Published in final edited form as:
Neurobiol Dis. 2014 December ; 72PB: 167–179. doi:10.1016/j.nbd.2014.08.014.

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

Gilles van Luijtelaar[a,*], **Filiz Yilmaz Onat**[b], and **Martin J. Gallagher**[c]

[a] Donders Centre of Cognition, Radboud University Nijmegen, Nijmegen, The Netherlands [b] Department of Pharmacology, School of Medicine, Marmara University, Istanbul, Turkey [c] Department of Neurology, Vanderbilt University, Nashville, TN, USA

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.

* Corresponding author at: Biological Psychology, Donders Centre for Cognition, Radboud University Nijmegen, Po Box 9104, 6500 HE Nijmegen, The Netherlands. Fax: +31 24 3616066. g.vanluijtelaar@donders.ru.nl (G. van Luijtelaar)..

Keywords

Genetic models; Absence epilepsy; Rats; WAG/Rij; Mice; Atypical absence models; Typical absence models; AY 9944; Sex differences; Puberty; Neurosteroids; Pregnancy; Ovarian cycle; $GABA_A$ receptors; Delta subunits; Alpha subunits

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 $\alpha 1$, $\beta 3$, and $\gamma 2$ $GABA_A$ 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 (EF-hand domain containing protein 1) 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 syndrome was actually more prevalent in boys (0.37/1000) than in girls (0.14/1000), although this difference was not statistically signifi-cant (Trevathan et al., 1997). Studies of Angelman syndrome are typically reported without mention of sex effects (Buntinx et al., 1995). However, the lack of information concerning sex effects in Angelman syndrome may arise because the syndrome is very rare and therefore less amenable to large epidemiological studies.

Taken together, these epidemiology studies suggested that epilepsy syndromes with typical absence seizures with onset in childhood and adolescence are more likely to occur in females. The existence of sex differences is less clear in adult typical absence epilepsy syndromes. Moreover, the question of whether there are sex differences in epilepsy syndromes with atypical absence seizures merits further investigation. Another neglected area in the human studies is whether there are sex differences in seizure characteristics such as seizure frequency and semi-ology in these different syndromes. Finally, we do not understand the mechanisms that predispose females to typical absence epilepsy syndromes; analyses of nonhuman models of sex dependent absence epilepsies are critical for revealing the physiological processes involved in increasing seizure susceptibility in females and if these processes can be modulated to reduce seizures. In the next paragraphs of Chapter 2, the persistent sex-dimorphic characteristics of seizure and seizure models are outlined. In the remainder of this review (see Networks involved in absence epilepsy to The paradoxical effects of progesterone on absence seizures: an opposite role of the δ subunit of the GABAA receptor sections) the absence epileptic network and the fluctuating reversible and dynamic effects of sex-hormone cycling affecting this network throughout life will be discussed. The conclusions will be presented in the Concluding remarks and future directions section.

Rodent models of absence epilepsy: is there a role for sex differences?

The majority of studies in animal models of typical and atypical absence seizures did not report sex-dependent effects on the epileptic phenotype. However, most of these investigations did not specifically test for sex-dependent effects. Only a few studies were aimed to test whether sex related differences, as were obvious from the epidemiological data, do exist in nonhuman absence models. The preference for using male rodents in most experiments is, to some extent, related to cyclic variations in the phenotypic expression of absence seizures and its correlation with fluctuations in the ovarian hormone progesterone during the estrus cycle, as was established in WAG/Rij rats (van Luijtelaar et al., 2001). The rodent models that did demonstrate sex-dependent effects on phenotype are presented in Table 1.

Rat models of typical absence epilepsy: sex differences?

In the 1980s, researchers from Strasbourg and Nijmegen described several of the most well-known rat models of absence epilepsy. In 1982, the Genetic Absence Epilepsy Rats from Strasbourg (GAERS) were discovered (Vergnes et al., 1982), and four years later, the Wistar Albino Glaxo rats originating from the city of Rijswijk (WAG/Rij) were reported (van

Luijtelaar and Coenen, 1986). The GAERS originated from a Wistar colony, in which about 38% of the rats (4 out of 5 females, and 20 out of 59 males) showed SWDs (Vergnes et al., 1982). Next rats with SWDs were selected and a selection line was created. Next, GAERS were further inbred with a 100% prevalence of SWDs. The WAG/Rij strain was already fully inbred when it was discovered that all subjects at an age of 6 months had several hundred SWDs per 24 h. For a comparison of SWD characteristics between WAG/Rij and GAERS see Akman et al. (2010). Many studies have since characterized the behavioral, electrophysiological, pathophysiological and pharmacological features of these models, which closely resemble human typical absence epilepsy. Both strains are now considered well-validated rat models for GGE with absence seizures (Avanzini, 1995; Danober et al., 1998; Crunelli and Leresche, 2002, Coenen and van Luijtelaar, 2003; van Luijtelaar and Sitnikova, 2006; Depaulis and van Luijtelaar, 2006; Onat et al., 2013).

In WAG/Rij rats, there were no sex dependent phenotype differences in the incidence of rats showing SWDs or the number, mean and cumulative duration of the spontaneous occurring SWDs at postnatal day 75 (young adolescent), 125, and 175 (both adult) (Coenen and van Luijtelaar, 1987). The presence of strain-dependent sex difference is not uncommon, and therefore it is very reasonable to investigate putative sex differences in GAERS. In a recent unpublished study, it was examined by Onat and co-workers whether sex differences exist on SWDs in GAERS. Age-matched, 4 month old, adult male (n = 11) and female (n = 11) GAERS were compared and no differences in number, mean and cumulative duration of SWDs were observed between male and female GAERS in an EEG morning session from 09.00 to 12.00 (Fig. 1). The total duration of SWDs in the 3-hour recording was 2810 ± 377 s in female GAERS and 3043 ± 355 s in male GAERS. These findings demonstrate that male and female GAERS have a comparable incidence of SWDs and that also female GAERS can be used for studies of the effects of drugs or the pathogenesis of absence epilepsy. However, there are no studies that investigated whether, or how the incidence or other seizure characteristics may fluctuate at different times in the estrus cycle. Considering that SWDs in GAERS are initiated around sexual maturity, it might be interesting to compare the development of SWDs in prepubertal and postpubertal male and female rats in relation to the concentrations of sex hormones in plasma and neurosteroids in the brain.

Studies of human absence epilepsy patients compared the prevalence of the disease in males and females. However, the prevalence of SWDs in WAG/Rij and GAERS rats is 100% in both males and females and this jeopardizes the direct comparison between any clinical population and inbred of selected rodent models. The difference is prevalence in the genetic rodent models and the clinical population can be due to inbreeding or selecting animals so that a putative sex difference present in the original population might have disappeared. This might occur in case there are at least two allele pairs involved, one for epilepsy that could code either high or low for seizures and a second allele pair not involved in epilepsy, but that interacts sex dependently with the first gene. With such a scenario a sex difference present in the original outbred population might disappear across generations. It should be kept in mind that the GAERS were not developed to study sex differences but were developed with the purpose to isolate the epileptic phenotype and to contrast them with the non-epileptic control (NEC). WAG/Rij's were already fully inbred when the epileptic phenotype was discovered and, indeed, all animals of this strain show the age-dependent

SWD. In contrast, in humans there is no known genetic mutation that confers a 100% penetrance for absence seizures; perhaps this variable penetrance allows sex-associated factors to influence the phenotype. Interestingly, a higher female prevalence can be inferred from the first paper of the Strasbourg Wistars (Vergnes et al., 1982), later named GAERS, when the rats were not fully inbred and not genetically homozygous for all autosomal genes.

The presence of SWDs is not unique for GAERS and WAG/Rij rats; other outbred and inbred strains are endowed with SWDs, including some Wistar, Long-Evans, Sprague–Dawley, Fisher 344, G/Cpb and Brown Norway (BN) rats, although the incidence is generally lower than in the two established models (Kleinlogel, 1995; Robinson and Gilmore, 1980; Willoughby and Mackenzie, 1992; Inoue et al., 1990; Jandó et al., 1995). Few or no sex effects were studied in any of these rat lines, with only a few exceptions. Fischer-344 and BN and their F1 and F2 descendants were used in a Mendelian cross breeding study and a sex dependent phenotype was found: SWDs occurred significantly more frequently and lasted longer in males of the parental BN strain and in males of the F1 and F2 offsprings than in their female counterparts. Also the incidence was much higher in male BN rats compared to female BN rats. There was also a sex difference in prevalence in the offspring: 100 and 77% of the males of the F1 and F2 respectively showed absences, and 56 and 69% of the females. Sex differences were not present in the other parental strain, F344 rats. The average age of EEG recordings of all groups was 7.5 months. The SWDs in the BN strain and in their F1 were characterized by a higher intratrain frequency of the SWDs, more tremors than the usual vibrissae and eyelid movements, and more often a bodily reaction at the end of a SWD, which was accompanied by an arousal reaction (desynchronization) in the EEG. Next there was a sex difference in SWD onset frequency, and males exhibited more frequent and longer duration SWD than females (Jandó et al., 1995). The authors indicated that although a sex-linked gene could account for the sex difference, one would have expected that the number of SWDs in F1 generation would have more resembled that of the mother's strain, suggesting that more complex factors than a simple X-chromosome linked effect are involved in the genetics of absence seizures. Another remark is that the more intense clinical characteristics of the seizures (both electrophysiological and clinical) in the BN model, including the sex difference, represent an atypical form of absence epilepsy.

This sex difference in the BN strain warrants further investigation, including whether, and how, testosterone and the estradiol are involved in these sex dependent phenotypes and whether they occur pre- or post-sexual maturity.

Maternal effects were proposed to explain the results of a cross breeding study between WAG/Rij and ACI rats. F1 rats from ACI mothers had fewer and shorter SWDs than F1 rats from WAG/Rij mothers (Peeters et al., 1990). Indeed, quality of maternal care was less in WAG/Rij rats compared to Wistar rats: pups were only slowly retrieved in a challenging environment (Dobryakova et al., 2008), WAG/Rij dams treated with haloperidol improved pup retrieval behavior and these pups had shorter SWDs at adulthood compared to saline control WAG/Rij's (Dobryakova et al., 2011). This demonstrates that environmental factors can influence seizure phenotypes, leaving room for extra-chromosomal effects on seizure characteristics, including a role for early hormonal effects as in the AY9944 model.

Rat models of atypical absence epilepsy: sex differences

Atypical models are highly important from a clinical perspective, although they were less commonly studied. For a recent comparison between typical and atypical rodent models see Onat et al. (2013). In a well-described animal model of atypical absence seizures, early post-natal treatment of Long Evans hooded rats with the cholesterol synthesis inhibitor, AY9944, confers a lifelong atypical recurrent spontaneous 5–6 Hz SWDs that are associated with behavioral, pharmacological, and cognitive features of human atypical absence seizures. These atypical absence seizures lasted longer in females than in males and this sex difference emerged before the onset of puberty (Cortez et al., 2002; Persad et al., 2002). The fact that these sex differences were prepubertal, suggested that the sex-related structural and functional changes developed earlier, perhaps during the critical period. The critical period occurs in rats postnatal; it is the sensitive period during which sex hormones shape and organize the brain and body involved in reproductive behavior. The changes induced by early treatment of AY may change the brain in such a way that seizures were aggravated in females. Changes in the neurosteroid pool during postnatal development, as induced by the administration of AY9944 at postnatal day 5, might play a role in the sex specific development of chronic epilepsy later in life.

There were no reports of sex differences in a Wistar derived tremor rat (tm/tm). This model develops tremor of the whole body at 2 weeks of age. The electroencephalogram (EEG) showed 5–7 Hz SW complexes that appeared synchronously in the cerebral cortex and hippocampus accompanied by absence-like seizures. The tremor gradually disappeared between 6 and 8 weeks of age (Serikawa et al., 1987). The disappearance at puberty is interesting, considering that absences also tend to disappear, or evolve in children with absence seizures. However, the mechanisms responsible for the remission of this phenotype remain unknown.

Pharmacological rat absence models: sex differences

Sex differences have been observed in pharmacological models of absence epilepsy in rats. One such model is produced from a systemic injection of a low dose of bicuculline, a $GABA_AR$ competitive antagonist. Because electrographic seizures were found in the hippocampus as well as in the cortex, it is thought that this model represents atypical absence seizures (Matejovska et al., 1998). Female rats with natural or exogenous estrogens exhibited these atypical absence seizures with a higher incidence than male rats. The possibility that progesterone is the cause for the enhancement of SWDs was however not considered. A proepileptic effect of estrogens is classically assumed (Velísková, 2007), although estrogens have also antiepileptic effects as was established on clonic seizures in a KA induced SE model (Velísková et al., 2000). In contrast to all this, β-estradiol had either no effects in a typical absence model or anti-absence effects (in the atypical absence model, see Ovarian cycle and acute pharmacological studies in typical and atypical absence models section).

