-evoked convulsive types of epilepsy models. In addition, acute pharmacological effects of progesterone on absence seizures during proestrus are opposite to those seen during pregnancy. 17β-Estradiol has anti-absence seizure effects, but it is only active in atypical absence models. It is speculated that the pro-absence action of progesterone, and perhaps also the delayed pro-absence action of testosterone, are mediated through the neurosteroid allopregnanolone and its structural and functional homolog, androstanediol. These two steroids increase extrasynaptic thalamic tonic GABAergic inhibition by selectively targeting neurosteroid-selective subunits of $GABA_A$ receptors ($GABA_A$Rs). Neurosteroids also modulate the expression of $GABA_A$R containing the γ2, α4, and δ subunits. It is hypothesized that differences in subunit expression during pregnancy and ovarian cycle contribute to the opposite effects of progesterone in these two hormonal states.

Contents

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Human syndromes with absence seizures: sex differences?

Absence seizures are characterized by a sudden loss of awareness without aura or postictal state and are accompanied by synchronous, bihemispheric spike-wave discharges (SWDs) on EEG. Absence seizures are classified as typical or atypical (Nolan et al., 2005; Snead, 1995; Stefan et al., 2008; Onat et al., 2013; Duron et al., 2005). Compared with typical absence seizures, atypical absence seizures are usually longer in duration, more gradual in clinical onset and offset, often associated with changes in postural tone, and less likely to be associated with automatisms. In addition, while typical absence seizures are accompanied by very rhythmic and synchronous SWDs on EEG at a frequency ≥3 Hz, the SWDs in atypical absence seizures often are less rhythmic, exhibit some bihemispheric asymmetry, and occur at frequencies <3 Hz (Panayiotopoulos, 2008).

Many of the genetic generalized epilepsy syndromes (GGE, previously called idiopathic generalized epilepsy syndromes) such as childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE), and juvenile myoclonic epilepsy (JME) are associated with typical absence seizures. In contrast, atypical absence seizures are seen in epileptic encephalopathy syndromes such as Lennox–Gastaut syndrome and myoclonic atonic epilepsy and the neurogenetic syndromes, Angelman syndrome and Dravet syndrome. Epilepsy syndromes with typical absence seizures are medically controlled in the majority of cases and are usually associated with minimal or no long term cognitive impairment (Callenbach et al., 2009; Brouwer, 2009). In contrast, epilepsy syndromes with atypical absence seizures are less common and less likely to be controlled by the classical antiabsence drugs, and generally associated with a severe impairment in cognition and neurodevelopment (Nolan et al., 2005; Gulhan et al., 2011). It is thus even more imperative to identify novel therapies for patients with syndromes conferring atypical absence seizures.

CAE typically begins at 4 to 9 years of age with multiple daily absence seizures and is usually associated with normal cognition and seizure remission during adolescence (Janz, 1997; Chaix et al., 2003; Trinka et al., 2004; Callenbach et al., 2005, 2009). JAE is a GGE with a later seizure onset (around 10 to 12 years of age), longer duration and a greater potential for developing other seizure types compared to CAE (Jallon and Latour, 2005; Gulhan et al., 2011). JME typically begins during adolescence. The preponderance of JME patients has myoclonic and generalized tonic clonic seizures and up to one third have absence seizures as well (Genton et al., 2013).

Although there are some exceptions, CAE and JAE have been reported to show prominent sex differences and are much more prevalent in females than in males (Nicolson et al., 2004; Trinka et al., 2004; Asadi-Pooya et al., 2012a; Asadi-Pooya et al., 2012b). In a retrospective analysis of a hospital-based cohort consisting of 163 patients who were classified as CAE, JAE, or an overlap group, 64% patients were female and 36% male (Trinka et al., 2004). Additional studies support this evidence for a preponderance of female patients, particularly beyond the age of 4 (Asadi-Pooya et al., 2012a,b). However, the female predominance in adult-onset GGE is less well defined: in a study of adult onset GGE, 55% patients were female and 45% were male, suggesting that the preponderance of females may diminish with age (Cutting et al., 2001). Moreover, a second study found a higher proportion of male patients in the adult onset group (≥20 years) (Nicolson et al., 2004).

There is no conclusive study concerning the effects of sex in myoclonic epilepsies. In early childhood myoclonic epilepsy, there was a slight male preponderance among probands (9 females, 12 males), but affected non-proband family members were often female with a ratio of 3:1. In studies of two JME subtypes, CAE evolving to JME, and classic JME, a greater fraction of probands were female (Duron et al., 2005). In addition, a study of 257 JME patients being characterized for genetic analysis found that 42% were male and 58% were female (Martínez-Juárez et al., 2006).

CAE, JAE, and JME are GGE syndromes and thus thought to have a genetic etiology. Because the vast majority of these cases are inherited with complex, polygenic inheritance, the epidemiology studies described above examined a heterogeneous group of patients of unknown genotypes and thus did not identify specific sex–gene interactions. The study of monogenic epilepsy syndromes offers the opportunity to uncover the effects of sex on the phenotypes produced by the alteration of specific genes. In other words, does a mutant epilepsy gene have a greater penetrance in males or females? Thus far, mutations in many of the epilepsy genes that confer GGE syndromes, such as the genes that encode the α1, β3, and γ2 $GABA_A$ receptor ($GABA_AR$) subunits, have not been identified in enough patients to be able to determine if there are statistically-significant sex–gene interactions (Cossette et al., 2002; Lachance-Touchette et al., 2011; Maljevic et al., 2006; Tanaka et al., 2008; Wallace et al., 2001). However, mutations in another epilepsy gene, EFHC1 (EF-hand domain containing protein), have been found in multiple GGE kindreds and, importantly, the penetrance of EFHC1 mutations is less than 100%. We quantified the number of affected and unaffected male and female GGE patients who possessed disruptive EFHC1 mutations that were identified in four different familial studies (Annesi et al., 2007; Jara-Prado et al., 2012; Suzuki et al., 2004, Medina et al., 2008). We found that of the patients that possessed EFHC1 mutations, 24/42 females (57%) and 15/36 males (42%) expressed a GGE syndrome, whereas the remainder lacked a discernable phenotype, or simply exhibited childhood febrile seizures, or an asymptomatic abnormal EEG. Although this 57% female/42% male penetrance is similar to the 58% female/42% male difference found in a large JME population (Martínez-Juárez et al., 2006), this interaction of female sex on the penetrance of mutant EFHC1 was not statistically significant ($\chi^2 = 1.857$; $P = 0.173$). However, statistical power calculations reveal that in order to detect a 58%/42% sex-based difference in penetrance with 80% power, one would have to study a population with 164 individuals in each group. Therefore, the identification of additional GGE families with EFHC1 mutations will help determine whether or not there are significant interactions between sex and the EFHC1 gene in the penetrance of the JME phenotype.

In contrast to CAE and JAE, there is no evidence thus far for a female predominance in Lennox–Gastaut syndrome or Angelman syndrome. A cross-sectional epidemiology study found that Lennox–Gastaut