Sex differences in mouse models of typical and atypical absence seizures

As with rats, the majority of mouse models of absence epilepsy do not exhibit sex-dependent phenotypes. Experiments in commonly used spontaneous inbred genetic mouse models of absence seizures (tottering, lethargic, stargazer) were performed in both males and females without any reported sex-dependent differences in the frequency of absence seizures (Aizawa et al., 1997; Noebels and Sidman, 1979; Lacey et al., 2012). Moreover, studies of atypical absence epilepsy phenotypes generated in mice transgenically overexpressing $GABA_B$ receptor R1a or Ra1b subunits did not report sex-dependent effects (Aizawa et al., 1997; Lacey et al., 2012; Noebels and Sidman, 1979; Stewart et al., 2009; Wu et al., 2007). Pharmacologically-evoked absence seizures in mice have been produced through the systemic administration of $GABA_AR$ antagonists and $GABA_BR$ agonists. None of the experiments that used these drugs suggested a sex-dependent phenotype; the studies were either reported without specifying mouse sex or were performed using only males or females without a stated rationale (Aizawa et al., 1997; IIshige et al., 1996; Weiergraber et al., 2008; Zaman et al., 2011; Choi et al., 2010).

Mice have also been produced to contain human epilepsy gene deletions or mutations. Angelman syndrome usually results from a de novo maternal deletion or mutation involving chromosome 15q11.2–q13, a region that contains the ubiquitin ligase 3A (UBE3A) gene as well as the genes that encode the β3, α5, and γ3 $GABA_AR$ subunits (Bird, 2014). Mice with a maternally-inherited heterozygous UBE3A deletion (hybrid C57BL/6/129SvEv) or a 1.6-Mb chromosomal deletion from Ube3a to Gabrb3 experience atypical absence-like seizures and other behavioral abnormalities, but do not demonstrate sex-dependent phenotypes (Jiang et al., 1998, 2010). Three other genetic models, the succi-nate semialdehyde dehydrogenase deletion mouse, the Efhc1 deletion mouse, and the $GABA_AR$ γ2(R43Q) subunit knock-in mouse also exhibit seizures without reported sex-selective effects (Matejovska et al., 1998; Suzuki et al., 2009; Errington et al., 2011; Reid et al., 2013; Tan et al., 2007).

Mutations in two other epilepsy genes, Gabrb3 and Gabra1, do produce sex-selective changes in behavior and seizures. The $GABA_AR$ β3 subunit is associated with CAE and Angelman syndrome. The human GABRB3 CAE missense mutations did not exhibit a female predominance in patients (Tanaka et al., 2008) and have not yet been reported in mice. However, the phenotype of a β3 subunit deletion mouse has been described and shown to experience both sex-dependent and parent of origin-dependent effects. Male mice with maternally-transmitted Gabrb3 deletion exhibited an increased abnormal synchronous theta activity (a possible correlate of an atypical absence seizure) and impaired contextual memory compared with female mice with maternally-inherited Gabrb3 deletions (Liljelund et al., 2005). In addition, male mice with a paternal deletion had more fast activity (12–16 Hz) than male mice with a maternal deletion or female mice with the β3 deletion inherited from either parent (although only the difference between the male mice with a paternal deletion and the female mice with a paternal deletion was statistically significant) (Liljelund et al., 2005).

Several loss-of-function mutations in the $GABA_AR$ α1 subunit have also been associated with genetic generalized epilepsy syndromes in human patients (Cossette et al., 2002;

Lachance-Touchette et al., 2011; Maljevic et al., 2006). Recently, Arain et al. reported that heterozygous α1 subunit deletion caused electrographic and behavioral absence-like seizures in both the DBA/2J and C57BL/6J strains of mice (Arain et al., 2012). In the DBA/2J strain, heterozygous α1 subunit deletion did not reduce viability in either sex and produced the same frequency of SWDs and absence seizures in male and female mice. However, in the C57BL/6J strain, female, but not male, heterozygous α1 subunit deletion mice exhibited reduced gains in body mass compared with wild type mice. Moreover female heterozygous knockout mice had a significantly greater incidence of SWDs than male heterozygous knockout mice. These experiments were performed in mice of age postnatal days 33– 37 (P33–37). Although female mice of this age have not experienced their first estrus, they do typically exhibit several signs of sexual maturity. Even though changes in $GABA_AR$ composition, physiology, and cell surface endocytosis have been observed in female heterozygous α1 subunit deletion mice (Zhou et al., 2013) the corresponding changes have not yet been explored in male mice and thus the mechanisms that underlie these sex differences remain unknown.

Conclusions

These mouse and rat absence epilepsy studies revealed that although the various models reproduced many of the electrographic, behavioral, and pharmacological features of human absence epilepsy, to date, only the rat AY9944 atypical absence model, the systemic injection of $GABA_AR$ antagonist rat model, and the Gabra1 deletion mouse in the C57BL/6J strain exhibited the female predominance as found in CAE, and only the AY9944 model the prepubertal preponderance. An opposite sex-related difference was found in BN rats and Gabrb3 deletion mice, perhaps mimicking the higher male prevalence in older absence patients. However, it is also clear that many studies did not specifically test for sex-dependent effects. Understandably, many experiments that evaluated drug effects in rodents were performed using only males. Therefore, it is possible that a reexamination of some of these models will uncover sex-dependent effects in seizure frequency.

Networks involved in absence epilepsy

Here we briefly discuss the networks involved in both typical and atypical absence epilepsy models (Fig. 2). Electrophysiology studies in rodent models and fMRI and EEG–fMRI studies in human subjects revealed that SWDs engage cortico-thalamo-cortical network with additional involvement of the hippocampi in atypical absence seizures (for review Onat et al., 2013; Huguenard and McCormick, 2007; van Luijtelaar et al., 2011; Pinault and O'Brien, 2005; Gotman et al., 2005; Moeller et al., 2013). Intracranial field recordings and in vivo whole cell recording in WAG/Rij and GAERS demonstrated that absence seizures begin within the somatosensory cortex before propagating to the thalamic nuclei (Sitnikova and van Luijtelaar, 2006; Lüttjohann and van Luijtelaar, 2012; Lüttjohann et al., 2013; David et al., 2008; Zheng et al., 2012; Lüttjohann et al., 2014). In addition, it is generally accepted that the relay nuclei in the ventrobasal part of the thalamus as well as the reticular thalamic nucleus (RTN), the main source of GABA-ergic inhibition in the rat's thalamus, play major roles in the generation of SWDs. A focal origin in the deep layers of the somatosensory cortex has been demonstrated in WAG/Rij, GAERS, Long Evans and PTZ

seizure models (Meeren et al., 2002; Polack et al., 2007; Chen et al., 2011), and lesions and network studies propose opposite roles for the rostral and caudal part of the RTN (Aker et al., 2006; Lüttjohann et al., 2014), and a prominent role of the ventrolateral thalamus and posterior nucleus of the thalamus (Crunelli and Leresche, 2002; Pinault and O'Brien, 2005; Meeren et al., 2009; Lüttjohann and van Luijtelaar, 2012). Studies in GAERS have revealed a strong modulatory role of the basal ganglia on the occurrence of SWDs which in turn could affect cortical neuron excitability and, consequently, the generation of cortical epileptic discharges (Paz et al., 2007). Although the hippocampus is not part of the circuit in which SWDs are expressed, the hippocampus has modulatory effects on SWD occurrence, as has been demonstrated in one of the typical absence models (Tolmacheva and van Luijtelaar, 2007b; Onat et al., 2013). We are not aware of neurophysiologic studies towards the initiation site and or place of origin of SWDs in the atypical models or in the mice models, except in mice in which cortical stimulation has led to the occurrence of SWDs (Paz et al., 2011).

The neurotransmitter systems involved in this cortico-thalamo-cortical network include GABA and glutamate, as is evident from combined electrophysiological and pharmacological studies performed both in vitro and in vivo (Huguenard and McCormick, 2007). Monoamines and acetylcholine have a modulatory effect on the occurrence of SWDs, as do some neuropeptides and neurosteroid hormones. Increased phasic and or tonic $GABA_A$-ergic or $GABA_B$-ergic inhibition in the cortex, thalamus and RTN are most likely crucial for seizure generation, spreading and maintenance, although there are differences between the various parts of the network in the different types of inhibition and between the various absence models (Blumenfeld, 2003; Citraro et al., 2006; Cope et al., 2009; Crunelli et al., 2011; Danober et al., 1998; Merlo et al., 2007; Snead, 1995; van Luijtelaar and Sitnikova, 2006).

The role of $GABA_AR$ neurotransmission and absence epilepsy

As discussed above, $GABA_AR$ plays a crucial role in the generation of absence seizures. Therefore, it is possible that sex-selective changes in $GABA_AR$ physiology or expression could contribute to the higher incidence of absence epilepsy in females. Here, we will discuss sex-related differences in $GABA_AR$ function and expression while a subsequent section will explore the effects of sex neurosteroids on $GABA_AR$. It is important to state that while there are proven effects of sex on $GABA_AR$ neurotransmission in models of epilepsy, these mechanisms have not been positively linked to the effects of sex on seizures.

Sex effects on the chloride gradient

The effects of $GABA_AR$ activation depend on factors pertaining to the $GABA_AR$ itself (e.g. $GABA_AR$ expression levels, receptor subunit composition, and subunit posttranslational modification) as well as factors pertaining to the physiology of the neuron. One of the best-studied aspects of neuronal physiology that impacts $GABA_AR$ function is the developmental change of the chloride gradient (Ben-Ari, 2002). Because of a delayed expression of the chloride transporter, KCC2, immature cerebral neurons typically possess a relatively large intracellular chlo-ride concentration and thus a relatively negative reversal potential for

chloride anions. Therefore, $GABA_AR$ activation in these neurons leads to chloride efflux and membrane depolarization. Galanopoulou et al. (2003) found sex-based differences in KCC2 expression in postnatal day 14–17 rat substantia nigra reticulata (SNR) neurons, a brain region that modulates the production of generalized seizures (Sperber et al., 1989). Female rats expressed increased KCC2 mRNA in the SNR compared with males and thus had a corresponding hyperpolarizing response to GABA agonist whereas males had a depolarizing response. These findings demonstrated that sex-based modulation of $GABA_AR$ transmission may involve other gene products besides those that directly interact with the $GABA_AR$.

Atypical absence model

A single paper was devoted to investigate the role of the $GABA_AR$ subunit γ2 in the somatosensory cortex and somatosensory thalamus in the atypical AY9944 model (Li et al., 2007). Newborn Long-Evans Hooded rats were given injections of AY9944 subcutaneously at postnatal days 1, 5, and 9. Expression of $GABA_A$ α1 and γ2 receptor subunit mRNA increased during postnatal development from postnatal day 7 to 60, and significantly differed between the somatosensory thalamus and somatosensory cortex as well as between males and females at ages postnatal days 35 and 60. Perinatal AY9944 treatment induced decreases in $GABA_A$ γ2 receptor subunits in the rat somatosensory thalamus and increases in the somatosensory cortex. Importantly, these changes were sex and age-specific. More precisely, the sexspecific changes in $GABA_AR$ α1 and γ2 subunits occurred during PND 35 and 60. In addition, the expression of α1 and γ2 subunits in the somatosensory cortex and thalamus was consistently lower in females compared to males. The findings suggest a mechanism for the higher prevalence of absence epilepsy which arises in prepubertal female rats. Whether it is also a mechanism for patients needs to be established considering it is not known whether atypical forms of absence epilepsy occur more often in females.

Gabrb3 deletion

As discussed above, male and female heterozygous $GABA_AR$ β3 subunit deletion mice in which the deletion was maternally- or paternally-inherited exhibit differences in epileptiform-like EEG discharges and behavioral abnormalities. Biochemical studies of whole brain extracts demonstrated both sex-dependent and parent-of-origin effects on β3 subunit protein expression. Male mice exhibited a severe reduction in β3 subunit protein expression with maternal, but not paternal transmission of the β3 subunit deletion. In contrast, female mice showed a severe reduction of β3 subunit when the deletion was transmitted through either parent (Liljelund et al., 2005). There is a possible correspondence between the extent of β3 subunit deletion and the EEG phenotype. Male mice with a paternally-inherited β3 subunit deletion had the smallest reduction in β3 subunit expression and the greatest abundance of fast activity on EEG. However, the difference in EEG fast activity was only statistically significant for the comparison between male and female mice with a paternal β3 subunit deletion and it was not clear from the paper if the authors compared the fast activity in male mice of paternal origin to male or female mice with a maternally-inherited deletion. Therefore, no definitive conclusions could be made

concerning the dependence of the sex-selective electrographic phenotypes on the sex-selective molecular phenotypes.

The role of stressors, sex steroids and phosphorylation in $GABA_AR$ subunit expression

Exposure to stressors can alter the expression of $GABA_AR$ subunits differently in male and female Gabrb3 deletion mice in different brain regions. In the prefrontal cortex, female mice expressed less α5 subunit mRNA after re-exposure to physical (restraint) or social (intruder mouse) stressor that they first experienced as juveniles. In contrast, male mice expressed less α2 subunit mRNA upon re-exposure to social stress. In the amygdala, female mice expressed increased α2, α3, and γ2 subunit mRNA upon re-exposure to physical stress and male mice expressed decreased α2, α3, and α5 subunit mRNA upon re-exposure to physical and social stresses (Jacobson-Pick et al., 2012). Sex-dependent differences in $GABA_AR$ subunit expression in different brain regions in response to early-life stressors could play a role in exacerbating CAE in girls. The mechanisms that produce the different levels of $GABA_AR$ subunit mRNA and protein expression in males and females is unknown, but may be related to the presence of sex steroids. Maguire et al. demonstrated in mice that compared with estrus, the high progesterone diestrus state was associated with higher hippocampal δ subunit expression and lower γ2 subunit expression as well as associated increased tonic current amplitudes (Maguire et al., 2005). Although the hippocampus is not thought to play a direct role in the expression of typical absence seizures, it is involved in atypical absence seizures and it modulates typical absence seizures (Stewart et al., 2009; Wu et al., 2007; Tolmacheva and van Luijtelaar, 2007a,b). In addition, it is possible that the increased δ subunit expression seen in the hippocampus during diestrus would also be seen in the relay nuclei of the thalamus and thereby cause an enhanced tonic current which would exacerbate absence seizures.

Cyclic alterations in the extent of $GABA_AR$ posttranscriptional modi-fication throughout the estrous cycle may contribute to these changes in $GABA_AR$ expression. Phosphorylation of $GABA_AR$ γ2 subunit residues, Y365 and Y367, inhibits $GABA_AR$ cell surface endocytosis (Kittler et al., 2008). Mice which heterozygously expressed γ2 subunit in which Y365 and Y367 were mutated to phenylalanines and thus were insensitive to phosphorylation, demonstrated sex-dependent responses (Nani et al., 2013). When γ2 subunit phosphorylation was inhibited, female, but not male mice, increased α4 and δ subunit expression as well as the amplitudes of phasic and tonic $GABA_AR$ currents in the lateral geniculate nucleus of the thalamus. Because increased tonic $GABA_AR$ currents in the ventrobasal nucleus are associated with absence seizures in several rodent models (Crunelli et al., 2011; Cope et al., 2009), a reduction of $GABA_AR$ receptor γ2 subunit tyrosine phosphorylation would be expected to increase absence seizures in females, but not in males.

Role of sex hormones on absence epilepsy and seizures

Ovarian cycle and acute pharmacological studies in typical and atypical absence models

The consequences of changes in plasma levels of sex hormones (they are steroid hormones which are known to cross the blood–brain barrier and affect behavioral, neurologic and

neuroendocrine functioning) during the ovarian cycle was investigated in a rat model for typical (WAG/Rij) absences and the AY9944 model of atypical absence seizures. The time course of SWDs in adult female WAG/Rij rats with a confirmed 4-day cycle during a 96 h EEG recording period was measured and it showed that the number of SWDs increased at specific hours of the proestrus day when the serum levels of progesterone reach their maximal value (van Luijtelaar et al., 2001). Interestingly, a single case was described in which the frequency of absence seizures was highest during the phase of the menstrual cycle when progesterone levels are highest (Grünewald et al., 1992). There was no increase in SWDs during dies-trus in the rat study, a time at which a second peak in progesterone is present. This dichotomy in the two progesterone peaks is puzzling and both hormonal and non-hormonal effects might be involved in the occurrence of SWDs. A hormonal factor that affects the increase of progesterone at diestrus can be the progesterone metabolite 20alpha-OH-progesterone. It peaks at the same hours as progesterone itself. Whether this metabolite modulates brain excitability opposite to progesterone is not known. Other hormones such as LH, FSH estradiol and prolactin do not peak at that moment and do not show changes at diestrus and therefore their role can be neglected. A second hormonal issue that can be proposed is that the composition of the GABA-subunits is different in different phases of the cycle and/or that the speed of change in progesterone levels is crucial for the type of changes in GABA subunits. Non-hormonal factors determining absence seizures are arousal, locomotor activity, and sleep (van Luijtelaar et al., 1991; Coenen et al., 1995; Drinkenburg et al., 1991; Osterhagen et al., 2010; Smyk et al., 2011). Early evidence suggested a significant modulation of locomotor activity and sleep–wake cycles by ovarian steroids in female rats (Colvin et al., 1968). Whether the changes in arousal, bodily activity and sleep parameters can sufficiently explain the lack of increase in SWD as predicted considering the increase in progesterone at diestrus, needs to be established.

In addition, other hormones which peak at the same time as progesterone (e.g. LH, FSH and prolactin) might also play a role in the effects of the ovarian cycle on SWDs. Interestingly, although β-estradiol is also known to modulate seizures in various convulsive models (Velísková, 2006; Hosseini et al., 2013), there were no changes in SWDs during the hours at which estradiol reached its maximal value. The data suggest a temporal association between a physiological increase in the concentration of serum progesterone and an increase in SWDs during proestrus. Although similar changes (increase in SWDs) were found during proestrus in the AY9944 model (Persad et al., 2004), the increase occurred during the hours at which estradiol levels were increased and progesterone just start to increase. However, because the plasma concentration of progesterone was 1000-fold higher than estradiol, the authors proposed that progesterone overrode estrogen's anti-absence effects (Persad et al., 2004). Therefore, it is not completely clear whether the data from studies in WAG/Rij rats and in the AY9944 model are 100% in concordance with respect to the relationship between the ovarian hormones during the ovarian cycle and SWDs (in neither study plasma or brain hormone concentrations were measured). However, different pharmacological studies showed that systemic administered progesterone and its metabolite, allopregnanolone (3-alpha-hydroxy-5alpha-pregnan-20-one (3α,5α-THP) a positive modulator of δ subunit-containing extrasynaptic $GABA_AR$ (Belelli and Lambert, 2005) rapidly enhanced the number of SWDs in a dose- and time-dependent manner in both the typical and atypical

absence models (Budziszewska et al., 1999; van Luijtelaar et al., 2001; Persad et al., 2004; Tolmacheva et al., 2007a). In contrast, systemic injections of 17β-estradiol and an antagonist of its intracellular receptor (tamoxifen) did not have any effects in the WAG/Rij model, and reduced seizures in the atypical absence model (Budziszewska et al., 1999; Persad et al., 2004). These data demonstrated that estradiol interacts differently in typical and atypical absence seizure models and that neither the effects of progesterone nor the effects of 17β-estradiol were mediated by intracellular receptors. For an overview of the role of progesterone, estradiol and testosterone on absence seizures in WAG/Rij model for typical absence epilepsy AY9944, atypical absence epilepsy and convulsive seizures see Table 2.

The dual acute effects of testosterone

It is well known that testosterone may have proepileptic effects on convulsive seizures, although the effects of testosterone depend on dose, the animal's age, and seizure type (Edwards et al., 1999a; Reddy, 2004; Frye et al., 2001). Acutely administered testosterone caused an immediate proepileptic effect (clonic spasms in high dose PTZ test) in mice and rats, and this effect was blocked by letrozole, an aromatase inhibitor which blocks the conversion of testosterone to β-estradiol (Reddy, 2004). These data demonstrated that the proepileptic action of testosterone in clonic seizures was mediated via the conversion of testosterone to 17β-estradiol, in agreement with the most often reported proconvulsive effects of 17β-estradiol, although it is acknowledged that estradiol's pro-epileptic effect is highly dependent on the seizure model, dose, and region of the brain (Scharfman et al., 2005). Few experiments examined the role of testosterone in absence seizures. Data from a pharmacological EEG study in the WAG/Rij model showed that systemic administration of testosterone suppressed SWDs for 1 h and then increased SWDs for 2 h (van Luijtelaar et al., 2009a,b). Since 17β-estradiol is not effective in the typical absence model, it is possible that the immediate effects were due to testosterone itself. In contrast, a second testosterone-derived neurosteroid, androstanediol, was however protective in the same convulsive models (Reddy et al., 2004). Tentatively, we can conclude that testosterone itself exhibits acute anti-absence effects, but that an active metabolite, most likely androstanediol, exhibits pro-absence effects.

Long term effects of sex hormones

Removal of peripheral sources of steroid hormones gives an opportunity to study the long term effects of steroid hormones on brain excitability in males and females, while studying physiological changes during the ovarian cycle and during pregnancy allows us to model the effects of dynamically changing physiological concentrations of progesterone and estradiol on excitability.

Young adolescent male and female WAG/Rij rats were castrated/ ovariectomized and studied three months later. Castrated males showed more SWD activity than intact males and ovariectomized and intact females, suggesting that testosterone protects males against absence seizures (van Luijtelaar et al., 1996). Others compared intact and ovariectomized female WAG/Rij rats and showed either an increase in SWD one week after the removal of the ovaries (Kayim Yildiz et al., 2013), or no change in SWD frequency 4 to 35 days post-surgery but an aggravation of SWD in ovariectomized rats after repeated exposure to

stressors (Tolmacheva and van Luijtelaar, 2007a). The reason for the lack of consistent outcomes in females (either no effects, or an increase) is not immediately clear. The studies are difficult to compare because different post-ovariectomy periods have been used. In addition, some of the studies used only a short EEG recording period (1 h which may yield less representative data, or the behavior of the animals during the recording period was not taken into account). Moreover, in none of these studies, plasma or brain concentrations of the relevant hormones were measured in parallel with the EEG studies.

Correlative studies of hormones and SWDs were undertaken in pregnant WAG/Rij rats. During pregnancy, plasma levels of progesterone dramatically increase from the first to the 19th day, decrease before partus (day 20), and increase again post-partum. SWDs showed an inverse relationship over days with the concentration of progesterone, while no relation between SWDs and daily estradiol levels was found. Although it is classically thought that the ratio of estradiol/progesterone is the crucial factor for determining the occurrence of seizures (Bäckström, 1977), no such relationship between this ratio and SWD could be found in these pregnant rats. These data suggest an inverse relationship between progesterone and SWDs during pregnancy (Tolmacheva et al., 2004).

These experiments led to the conclusion that progesterone has a pro-absence action when acutely administered and during the ovarian cycle, 17β-estradiol is anti-absence but it is only active in atypical absence models, and both hormones act oppositely in absence models compared with most of the convulsive models. Another conclusion is that physiological increases in progesterone concentrations, as seen during pregnancy, have a diametrical opposite effect on SWDs as increases in progesterone during the proestrus phase and in acute pharmacological studies. It is unclear why the second progesterone peak that occurred during diestrus is not accompanied by an increase in SWDs.

Age-related changes in SWDs and thalamic GABA subunits

Cortical and thalamic concentrations of the most potent endogenous positive modulators of $GABA_AR$ (allopregnanolone and 3α,5α-TH-DOC) were compared between presymptomatic (2 months) and symptomatic (6 months) WAG/Rij and age-matched Wistar rats. Significant age-dependent decreases in both neurosteroids were found in the thalamus but not in the cortex in WAG/Rij rats, but not the nonepileptic Wistar rats. This effect in neurosteroid concentration was accompanied by an increase in α_4 $GABA_AR$ subunit expression in some dorsal thalamic nuclei in WAG/Rij rats and an age-dependent increase in δ subunits in both the WAG/Rij and Wistar rats. Both α4 and δ subunits are found in extrasynaptic $GABA_AR$, where they facilitate tonic inhibition. Therefore, the authors hypothesized that the age dependent increase in α4 and δ subunits increases tonic inhibition in thalamic relay neurons which then contributes to the age dependent increase in SWDs (Pisu et al., 2008).

The paradoxical effects of progesterone on absence seizures: an opposite role of the δ subunit of the $GABA_A$ receptor?

Local injections of progesterone and allopregnanolone in the ventral basal complex of the thalamus caused dose-dependent increases in SWDs, a finding that suggested that the acute effects of systemic administration of progesterone are caused by its modulatory effect of its

active metabolite, allopregnanolone, on the thalamic $GABA_AR$ (Wohlfarth et al., 2002; Citraro et al., 2006). However, steroid hormones also affect other aspects of GABAergic transmission including $GABA_AR$ subunit expression and posttranslational modification, both of which can modulate SWDs during development (age dependent increase of SWDs, see Age related changes in SWDs and thalamic GABA subunits section), the estrus cycle and pregnancy and account for the sex differences found in some of the absence models.

It should be taken into account that the increase in concentration of progesterone and allopregnanolone from conception to the 18th day of pregnancy (Concas et al., 1998) is much more robust than the increase from the estrus to the late diestrus phase of the ovarian cycle. As mentioned, steroid hormones also affect $GABA_AR$ subunit expression. Of the many $GABA_AR$ isoforms, only a few are sensitive to physiological concentrations of neurosteroids, and only a few show functional changes on brain excitability during the ovarian cycle, as was established in mice and in rats (Maguire et al., 2005; Lovick et al., 2005), although it is not certain that similar changes occur in both species.

As mentioned in the Gabrb3 deletion section, relative to the lowprogesterone estrus phase, mouse hippocampus increases $GABA_AR$ δ subunit expression and reduces γ2 subunit expression during late dies-trus when progesterone levels peak (Maguire and Mody, 2008). The relationship between progesterone levels and γ2/δ subunit expression observed during the ovarian cycle differs during pregnancy. At day 19 of pregnancy, the peak progesterone levels are accompanied by reduced expression of both δ and γ2 subunits (Maguire and Mody, 2008). Increased density of δ subunit immunoreactivity during late diestrus was also found in the periaquaductal gray in Wistar rats (Lovick et al., 2005), suggesting that the changes in subunit receptor proteins can occur quickly (within hours) and are not unique for the hippocampus in mice. Indeed, the decrease in δ subunit expression during pregnancy as found in the hippocampal dentate gyrus and CA1 region was also found in thalamus and striatum, but not in the cerebral cortex (Maguire et al., 2009). Although it is rather premature to extrapolate from expression data in mice to rats, we carefully propose that this reduction of this $GABA_AR$ δ subunit expression in the lateral basal complex of the thalamus might reduce tonic inhibition and reduce SWDs during pregnancy.

Assuming that these ovarian- and pregnancy-associated changes in hippocampal $GABA_AR$ subunit expression discussed above also occur in the rat thalamus (at least the age-related changes in subunit expression functionality occurred in thalamic neurons in WAG/Rij rats), hormone modulation of $GABA_AR$ subunit expression may explain observations of rat physiology. During the progesterone peak in the late rat diestrus phase, tonic hippocampal inhibition and SWD frequency were increased in both typical and atypical absence models (see Ovarian cycle and acute pharmacological studies in typical and atypical absence models section), but tonic and phasic hippocampal inhibitions were reduced during the progesterone peak during pregnancy as was the number of SWD (Tolmacheva and van Luijtelaar, 2004). The difference between progesterone's effect on δ subunit expression and tonic inhibition during the estrus cycle and pregnancy may explain the opposite effects of progesterone on rat SWDs during the ovarian cycle and pregnancy. Clearly, this hypothesis needs experimental verification.

Do the $GABA_A$Rs mediate the effects of testosterone?

As discussed in the The dual acute effects of testosterone section, testosterone has at least two effects on seizures. First, it has a proepileptic effect by enhancing clonic spasms in high dose PTZ test, an action that is likely related to its 17β-estradiol metabolite. Second acute administration of testosterone initially suppressed SWDs for 1 h before increasing them for 2 h (van Luijtelaar et al., 2009a,b). The early and late effects of testosterone may be mediated by two distinct pathways. First, aromatization of the A-ring converts testosterone into 17β-estradiol. Although 17β-estradiol is often found to have a proepileptic action, our acute pharmacological study, the 96 hr recording study, and the pregnancy study (see Ovarian cycle and acute pharmacological studies in typical and atypical absence models section) suggest that 17β-estradiol is not involved in the modulation of typical SWDs. In the second pathway, testosterone is reduced to 5α-dihydrotestosterone which is then converted to the neurosteroid androstanediol by glial cells and principal neurons in the hippocampus (Reddy and Jian, 2010). Androstanediol is a powerful and positive $GABA_A$R modulator causing a neuronal inhibition and protecting against convulsive seizures (e.g. in the hippocampal kindling mice model). An action via the classical intracellular androgen receptor was excluded in experiments with flutamide (Reddy and Jian, 2010). Androstanediol and allopregnanolone are structural and functional homologs. Because allopregnanolone exacerbates absence seizures, it is thought that the delayed pro-absence action of the acute administration of testosterone is due to the GABA-mimetic action of androstanediol. In contrast, the immediate anti-absence effects are mediated via testosterone itself, or via its first metabolite, 5α-dihydrotestosterone, which can act as NMDA antagonists (most NMDA antagonists reduce absence seizures, van Luijtelaar and Zobeiri, 2014). It is known that plasma levels of testosterone correlate with seizure modulating effects (Reddy and Jian, 2010). In addition, castration protects dogs against focal and tonic–clonic seizures, but increases spontaneous absence seizures in the WAG/Rij model. It can be concluded that the acute and delayed effects of testosterone on SWDs are opposite in a genetic absence epilepsy model and that the delayed proabsence effects are opposite to what is generally found in convulsive seizure models (Belelli et al., 1989; Reddy, 2004). However, whether and how the $GABA_A$R structure and function is influenced, whether changes in $GABA_A$R subunit expression play a role in the pro-absence action of castration, and whether these proabsence effects can be explained by an increase in thalamic tonic and or phasic inhibition, need to be clarified.

Concluding remarks and future directions

Although sex differences in human CAE and JAE are well known, clinical studies have not sufficiently differentiated the subtypes of GGE patients or accounted for variations in seizure characteristics. In particular, although the epidemiology studies found a higher incidence of CAE and JAE in females, they did not determine whether sex influences the severity of the disease (e.g. daily seizure frequency or long-term outcome). Studies that determine the age of onset of absences and whether the female preponderance disappears in adult patients are badly needed. Similarly, epidemiology studies have not identified a sex difference in incidence of diseases that confer atypical absence seizures or determined whether the frequency of atypical absence seizures differs in males and females who have

the same syndrome. Finally, none of the human studies measured the relationship of seizure frequency to serum levels of sex hormones. Although the onset of CAE occurs prior to puberty, even prepubertal girls possess significantly higher levels of 17β estradiol and other sex hormones than boys (Courant et al., 2010). Does the frequency of seizures and SWDs correlate with the levels of sex hormones, and, importantly, can they be reduced by safely manipulating sex steroid concentrations?

The mechanisms that contribute to these findings as well as the extent of sex–age and sex–gene interactions remain to be elucidated. The identification of sex effects in nonhuman absence epilepsy models will allow us to better elucidate their mechanistic bases. Unfortunately, sex differences were neither found in the most common rat genetic models with their 100% prevalence of seizures, perhaps the sex difference might have disappeared in the course of the inbreeding or selection process, nor in the classical genetic mice models. It should be considered that sex differences in prevalence in randomly bred rat strains might have been present (e.g. see Vergnes et al., 1982). Another difference between incidence and most of the rodent studies is that sex difference in humans shows up as incidence of patients diagnosed with epilepsy; in rodent models it is often the frequency of the seizures.

Sex differences were observed in the atypical absence models (and indeed AY9944 is not a genetic model), in which age and sex specific changes in $GABA_AR$ subunits, modulated by the neurosteroids, play a crucial role. In particular, the atypical absence AY9944 model is an interesting model with functional consequences of early changes in neurosteroid pool and seizures that occur prepubertal and remain throughout life. The sex differences are accompanied by changes in expression of certain $GABA_AR$ subunits. The AY9944 model allows the study of how neurosteroids given early in development affect the brain throughout life and cause sex dependent differences in seizures. The finding of sex-based differences in the frequency of atypical absence seizures in the AY9944 model is of particular clinical importance. Human syndromes that confer atypical absence seizures are frequently refractory to medical treatment and thus in urgent need of new therapies, including hormonal modulation, that work by novel mechanisms.

In addition to the AY9944 model, sex-dependent effects were found in the BN rat model and in the Gabrb3 and Gabra1 knockout mice. In the BN strain and Gabrb3 knockout mouse, however, males were more severely affected than females, possibly reflecting the increased incidence of adult-onset genetic generalized epilepsy. In addition, as described above, no studies have been performed that quantify the frequency of absence seizures in patients with these syndromes and thus it is possible that an additional male-predominant phenotype may be found in humans.

When expressed in the C57BL/6J strain, the Gabra1 knockout mouse exhibited a more severe phenotype in females and thus recapitulated the female predominance found in human CAE and JAE. Because loss-of-function GABRA1 mutations are associated with absence epilepsy in human patients, this mouse model may help de-fine some sex–gene interactions in a human epilepsy syndrome. The sex-effect was absent when the Gabra1 deletion was expressed in the DBA/2J strain, a finding which suggests that modifier genes are critical for the expression of sex effects and highlights the importance of examining for

sex-effects in multiple background strains when evaluating human monogenic epilepsies. Absence seizures in the Gabra1 deletion mice were identified at P33–37, an age before sexual maturity, but after the completion of several sexual developmental milestones. Future experiments will need to determine when, in development, these sex differences appear, their dependence on levels of sex hormones, and the corresponding differences in the expression of $GABA_AR$ and other proteins.

Sex hormones and their metabolites (e.g. neurosteroids) affect brain excitability and absence seizures acutely but also throughout lifetime, such as during pregnancy. Interestingly, the effects established in absence models are most often diametrically opposite to what has been found in the convulsive models: progesterone has a pro-absence action, β-estradiol is anti-absence, but it is only active in atypical absence models, and testosterone has dual effects: first anti-absence in the first hour and later pro-absence in subsequent hours. The opposite effects of progesterone on convulsive and absence seizures are in agreement with the role of most GABAergic drugs in convulsive vs non-convulsive types of epilepsies. This observation may be related to the finding that sex hormones are metabolized in the brain to neurosteroids which have direct effects on $GABA_AR$ with a δ subunit and also modulate the expression of $GABA_ARs$ containing γ2, α4, and δ subunits. It is proposed that these differences in subunit expression can also explain the diametrically opposite effects found in absence seizures during the progesterone peak during the ovarian cycle and during pregnancy.

Conditions other than pregnancy and phasic changes during the ovarian cycle also modulate seizures. For example, puberty in mice is associated with an increase in the expression of α4 and δ subunits at the apical dendrites of CA1 hippocampal pyramidal cells which is accompanied by an increase in tonic inhibitory current at puberty and neuronal excitability (Smith et al., 2009). Puberty is also associated with stress and the release of corticosteroids. It is well known that corticosteroids or their metabolites (e.g. tetrahydrodeoxycorticosterone) also affect hippocampal excitability and involve both excitatory and inhibitory processes (Romeo et al., 2006) and affect SWDs (Schridde and van Luijtelaar, 2004; Tolmacheva et al., 2012). Again, whether these changes in hippocampal excitation and inhibition can explain changes in cortico-thalamo-cortical network excitability or whether changes in thalamic subunit expression have direct effects on thalamic subunits when the absences disappear in CAE around puberty, or become worse as is the case in JAE, needs to be established, although the feasibility of this hypothesis can be inferred from kindling studies, which showed that the excitability of the cortico-thalamo-cortical network was changed after hippocampal kindling or amygdaloid KA injections in either GAERS or WAG/Rij rats (Onat et al., 2007; Gurbanova et al., 2008; Akman et al., 2008) and by the thalamic changes in α4 and δ subunit expression and function during development (Pisu et al., 2008).

Except for the Gabra1 knockout mouse, the other typical absence models do not show obvious sex differences. A sex difference could suggest that one of the genes (absence is a polygenetic disease in the vast majority of cases) for absence epilepsy is linked to the X chromosome. Most likely the genes involved in absence epilepsy in GAERS and WAG/Rij

rats are not linked to the sex chromosome. Until now, the genes involved in the pathogenesis of absence epilepsy are neither found sufficiently in humans, nor in the genetic rat models.

Another question is whether the lack of gender differences in the typical absence epilepsy or seizure models might imply that these models incompletely model childhood-onset absence epilepsy and or juvenile absence epilepsy. It can be supposed that this might be due to the fact that different combinations of genes govern typical absence seizures in patients and in the models or that there are species differences in the organizational effects of neurosteroids. Another possibility is that certain mutations (i.e. $GABA_AR$) that affect the action of neurosteroids that predispose to gender differences in combination with a genetic predisposition for absence epilepsy have not been detected in any rodent model.

Also more attention should be placed on sex differences in absence epilepsy models. Most studies that discussed mouse or rat absence epilepsy models did not even include a statement whether or not there were any statistically significant sex-based differences in the phenotypes. The search for the mechanisms that lead to the sex-based differences in the models may include the question when, in development, do these sex-based differences first appear? For the Gabra-KO model, mice were tested between P33 and 37 (i.e. before sexual maturity). Do the absence seizures occur before this time point? If so, do sex-based differences correlate with sex hormone concentrations throughout development?

The effect of sex hormones is a second obvious target. What is the effect of manipulating sex hormone levels early vs later in life on the development of epilepsy in male and female mice? One can also use spontaneous fluctuations in hormone concentrations and measure expression of GABA subunits during the different phases of the ovarian cycle and peripregnancy in combination with monitoring plasma and or brain levels, receptor expression studies and in vivo electrophysiology, in which the EEG is still excellent for determining excitability in vivo over a prolonged period of time in the absence models. It is also obvious that research on sex differences and excitability changes throughout life and hormonal effects should focus on the thalamus and cortex and should not consider either the entire cortex or the entire thalamus as unified. The presence of hundreds of spontaneous occurring SWDs per day in the genetic models shown to be sensitive to physiological fluctuations in brain concentrations of progesterone during the ovarian cycle and during pregnancy yields an excellent opportunity for studies towards mechanisms determining the role of sex hormones and neurosteroids on excitability in the cortex and thalamus.

Acknowledgments

F.Y. Onat was supported by the Marmara University grant SAG-D-060510-127, M.J. Gallagher was supported by the National Institutes of Health grant R01 NS064286.

References

Aizawa M, Ito Y, Fukuda H. Pharmacological profiles of generalized absence seizures in lethargic, stargazer and gamma-hydroxybutyrate-treated model mice. Neurosci. Res. 1997; 29:17–25. [PubMed: 9293489]

Aker RG, Özkara C, Dervent A, Onat FY. Enhancement of spike and wave discharges by microinjection of bicuculline into the reticular nucleus of rats with absence epilepsy. Neurosci. Lett. 2002; 322:71–74. [PubMed: 11958846]

Aker RG, Ozyurt HB, Yananli HR, Cakmak YO, Ozkaynakçi AE, Sehirli U, Saka E, Cavdar S, Onat FY. GABA(A) receptor mediated transmission in the thalamic reticular nucleus of rats with genetic absence epilepsy shows regional differences: functional implications. Brain Res. 2006; 1111:213–221. [PubMed: 16919245]

Akman O, Karson A, Aker RG, Ates N, Onat FY. Hippocampal kindling in rats with absence epilepsy resembles amygdaloid kindling. Epilepsy Res. 2008; 81:211–219. [PubMed: 18657396]

Akman O, Demiralp T, Ates N, Onat FY. Electroencephalographic differences between WAG/Rij and GAERS rat models of absence epilepsy. Epilepsy Res. 2010; 89:185–193. [PubMed: 20092980]

Annesi F, Gambardella A, Michelucci R, Bianchi A, Marini C, Canevini MP, Capovilla G, Elia M, Buti D, Chifari R, Striano P, Rocca FE, Castellotti B, Cali F, Labate A, Lepiane E, Besana D, Sofia V, Tabiadon G, Tortorella G, Vigliano P, Vignoli A, Beccaria F, Annesi G, Striano S, Aguglia U, Guerrini R, Quattrone A. Mutational analysis of EFHC1 gene in Italian families with juvenile myoclonic epilepsy. Epilepsia. 2007; 48:1686–1690. [PubMed: 17634063]

Arain FM, Boyd KL, Gallagher MJ. Decreased viability and absence-like epilepsy in mice lacking or deficient in the GABAA receptor a1 subunit. Epilepsia. 2012; 53:161–165. [PubMed: 22612821]

Asadi-Pooya AA, Emami M, Nikseresht A. Early-onset versus typical childhood absence epilepsy; clinical and electrographic characteristics. Seizure. 2012a; 21:273–275. [PubMed: 22365586]

Asadi-Pooya AA, Emami M, Sperling MR. Age of onset in idiopathic (genetic) generalized epilepsies: clinical and EEG findings in various age groups. Seizure. 2012b; 21:417–421. [PubMed: 22560254]

Avanzini G. Animal models relevant to human epilepsies. Ital. J. Neurol. Sci. 1995; 16:5–8. [PubMed: 7642352]

Avanzini G, de Curtis M, Marescaux C, Panzica F, Spreafico R, Vergnes M. Role of the thalamic reticular nucleus in the generation of rhythmic thalamo-cortical activities subserving spike and waves. J. Neural Transm. Suppl. 1992; 35:85–95. [PubMed: 1512596]

Bäckström T. Estrogen and progesterone in relation to different activities in the central nervous system. Acta Obstet. Gynecol. Scand. Suppl. 1977; 66:1–17. [PubMed: 20730]

Bazyan AS, van Luijtelaar G. Neurochemical and behavioral features in genetic absence epilepsy and in acutely induced absence seizures. ISRN Neurol. 2013; 2013:875834. http://dx.doi.org/10.1155/2013/875834. Print 2013. [PubMed: 23738145]

Belelli D, Lambert JJ. Neurosteroids: endogenous regulators of the GABA(A) receptor. Nat. Rev. Neurosci. 2005; 6:565–575. [PubMed: 15959466]

Belelli D, Bolger MB, Gee KW. Anticonvulsant profile of the progesterone metabolite 5 alpha-pregnan-3 alpha-ol-20-one. Eur. J. Pharmacol. 1989; 166:325–329. [PubMed: 2792198]

Ben-Ari Y. Excitatory actions of gaba during development: the nature of the nurture. Nat. Rev. Neurosci. 2002; 3:728–739. [PubMed: 12209121]

Berzaghi Mda P, Amado D, Cavalheiro EA. Pregnancy decreases the frequency of spontaneous recurrent seizures in rats with kainic acid lesions of the hippocampus. Epilepsy Res. 1987; 1:142–144. [PubMed: 3504390]

Bird LM. Angelman syndrome: review of clinical and molecular aspects. Appl. Clin. Genet. 2014; 7:93–104. [PubMed: 24876791]

Blumenfeld H. From molecules to networks: cortical/subcortical interactions in the pathophysiology of idiopathic generalized epilepsy. Epilepsia. 2003; 44(S2):7–15. [PubMed: 12752456]

Bouwman BM, Suffczynski P, Lopes da Silva FH, Maris E, van Rijn CM. GABAergic mechanisms in absence epilepsy: a computational model of absence epilepsy simulating spike and wave discharges after vigabatrin in WAG/Rij rats. Eur. J. Neurosci. 2007; 25:2783–2790. [PubMed: 17561843]

Brouwer OF. Long-term outcome of childhood absence epilepsy: Dutch Study of Epilepsy in Childhood. Epilepsy Res. 2009; 83:249–256. [PubMed: 19124226]

Budziszewska B, van Luijtelaar G, Coenen A, Leskiewicz M, Lason W. Effects of neurosteroids on spike-wave discharges in the genetic epileptic WAG/Rij rat. Epilepsy Res. 1999; 33:23–29. [PubMed: 10022363]

Buntinx IM, Hennekam RC, Brouwer OF, Stroink H, Beuten J, Mangelschots K, et al. Clinical profile of Angelman syndrome at different ages. Am. J. Med. Genet. 1995; 56:176–183. [PubMed: 7625442]

Callenbach PM, van den Maagdenberg AM, Frants RR, Brouwer OF. Clinical and genetic aspects of idiopathic epilepsies in childhood. Eur. J. Paediatr. Neurol. 2005; 9:91–103. [PubMed: 15843076]

Callenbach PM, Bouma PA, Geerts AT, Arts WF, Stroink H, Peeters EA, van Donselaar CA, Peters AC, Brouwer OF. Long-term outcome of childhood absence epilepsy: Dutch Study of Epilepsy in Childhood. Epilepsy Res. 2009; 83:249–256. [PubMed: 19124226]

Chaix Y, Daquin G, Monteiro F, Villeneuve N, Laguitton V, Genton P. Absence epilepsy with onset before age three years: a heterogeneous and often severe condition. Epilepsia. 2003; 44:944–949. [PubMed: 12823578]

Chen SD, Yeh KH, Huang YH, Shaw FZ. Effect of intracranial administration of ethosuximide in rats with spontaneous or pentylenetetrazol-induced spike-wave discharges. Epilepsia. 2011; 52:1311–1318. [PubMed: 21729038]

Choi JH, Koch KP, Poppendieck W, Lee M, Shin HS. High resolution electroencephalography in freely moving mice. J. Neurophysiol. 2010; 104:1825–1834. [PubMed: 20610789]

Citraro R, Russo E, Di Paola ED, Ibbadu GF, Gratteri S, Marra R, De Sarro G. Effects of some neurosteroids injected into some brain areas of WAG/Rij rats, an animal model of generalized absence epilepsy. Neuropharmacology. 2006; 50:1059–1071. [PubMed: 16631210]

Coenen AML, van Luijtelaar ELJM. The WAG/Rij rat model for absence epilepsy: age and sex factors. Epilepsy Res. 1987; 1:297–301. [PubMed: 3143552]

Coenen AM, Blezer EH, van Luijtelaar EL. Effects of the GABA-uptake inhibitor tiagabine on electroencephalogram, spike-wave discharges and behaviour of rats. Epilepsy Res. 1995; 21:89–94. [PubMed: 7588592]

Colvin GB, Whitmoyer DI, Lisk RD, Walter DO, Sawyer CH. Changes in sleep– wakefulness in female rats during circadian and estrous cycles. Brain Res. 1968; 7:173–181. [PubMed: 5689033]

Commission. Commission on Classification and Terminology of the International League Against Epilepsy: proposal for revised classification of epilepsies and epileptic syndromes. Epilepsia. 1989; 30:389–399. [PubMed: 2502382]

Concas A, Mostallino MC, Porcu P, Follesa P, Barbaccia ML, Trabucchi M, Purdy RH, Grisenti P, Biggio G. Role of brain allopregnanolone in the plasticity of gamma-aminobutyric acid type A receptor in rat brain during pregnancy and after delivery. Proc. Natl. Acad. Sci. U. S. A. 1998; 95:13284–13289. [PubMed: 9789080]

Cope DW, Di Giovanni G, Fyson SJ, Orban G, Errington AC, Lorincz ML, et al. Enhanced tonic GABAA inhibition in typical absence epilepsy. Nat. Med. 2009; 15:1392–1398. [PubMed: 19966779]

Cortez MA, Cunnane SC, Snead OC III. Brain sterols in the AY-9944 rat model of atypical absence seizures. Epilepsia. 2002; 43:3–8. [PubMed: 11879380]

Cossette P, Liu L, Brisebois K, Dong H, Lortie A, Vanasse M, et al. Mutation of GABRA1 in an autosomal dominant form of juvenile myoclonic epilepsy. Nat. Genet. 2002; 31:184–189. [PubMed: 11992121]

Courant F, Aksglaede L, Antignac JP, Monteau F, Sorensen K, Andersson AM, et al. Assessment of circulating sex steroid levels in prepubertal and pubertal boys and girls by a novel ultrasensitive gas chromatography-tandem mass spectrometry method. J. Clin. Endocrinol. Metab. 2010; 95:82–92. [PubMed: 19933393]

Crunelli V, Leresche N. Childhood absence epilepsy: genes, channels, neurons and networks. Nat. Rev. Neurosci. 2002; 3:371–382. [PubMed: 11988776]

Crunelli V, Cope DW, Terry JR. Transition to absence seizures and the role of GABA(A) receptors. Epilepsy Res. 2011; 97:283–289. [PubMed: 21889315]

Cutting S, Lauchheimer A, Barr W, Devinsky O. Adult-onset idiopathic generalized epilepsy: clinical and behavioral features. Epilepsia. 2001; 42:1395–1398. [PubMed: 11879340]

Danober L, Deransart C, Depaulis A, Vergnes M, Marescaux C. Pathophysiological mechanisms of genetic absence epilepsy in the rat. Prog. Neurobiol. 1998; 55:27–57. [PubMed: 9602499]

David O, Guillemain I, Saillet S, Reyt S, Deransart C, Segebarth C, Depaulis A. Identifying neural drivers with functional MRI: an electrophysiological validation. PLoS Biol. 2008; 6:2683–2697. [PubMed: 19108604]

Depaulis, A.; van Luijtelaar, G. Genetic models of absence epilepsy in the rat.. In: Pitkänen, A.; Schwartkroin, PA.; Moshé, SL., editors. Models of Seizures and Epilepsy. Elsevier; Amsterdam: 2006. p. 233-248.

Depaulis A, Deransart C, Vergnes M, Marescaux C. GABAergic mechanisms in generalized epilepsies: the neuroanatomical dimension. Rev. Neurol. (Paris). 1997; 153(Suppl. 1):S8–S13. [PubMed: 9686242]

Dobryakova YV, A Dubynin V, van Luijtelaar G. Maternal behavior in a genetic animal model of absence epilepsy. Acta Neurobiol. Exp. (Wars.). 2008; 68:502–508. [PubMed: 19112473]

Dobryakova YV, Dubynin VA, van Luijtelaar G. The effect of haloperidol on maternal behavior in WAG/Rij rats and its consequences in the offspring. Acta Neurobiol. Exp. (Wars.). 2011; 71:339–347. [PubMed: 22068743]

Duron RM, Medina MT, Martinez-Juarez IE, Bailey JN, Perez-Gosiengfiao KT, Ramos-Ramirez R, Lopez-Ruiz M, Alonso ME, Ortega RH, Pascual-Castroviejo I, Machado-Salas J, Mija L, Delgado-Escueta AV. Seizures of idiopathic generalized epilepsies. Epilepsia. 2005; 46(Suppl. 9): 34–47. [PubMed: 16302874]

Edwards HE, Burnham WM, MacLusky NJ. Testosterone and its metabolites affect after discharge thresholds and the development of amygdala kindled seizures. Brain Res. 1999a; 838:151–157. [PubMed: 10446327]

Edwards HE, Burnham WM, Mendonca A, Bowlby DA, MacLusky NJ. Steroid hormones affect limbic after discharge thresholds and kindling rates in adult female rats. Brain Res. 1999b; 838:136–150. [PubMed: 10446326]

Errington AC, Gibson KM, Crunelli V, Cope DW. Aberrant GABA(A) receptor-mediated inhibition in cortico-thalamic networks of succinic semialdehyde dehydrogenase deficient mice. PLoS One. 2011; 6:e19021. [PubMed: 21526163]

Farrant M, Nusser Z. Variations on an inhibitory theme: phasic and tonic activation of GABA(A) receptors. Nat. Rev. Neurosci. 2005; 6:215–229. [PubMed: 15738957]

Frye CA, Rhodes ME, Walf AA, Harney JP. Testosterone reduces pentylenetetrazole-induced ictal activity of wildtype mice but not those deficient in type I 5alpha-reductase. Brain Res. 2001; 918:182–186. [PubMed: 11684057]

Galanopoulou AS, Kyrozis A, Claudio OI, Stanton PK, Moshe SL. Sex-specific KCC2 expression and GABA(A) receptor function in rat substantia nigra. Exp. Neurol. 2003; 183:628–637. [PubMed: 14552904]

Genton P, Thomas P, Kasteleijn-Nolst Trenité DG, Medina MT, Salas-Puig J. Clinical aspects of juvenile myoclonic epilepsy. Epilepsy Behav. 2013; 28(Suppl. 1):S8–S14. [PubMed: 23756488]

Gotman J, Grova C, Bagshaw A, Kobayashi E, Aghakhani Y, Dubeau F. Generalized epileptic discharges show thalamocortical activation and suspension of the default state of the brain. Proc. Natl. Acad. Sci. U. S. A. 2005; 102:15236–15240. [PubMed: 16217042]

Grünewald RA, Aliberti V, Panayiotopoulos CP. Exacerbation of typical absence seizures by progesterone. Seizure. 1992; 1:137–138. [PubMed: 1344329]

Gulhan, RA.; Onat, FY.; Kınay, D. Chemically induced experimental models of absence epilepsy.. In: Tan, FR., editor. Chemical-induced Seizures: Mechanism, Consequences and Treatment. Bentham Science Publisher; Singapore: 2011. p. 67-79.

Gurbanova AA, Aker RG, Sirvanci S, Demiralp T, Onat FY. Intra-amygdaloid injection of kainic acid in rats with genetic absence epilepsy: the relationship of typical absence epilepsy and temporal lobe epilepsy. J. Neurosci. 2008; 28:7828–7836. [PubMed: 18667615]

Hosseini M, Sadeghinia HR, Salehabadi S, Soukhtanloo M. Contribution of estradiol in sex-dependent differences of pentylenetetrazole-induced seizures in rats. Acta Physiol. Hung. 2013; 100:237–245. [PubMed: 23524184]

Huguenard JR, McCormick DA. Thalamic synchrony and dynamic regulation of global forebrain oscillations. Trends Neurosci. 2007; 30:350–356. [PubMed: 17544519]

IIshige K, Aizawa M, Ito Y, Fukuda H. Gamma-butyrolactone-induced absence-like seizures increase nuclear CRE- and AP-1 DNA-binding activities in mouse brain. Neuropharmacology. 1996; 35:45–55. [PubMed: 8684596]

Inoue M, Peeters BW, van Luijtelaar EL, Vossen JM, Coenen AM. Spontaneous occurrence of spike-wave discharges in five inbred strains of rats. Physiol. Behav. 1990; 48:199–201. [PubMed: 2122483]

Jacobson-Pick S, Audet MC, McQuaid RJ, Kalvapalle R, Anisman H. Stressor exposure of male and female juvenile mice influences later responses to stressors: modulation of GABAA receptor subunit mRNA expression. Neuroscience. 2012; 215:114–126. [PubMed: 22542673]

Jallon P, Latour P. Epidemiology of idiopathic generalized epilepsies. Epilepsia. 2005; 46(Suppl. 9): 10–14. [PubMed: 16302871]

Jandó G, Carpi D, Kandel A, Urioste R, Horvath Z, Pierre E, Vadi D, Vadasz C, Buzsáki G. Spike-and-wave epilepsy in rats: sex differences and inheritance of physiological traits. Neuroscience. 1995; 64:301–317. [PubMed: 7700522]

Janz D. The idiopathic generalized epilepsies of adolescence with childhood and juvenile age of onset. Epilepsia. 1997; 38:4–11. [PubMed: 9024180]

Jara-Prado A, Martinez-Juarez IE, Ochoa A, Gonzalez VM, Fernandez-Gonzalez-Aragon MC, Lopez-Ruiz M, et al. Novel myoclonin1/EFHC1 mutations in Mexican patients with juvenile myoclonic epilepsy. Seizure. 2012; 21:550–554. [PubMed: 22727576]

Jiang YH, Armstrong D, Albrecht U, Atkins CM, Noebels JL, Eichele G, et al. Mutation of the Angelman ubiquitin ligase in mice causes increased cytoplasmic p53 and deficits of contextual learning and long-term potentiation. Neuron. 1998; 21:799–811. [PubMed: 9808466]

Jiang YH, Pan Y, Zhu L, Landa L, Yoo J, Spencer C, et al. Altered ultrasonic vocalization and impaired learning and memory in Angelman syndrome mouse model with a large maternal deletion from Ube3a to Gabrb3. PLoS One. 2010; 5:e12278. [PubMed: 20808828]

Kanemoto K, Miyamoto T, Abe R. Ictal catatonia as a manifestation of de novo absence status epilepticus following benzodiazepine withdrawal. Seizure. 1999; 8:364–366. [PubMed: 10512781]

Kayim Yildiz O, Yildiz C, Durmus N, Gulturk S, Benek S, Cetin A. Ovariectomy enhances spike-wave discharges in WAG/Rij rats. Neurol. Psychiatry Brain Res. 2013; 17:67–70.

Kittler JT, Chen G, Kukhtina V, Vahedi-Faridi A, Gu Z, Tretter V, et al. Regulation of synaptic inhibition by phospho-dependent binding of the AP2 complex to a YECL motif in the GABAA receptor gamma2 subunit. Proc. Natl. Acad. Sci. U. S. A. 2008; 105:3616–3621. [PubMed: 18305175]

Kleinlogel H. Spontaneous EEG paroxysms in the rat: effects of psychotropic and alpha-adrenergic agents. Neuropsychobiology. 1995; 13:206–213. [PubMed: 2864656]

Lacey CJ, Bryant A, Brill J, Huguenard JR. Enhanced NMDA receptor-dependent thalamic excitation and network oscillations in stargazer mice. J. Neurosci. 2012; 32:11067–11081. [PubMed: 22875939]

Lachance-Touchette P, Brown P, Meloche C, Kinirons P, Lapointe L, Lacasse H, et al. Novel a1 and g2 GABAA receptor subunit mutations in families with idiopathic generalized epilepsy. Eur. J. Neurosci. 2011; 34:237–249. [PubMed: 21714819]

Li H, Huguenard JR, Fisher RS. Gender and age differences in expression of GABAA receptor subunits in rat somatosensory thalamus and cortex in an absence epilepsy model. Neurobiol. Dis. 2007; 25:623–630. [PubMed: 17208003]

Liljelund P, Handforth A, Homanics GE, Olsen RW. GABAA receptor beta3 subunit gene-deficient heterozygous mice show parent-of-origin and gender-related differences in beta3 subunit levels, EEG, and behavior. Brain Res. Dev. Brain Res. 2005; 157:150–161.

Lovick TA, Griffiths JL, Dunn SM, Martin IL. Changes in GABA(A) receptor subunit expression in the midbrain during the oestrous cycle in Wistar rats. Neuroscience. 2005; 131:397–405. [PubMed: 15708482]

Lüttjohann A, van Luijtelaar G. The dynamics of cortico-thalamo-cortical interactions at the transition from pre-ictal to ictal LFPs in absence epilepsy. Neurobiol. Dis. 2012; 47:47–60.

Lüttjohann A, Stoffelen JM, van Luijtelaar G. Peri-ictal network dynamics of spike-wave discharges: phase and spectral characteristics. Exp. Neurol. 2013; 239:235–247. [PubMed: 23124095]

Lüttjohann A, Schoffelen JM, van Luijtelaar G. Termination of ongoing spike-wave discharges investigated by cortico-thalamic network analyses. Neurobiol. Dis. 2014; 70C:127–137. [PubMed: 24953875]

Macdonald RL, Kang JQ, Gallagher MJ. Mutations in GABA-A receptor subunits associated with genetic epilepsies. J. Physiol. 2010; 588:1861–1869. [PubMed: 20308251]

Maguire J, Mody I. GABA(A)R plasticity during pregnancy: relevance to postpartum depression. Neuron. 2008; 59:207–213. [PubMed: 18667149]

Maguire JL, Stell BM, Rafizadeh M, Mody I. Ovarian cycle-linked changes in GABA(A) receptors mediating tonic inhibition alter seizure susceptibility and anxiety. Nat. Neurosci. 2005; 8:797–804. [PubMed: 15895085]

Maguire J, Ferando I, Simonsen C, Mody I. Excitability changes related to GABAA receptor plasticity during pregnancy. J. Neurosci. 2009; 29:9592–9601. [PubMed: 19641122]

Maljevic S, Krampfl K, Cobilanschi J, Tilgen N, Beyer S, Weber YG, et al. A mutation in the GABA(A) receptor alpha(1)-subunit is associated with absence epilepsy. Ann. Neurol. 2006; 59:983–987. [PubMed: 16718694]

Martínez-Juárez IE, Alonso ME, Medina MT, Durón RM, Bailey JN, López-Ruiz M, Ramos-Ramírez R, León L, Pineda G, Castroviejo IP, Silva R, Mija L, Perez-Gosiengfiao K, Machado-Salas J, Delgado-Escueta AV. Juvenile myoclonic epilepsy subsyndromes: family studies and long-term follow-up. Brain. 2006; 129(Pt 5):1269–1280. [PubMed: 16520331]

Matejovska I, Veliskova J, Velisek L. Bicuculline-induced rhythmic EEG episodes: gender differences and the effects of ethosuximide and baclofen treatment. Epilepsia. 1998; 39:1243–1252. [PubMed: 9860058]

Meeren HK, Pijn JP, van Luijtelaar EL, Coenen AM, Lopes da Silva FH. Cortical focus drives widespread corticothalamic networks during spontaneous absence seizures in rats. J. Neurosci. 2002; 22:1480–1495. [PubMed: 11850474]

Meeren HK, Veening JG, Möderscheim TA, Coenen AM, van Luijtelaar G. Thalamic lesions in a genetic rat model of absence epilepsy: dissociation between spike-wave discharges and sleep spindles. Exp. Neurol. 2009; 217:25–37. [PubMed: 19416679]

Merlo D, Mollinari C, Inaba Y, Cardinale A, Rinaldi AM, D'Antuono M, D'Arcangelo G, Tancredi V, Ragsdale D, Avoli M. Reduced GABAB receptor subunit expression and paired-pulse depression in a genetic model of absence seizures. Neurobiol. Dis. 2007; 25:631–641. [PubMed: 17207629]

Mikkelsen B, Birket-Smith E, Bradt S, Holm P, Parm B, Lung M, et al. Clonazepam in the treatment of epilepsy. A controlled clinical trial in simple absences, bilateral massive epileptic myoclonus, and atonic seizures. Arch. Neurol. 1976; 33:322–325. [PubMed: 817696]

Moeller F, Stephani U, Siniatchkin M. Simultaneous EEG and fMRI recordings (EEG–fMRI) in children with epilepsy. Epilepsia. 2013; 54:971–982. [PubMed: 23647021]

Nani F, Bright DP, Revilla-Sanchez R, Tretter V, Moss SJ, Smart TG. Tyrosine phosphorylation of GABAA receptor gamma2-subunit regulates tonic and phasic inhibition in the thalamus. J. Neurosci. 2013; 33:12718–12727. [PubMed: 23904608]

Nicolson A, Chadwick DW, Smith DF. A comparison of adult onset and “classical” idiopathic generalised epilepsy. J. Neurol. Neurosurg. Psychiatry. 2004; 75:72–74. [PubMed: 14707311]

Noebels JL, Sidman RL. Inherited epilepsy: spike-wave and focal motor seizures in the mutant mouse tottering. Science. 1979; 204:1334–1336. [PubMed: 572084]

Nolan M, Bergazar M, Chu B, Cortez MA, Snead OC III. Clinical and neurophysiologic spectrum associated with atypical absence seizures in children with intractable epilepsy. J. Child Neurol. 2005; 20:404–410. [PubMed: 15968924]

Onat FY, Aker RG, Gurbanova AA, Ateş N, van Luijtelaar G. The effect of generalized absence seizures on the progression of kindling in the rat. Epilepsia. 2007; 48(Suppl. 5):150–156. [PubMed: 17910595]

Onat FY, van Luijtelaar G, Nehlig A, Snead OC. The involvement of limbic structures in typical and atypical absence epilepsy. Epilepsy Res. 2013; 103:111–123. [PubMed: 22989853]

Osterhagen L, Breteler M, van Luijtelaar G. Does arousal interfere with operant conditioning of spike-wave discharges in genetic epileptic rats? Epilepsy Res. 2010; 90:75–82. [PubMed: 20388587]

Panayiotopoulos CP. Typical absence seizures and related epileptic syndromes: assessment of current state and directions for future research. Epilepsia. 2008; 49:2131–2139. [PubMed: 19049569]

Paz JT, Chavez M, Saillet S, Deniau JM, Charpier S. Activity of ventral medial thalamic neurons during absence seizures and modulation of cortical paroxysms by the nigrothalamic pathway. J. Neurosci. 2007; 27:929–941. [PubMed: 17251435]

Paz JT, Bryant AS, Peng K, Fenno L, Yizhar O, Frankel WN, Deisseroth K, Huguenard JR. A new mode of corticothalamic transmission revealed in the Gria4(−/−) model of absence epilepsy. Nat. Neurosci. 2011; 14:1167–1173. [PubMed: 21857658]

Peeters BWMM, Kerbusch JML, van Luijtelaar ELJM, Vossen JMH, Coenen AML. Genetics of absence epilepsy in rats. Behav. Genet. 1990; 20:453–460. [PubMed: 2116125]

Persad V, Cortez MA, Snead OC III. A chronic model of atypical absence seizures: studies of developmental and gender sensitivity. Epilepsy Res. 2002; 48:111–119. [PubMed: 11823115]

Persad V, Ting Wong CG, Cortez MA, Wang YT, Snead OC III. Hormonal regulation of atypical absence seizures. Ann. Neurol. 2004; 55:353–361. [PubMed: 14991813]

Pinault D. Cellular interactions in the rat somatosensory thalamocortical system during normal and epileptic 5–9 Hz oscillations. J. Physiol. 2003; 552:881–905. [PubMed: 12923213]

Pinault D, O'Brien TJ. Cellular and network mechanisms of genetically-determined absence seizures. Thalamus Relat. Syst. 2005; 3:181–203. [PubMed: 21909233]

Pisu MG, Mostallino MC, Dore R, Mura ML, Maciocco E, Russo E, De Sarro G, Serra M. Neuroactive steroids and GABAA receptor plasticity in the brain of the WAG/Rij rat, a model of absence epilepsy. J. Neurochem. 2008; 106:2502–2514. [PubMed: 18624910]

Polack PO, Guillemain I, Hu E, Deransart C, Depaulis A, Charpier S. Deep layer somatosensory cortical neurons initiate spike-and-wave discharges in a genetic model of absence seizures. J. Neurosci. 2007; 27:6590–6599. [PubMed: 17567820]

Pro S, Vicenzini E, Randi F, Pulitano P, Mecarelli O. Idiopathic late-onset absence status epilepticus: a case report with an electroclinical 14 years follow-up. Seizure. 2011; 20:655–658. [PubMed: 21507682]

Reddy DS. Testosterone modulation of seizure susceptibility is mediated by neurosteroids 3alpha-androstanediol and 17beta-estradiol. Neuroscience. 2004; 129:195–207. [PubMed: 15489042]

Reddy DS, Jian K. The testosterone-derived neurosteroid androstanediol is a positive allosteric modulator of GABAA receptors. J. Pharmacol. Exp. Ther. 2010; 334:1031–1041. [PubMed: 20551294]

Reid CA, Kim T, Phillips AM, Low J, Berkovic SF, Luscher B, et al. Multiple molecular mechanisms for a single GABAA mutation in epilepsy. Neurology. 2013; 80:1003–1008. [PubMed: 23408872]

Robinson PF, Gilmore SA. Spontaneous generalized spike-wave discharges in the electrocorticograms of albino rats. Brain Res. 1980; 201:452–458. [PubMed: 7417856]

Romeo RD, Karatsoreos IN, McEwen BS. Pubertal maturation and time of day differentially affect behavioral and neuroendocrine responses following an acute stressor. Horm. Behav. 2006; 50:463–468. [PubMed: 16836997]

Sanna E, Mostallino MC, Murru L, Carta M, Talani G, Zucca S, Mura ML, Maciocco E, Biggio G. Changes in expression and function of extrasynaptic GABAA receptors in the rat hippocampus during pregnancy and after delivery. J. Neurosci. 2009; 29:1755–1765. [PubMed: 19211882]

Scharfman HE, Goodman JH, Rigoulot M, Berger RE, Walling SG, Mercurio TC, Stormes T, Maclusky NJ. Seizure susceptibility in intact and ovariectomized female rats treated with the convulsant pilocarpine. Exp. Neurol. 2005; 196:73–86. [PubMed: 16084511]

Schridde U, van Luijtelaar G. Corticosterone increases spike-wave discharges in a dose- and time-dependent manner in WAG/Rij rats. Pharmacol. Biochem. Behav. 2004; 78:369–375. [PubMed: 15219779]

Serikawa T, Ohno Y, Sasa M, Yamada J, Takaori SA. A new model of petit mal epilepsy: spontaneous spike and wave discharges in tremor rats. Lab. Anim. 1987; 21:68–71. [PubMed: 3104669]

Smith SS, Aoki C, Shen H. Puberty, steroids and GABA(A) receptor plasticity. Psychoneuroendocrinology. 2009; 34(Suppl. 1):S91–S103. [PubMed: 19523771]

Smyk MK, Coenen AM, Lewandowski MH, van Luijtelaar G. Endogenous rhythm of absence epilepsy: relationship with general motor activity and sleep-wake states. Epilepsy Res. 2011; 93:120–127. [PubMed: 21146957]

Snead OC III. Basic mechanisms of generalized absence seizures. Ann. Neurol. 1995; 37:146–157. [PubMed: 7847856]

Snead OC III, Banerjee PK, Burnham M, Hampson D. Modulation of absence seizures by the GABA(A) receptor: a critical role for metabotropic glutamate receptor 4 (mGluR4). J. Neurosci. 2000; 20:6218–6224. [PubMed: 10934271]

Sperber EF, Wurpel JN, Zhao DY, Moshe SL. Evidence for the involvement of nigral GABAA receptors in seizures of adult rats. Brain Res. 1989; 480:378–382. [PubMed: 2540881]

Stefan, H.; Snead, OC., III; Eeg-Olofsson, O. Typical and atypical absence seizures, myoclonic absences, and eyelid myoclonia, in epilepsy. In: Engel, J., Jr.; Pedley, TA.; Aicardi, J.; Moshé, SL.; Dichter, MA.; Trimble, MR.; Perucca, E., editors. A Comprehensive Textbook. 2nd edn. Wolters Kluver/Lippincott Williams & Wilkins; Philadelphia, PA: 2008. p. 573-584.

Stewart LS, Wu Y, Eubanks JH, Han H, Leschenko Y, Perez Velazquez JL, et al. Severity of atypical absence phenotype in GABAB transgenic mice is subunit specific. Epilepsy Behav. 2009; 14:577–581. [PubMed: 19435582]

Suzuki T, Delgado-Escueta AV, Aguan K, Alonso ME, Shi J, Hara Y, et al. Mutations in EFHC1 cause juvenile myoclonic epilepsy. Nat. Genet. 2004; 36:842–849. [PubMed: 15258581]

Suzuki T, Miyamoto H, Nakahari T, Inoue I, Suemoto T, Jiang B, et al. Efhc1 de-ficiency causes spontaneous myoclonus and increased seizure susceptibility. Hum. Mol. Genet. 2009; 18:1099–1109. [PubMed: 19147686]

Tan HO, Reid CA, Single FN, Davies PJ, Chiu C, Murphy S, et al. Reduced cortical inhibition in a mouse model of familial childhood absence epilepsy. Proc. Natl. Acad. Sci. U. S. A. 2007; 104:17536–17541. [PubMed: 17947380]

Tanaka M, Olsen RW, Medina MT, Schwartz E, Alonso ME, Duron RM, et al. Hyperglycosylation and reduced GABA currents of mutated GABRB3 polypeptide in remitting childhood absence epilepsy. Am. J. Hum. Genet. 2008; 82:1249–1261. [PubMed: 18514161]

Terasawa EI, Timiras PS. Electrical activity during the estrous cycle of the rat: cyclic changes in limbic structures. 1968; 83:207–216.

Thomas P, Lebrun C, Chatel M. De novo absence status epilepticus as a benzodiazepine withdrawal syndrome. Epilepsia. 1993; 34:355–358. [PubMed: 8384109]

Tolmacheva EA, van Luijtelaar G. The role of ovarian steroid hormones in the regulation of basal and stress induced absence seizures. J. Steroid Biochem. Mol. Biol. 2007a; 104:281–288. [PubMed: 17493800]

Tolmacheva EA, van Luijtelaar G. Absence seizures are reduced by the enhancement of GABA-ergic inhibition in the hippocampus in WAG/Rij rats. Neurosci. Lett. 2007b; 416:17–21. [PubMed: 17280780]

Tolmacheva EA, Chepurnov SA, Chepurnova NE, Kochetkov YA, van Luijtelaar G. Absence seizures during pregnancy in WAG/Rij rats. Physiol. Behav. 2004; 81:623–627. [PubMed: 15178155]

Tolmacheva EA, Oitzl MS, van Luijtelaar G. Stress, glucocorticoids and absences in a genetic epilepsy model. Horm. Behav. 2012; 61:706–710. [PubMed: 22465594]

Trevathan E, Murphy CC, Yeargin-Allsopp M. Prevalence and descriptive epidemiology of Lennox–Gastaut syndrome among Atlanta children. Epilepsia. 1997; 38:1283–1288. [PubMed: 9578523]

Trinka E, Baumgartner S, Unterberger I, Unterrainer J, Luef G, Haberlandt E, Bauer G. Long-term prognosis for childhood and juvenile absence epilepsy. J. Neurol. 2004; 251:1235–1241. [PubMed: 15503104]

van Luijtelaar EL, Coenen AM. Two types of electrocortical paroxysms in an in-bred strain of rats. Neurosci. Lett. 1986; 70:393–397. [PubMed: 3095713]

van Luijtelaar G, Sitnikova E. Global and focal aspects of absence epilepsy: the contribution of genetic models. Neurosci. Biobehav. Rev. 2006; 30:983–1003. [PubMed: 16725200]

van Luijtelaar G, Zobeiri M. Progress and outlooks in a genetic absence epilepsy model (WAG/Rij). Curr. Med. Chem. 2014; 21:704–721. [PubMed: 24251564]

van Luijtelaar ELJM, Dirksen R, Vree T, van Haaren F. Effects of acute and chronic cocaine administration on EEG and behaviour in intact and castrated male and intact and ovariectomized female rats. Brain Res. Bull. 1996; 40:43–50. [PubMed: 8722752]

van Luijtelaar G, Budziszewska B, Jaworska-Feil L, Ellis J, Coenen A, Lason W. The ovarian hormones and absence epilepsy: a long-term EEG study and pharmacological effects in a genetic absence epilepsy model. Epilepsy Res. 2001; 46:225–239. [PubMed: 11518624]

van Luijtelaar, G.; Budziszewska, B.; Tolmacheva, EA. Hormones and absence epilepsy.. In: Schwartzkroin, PA., editor. Encyclopedia of Basic Epilepsy Research. Vol. 1. Academic Press; Oxford: 2009a. p. 488-495.(Elsevier)

van Luijtelaar, G.; Budziszewska, B.; Tolmacheva, EA. Hormones and absence epilepsy.. In: Schwartzkroin, Philip, editor. Encyclopedia of Basic Epilepsy Research. Vol. 1. Academic Press; Oxford: 2009b. p. 488-495.

van Luijtelaar G, Sitnikova E, Lüttjohann A. On the origin and suddenness onset of absences in genetic absence models. Clin. EEG Neurosci. 2011; 42:83–97. [PubMed: 21675598]

Velísková J. The role of estrogens in seizures and epilepsy: the bad guys or the good guys? Neuroscience. 2006; 138:837–844. [PubMed: 16310960]

Velísková J. Estrogens and epilepsy: why are we so excited? Neuroscientist. 2007; 13:77–88. [PubMed: 17229977]

Velísková J, Velísek L, Galanopoulou AS, Sperber EF. Neuroprotective effects of estrogens on hippocampal cells in adult female rats after status epilepticus. Epilepsia. 2000; 41(S 6):S30–S35. [PubMed: 10999516]

Vergnes M, Marescaux C, Micheletti G, Reis J, Depaulis A, Rumbach L, Warter JM. Spontaneous paroxysmal electroclinical patterns in rat: a model of generalized non-convulsive epilepsy. Neurosci. Lett. 1982; 33:97–101. [PubMed: 6818498]

Wallace RH, Marini C, Petrou S, Harkin LA, Bowser DN, Panchal RG, et al. Mutant GABA(A) receptor gamma2-subunit in childhood absence epilepsy and febrile seizures. Nat. Genet. 2001; 28:49–52. [PubMed: 11326275]

Weiergraber M, Henry M, Ho MS, Struck H, Hescheler J, Schneider T. Altered thalamocortical rhythmicity in Ca(v)2.3-deficient mice. Mol. Cell. Neurosci. 2008; 39:605–618. [PubMed: 18834942]

Willoughby JO, Mackenzie L. Nonconvulsive electrocorticographic paroxysms (absence epilepsy) in rat strains. Lab. Anim. Sci. 1992; 42:551–554. [PubMed: 1479805]

Wohlfarth KM, Bianchi MT, Macdonald RL. Enhanced neurosteroid potentiation of ternary GABA(A) receptors containing the delta subunit. J. Neurosci. 2002; 22:1541–1549. [PubMed: 11880484]

Wu Y, Chan KF, Eubanks JH, Guin Ting WC, Cortez MA, Shen L, et al. Transgenic mice over-expressing GABA(B)R1a receptors acquire an atypical absence epilepsy-like phenotype. Neurobiol. Dis. 2007; 26:439–451. [PubMed: 17363260]

Zaman T, Lee K, Park C, Paydar A, Choi JH, Cheong E, et al. Cav2.3 channels are critical for oscillatory burst discharges in the reticular thalamus and absence epilepsy. Neuron. 2011; 70:95–108. [PubMed: 21482359]

Zheng TW, O'Brien TJ, Morris MJ, Reid CA, Jovanovska V, O'Brien P, van Raay L, Gandrathi AK, Pinault D. Rhythmic neuronal activity in S2 somatosensory and insular cortices contribute to the initiation of absence-related spike-and-wave discharges. Epilepsia. 2012; 53:1948–1958. [PubMed: 23083325]

Zhou C, Huang Z, Ding L, Deel ME, Arain FM, Murray CR, et al. Altered cortical GABAA receptor composition, physiology, and endocytosis in a mouse model of a human genetic absence epilepsy syndrome. J. Biol. Chem. 2013; 288:21458–21472. [PubMed: 23744069]

Highlights

- A female prevalence in childhood/adolescence-onset syndromes may disappear in adult-onset syndromes.
- Models of atypical syndromes allow the investigation of mechanisms involved in sex differences.
- Sex hormones act opposite in absence epilepsy and in most convulsive models.
- Changes in the expression of $GABA_AR$ subunits are major determinants of tonic thalamic inhibition.

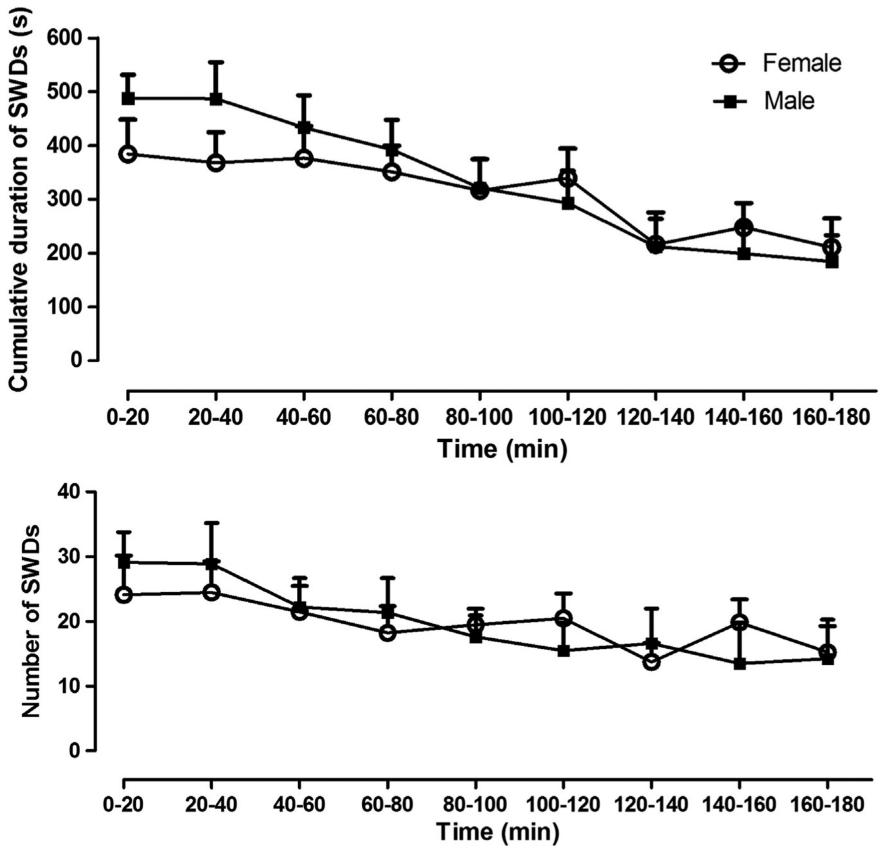

Fig. 1.

The mean of cumulative duration and number of SWDs per 20 min in male and female GAERS as recorded during 3 h (09.00 to 12.00). Data are expressed as mean ± SEM.

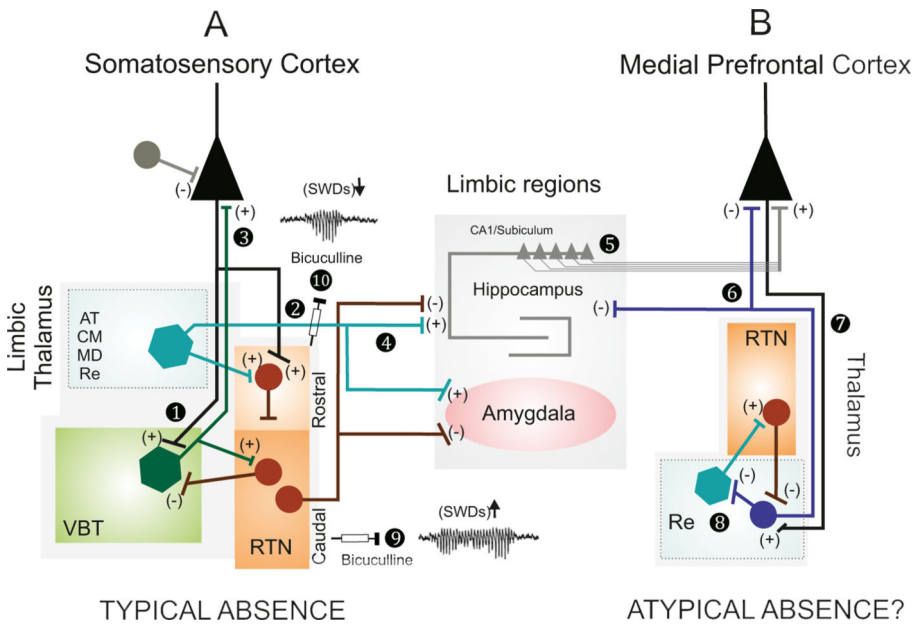

Fig. 2.

A) Schematic representation of the neuronal circuitry of typical absence seizures which includes the well-established involvement of reciprocal connections between layers 5 and 6 of the perioral region of somatosensory cortex (3) where the seizures are initiated (Meeren et al., 2002; Polack et al., 2007), the ventrobasal thalamus (VBT) (1), and the rostral and caudal reticular nucleus of the thalamus (RTN) with opposite functions (2). To this classical circuit the limbic thalamus was added, consisting of the anterior thalamic (AT), centromedian (CM), medial dorsal (MD) and reuniens (Re) nuclei, all of which project to the limbic regions, hippocampus and amygdala, and to the RTN (4). The latter also has its own connections to hippo-campus and amygdala. B) Hypothesized circuitry of atypical absence seizures. The initiating epileptiform event for an atypical absence seizure is postulated to occur in layer 5/6 of the medial prefrontal cortex (mPFC) and then project to the Re of the thalamus (7) which projects back to the mPFC and monosynaptically to the CA1 (6) which in turn projects to the mPFC (5). This reverberating circuit is modulated and driven by reciprocal intrathalamic connections between the Re and rostral RTN (8). In typical absence epilepsy, pharmacological, lesion, and signal analytical studies indicate opposite roles for the rostral and caudal part of the RTN (Aker et al., 2002, 2006; Meeren et al., 2009; Lüttjohann and van Luijtelaar, 2012). To illustrate, administration of bicuculline into the caudal RTN produced increases in the duration of SWDs (9), whereas injections into the rostral RTN produced significant decreases (10). (−) indicates inhibition; (+) indicates excitation.

The figure has been adapted and modified from Onat et al. (2013) with permission from Elsevier.

Table 1

Rodent absence seizure models exhibiting sex-dependent phenotypes.

Species	Model	Sex-dependent phenotype	Reference
Rat	Brown Norway	Males have higher prevalence, more frequent, longer duration and more intense spontaneous SWD than females	Jandó et al. (1995)
Rat	AY9944-treated Long Evans rats	Atypical absence seizures last longer in females than males; sex-difference emerged before puberty	Cortez et al., 2001, Persad et al. (2002)
Rat	Bicuculline-treated Wistar rats	5–6 Hz SWD occurring in 70% males and 100% intact, OVX, OVX + E, females. Intact and OVX + E had lower SWD latency than males	Matejovska et al. (1998)
Mouse	Heterozygous Gabrb3 deletion	With maternally-transmitted Gabrb3 deletions, males had increased spontaneous seizure-like discharges and impaired memory compared with females	Liljelund et al. (2005)
Mouse	Heterozygous Gabra1 deletion	In the C57BL/6J strain, females had reduced gains in body mass and increased SWD than males. Mice tested at P33–37	Arain et al. (2012)

OVX = ovariectomized; OVX + E = ovariectomized + estrogen replacement; SWD = spike wave discharges.

Table 2

Effects of sex hormones on spontaneous occurring SWDs in WAG/Rij rats (model of typical absence epilepsy) and perinatal treated AY9944 Long-Evans rats (atypical model), and in various convulsive seizure models for GTCS.

	Prog acutely administered	At peak concentrations of Prog during ovarian cycle	Prog during pregnancy	Estradiol acutely administered	At peak concentrations of estradiol during ovarian cycle	Estradiol during pregnancy	Testosterone acutely administered
Incidence of seizures in WAG/Rij model	↑ [a]	↑ [a]	↓ [b]	0 [a]	0 [a]	0 [b]	↓ – ↑ [c]
Incidence of seizures in AY9944 model	↑ [d]	↑ [d]	n.a.	↓ [d]	↓ [d]	n.a.	n.a.
Convulsive seizures	↓ [e]	↓ [f]	↓ [g]	↑ [h]	↑ [i]	↓ [g]	↑ [j]

Prog = Progesterone. ↑, preepileptic; ↓, antiepileptic; 0, no effect; n.a., not accessed. Convulsive seizures were determined with PTZ by Seyle (1942), intrahippocampal injected dose of KA, inducing generalized tonic–clonic convulsive seizures by Berzaghi Mda et al. (1987), seizure threshold in the dorsal hippocampus by Terasawa and Timiras (1968), and AD threshold in amygdala kindled rats by Edwards et al. (1999b).

Data from:

[a] van Luijtelaar et al. (2001)

[b] Tolmacheva et al. (2004).

[c] van Luijtelaar et al. (2009a,b).

[d] Persad et al. (2004).

[e] Selye (1942).

[f] Edwards et al. (1999b).

[g] Berzaghi Mda et al. (1987).

[h] Woolley and Schwartzkroin (1998).

[i] Terasawa and Timiras (1968).

[j] Reddy (2004).