Title: Experimental Models of Absence Epilepsy: A Review Article

Running title: Different Animal Models of Absence Seizures

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Abstract

Background: Absence epilepsy is a brief non-convulsive seizure that associated with sudden abrupt in consciousness. Because of the unpredictable occurrence of absence seizures and ethic limitation of human investigation on the pathogenesis and drug assessment led to the tendency to animal models. The aim of this paper is reviewing the advantages and disadvantages of several animal models of non-convulsive induced seizure.

Methods: The articles were published from years of 1990 were assessed. The number of publications used genetic animals was analyzed. In addition, we reviewed possible application methods of each model, clinical types of seizures induced, purposed mechanism of epileptogenesis, validity and attributable to the absence epileptic patients.

Results: The number of studies that used genetic models of absence epilepsy from years of 2000 was noticeably more than pharmacological models. Genetic animal models have a close correlation of electroencephalogram features and epileptic behaviors to the human condition.

Conclusion: The validity of genetic models of absence epilepsy would motivate the researches to focus on genetic modes in their studies. As there are some differences in the pathophysiology of absence epilepsy between animal models and human, to better understand the epileptogenic process and, or discovery of novel therapies for this disorder, development of new animal models is necessary.

Keywords: Epilepsy, Absence, Animal Models, Seizures, Genetic Models
**Introduction**

Absence epilepsy, as a childhood disease, is characterized by generalized epileptic activities in both hemispheres of the brain and accompanied with unconsciousness. Absence epilepsy as a non-convulsive seizure can be classified into typical and atypical forms (Berg et al., 2010; Manning, Richards, & Bowery, 2003; Snead, 1995).

Typical absence seizures are defined behaviorally by a paroxysmal loss of consciousness without aura or postictal mood and accompanied with bilateral synchronous spike and wave discharges (SWDs) about, 3 Hz in the electroencephalogram (EEG). Ordinary, duration of the seizure, persist for, 3-10 seconds (Fig 1A). Misinterpretation with day-dreaming happens in such episodes because they are associated with a fixed and gaze, especially in children (Manning et al., 2003).

Atypical absence seizures are described with complex orofacial automatisms, abnormal neurodevelopmental outcome and cognitive impairment in patients. Such atypical episodes are more frequent and lasted more than typical seizure duration. SWDs frequency is less than 3 Hz. Seizure onset and offset are gradual, and there is minor coordinate between the EEG and behavioral changes. For instance, during seizure episodes children might be able to walk or talk (Manning et al., 2003).

The incidence of absence epilepsy in children up to the age of sixteen years old is about two and eight out of every one hundred thousand children, and with a prevalence of ten percentage of children with any form of epilepsy (Crunelli & Leresche, 2002). Since precise etiology of absence epilepsy is unknown and multiple mechanisms involve in the pathophysiology (Karimzadeh, Mousavi, Alipour, et al., 2017), hopefully, most of our
knowledge about mechanisms and treatment of human absence epilepsy arise from the use of appropriate chemical and genetic animal models. This study was aimed to review the pathophysiology of absence epilepsy as well as different kinds of experimental models. In addition, the validity and similarity of absence epilepsy models have been illustrated.

**Search strategy**

We search the publications in the PUB-MED, Wiley and Google scholar. The keywords of absence epilepsy, absence seizure, animal model, pharmacological animal models, chemical models, and genetic models were used in the title and abstract of articles. The articles were searched between 1990 of years to 2018. To indicate most researchers' focus on the genetic models, the number of publications used genetic animals was analyzed.

**Statistical analysis**

The number of publications was analyzed by one-way analysis of variance (ANOVA) followed by Tukey’s post hoc test in the SPSS 20 software. Significance was established by $p \leq 0.05$. 
Pathogenesis of absence epilepsy

Studies reveal absence epilepsy arises from an aberration of the interplay between some areas of the cortex especially somatosensory cortex and the thalamus. Investigations in human and animal models identified hypersynchronization in the thalamocortical circuit generate SWDs in absence seizure (Avoli, Gloor, Kostopoulos, & Gotman, 1983). In typical absence seizures, Main components of the thalamocortical circuit contribute in the creating SWDs contains the reticular and ventrobasal (medial and, lateral) nuclei of the thalamus and somatosensory perioral region of the somatosensory cortex (H. Meeren, van Luijtelaar, da Silva, & Coenen, 2005). In addition, the channelopathy and imbalance of excitatory and inhibitory receptors in the other thalamocortical neurons such as intrathalamic and dorsal thalamic nuclei are involved in SWDs generation (Karimzadeh, Mousavi, Ghadiri, et al., 2017). In the atypical absence seizure involve both thalamocortical circuit and limbic system (Cortez, McKerlie, & Snead, 2001). Absence epilepsy may be related to several malfunctions in the nerves system. Hyperexcitability of the cortex and hyperfunction of the GABAergic tonus in the thalamus trigger hyperactivity of low-threshold T-type calcium currents activated by hyperpolarization in the thalamus. Naturally, there are reciprocal excitatory glutamatergic and inhibitory GABAergic projections between cortex and thalamus. These neurons can produce both tonics and burst firings in different conditions which are specialized for the flow of information and sleep spindles at the network, but hyperactivation of the GABAergic neurons in the reticular nucleus of the thalamus lead to a burst of synchronized firing and causing inhibitory postsynaptic potentiation in thalamocortical neurons (Fig. 1). Gamma-aminobutyric acid (GABA) induced hyperpolarization especially through GABAB receptors in the specific
relay nuclei and the reticular nuclei of the thalamus and then hyperactivation of the low-voltage-activated T-type calcium currents that create a rebound burst of fast spikes leading to the next cycle of the oscillation (Budde, Pape, Kumar, & Huguenard, 2006; H. K. Meeren, Pijn, Van Luijtelaar, Coenen, & da Silva, 2002; Polack et al., 2007).

**Animal models of absence epilepsy**

The validity of animal models in the experimental studies is identified by three characters including reproducible, predictable and quantifiable. There are several animal models for absence epilepsy such as electrical stimulation, chemical injection and genetic models of Drosophila, mice, rats, baboons, and cats. They should be comparable behaviorally, electroencephalographic, ontogenetic, etiologic and pharmacologically with human absence epileptic disease. These models must indicate SWDs in the EEG as the hallmark of absence epilepsy in human, but there are some differences in some clinical criteria in the animal models that have been shown in table 1. Therefore researchers should select the models based on the aim of the study with considering the limitation of each model (Fisher, 1989; Manning et al., 2003; Pitkänen, Schwartzkroin, & Moshé, 2005).

**Pharmacological animal models of absence epilepsy**

There are several pharmacological compounds to induce acute or chronic absence seizures (Table. 2). Penicillin, Low-dose pentylenetetrazole (L-PTZ), the 4,5,6,7 tetrahydroisoxazolo [4,5,-c] pyridine-3-ol (THIP), and gamma-Hydroxy butyrate (GHB) are most common compounds for induction of typical absence epilepsy as well as AY-9944 (trans-1, 4-bis[2-chloro-benzylamino-ethyl] cyclohexane dihydrochloride) and methylazoxymethanol acetate.

**Chemical models of typical absence epilepsy**

*Penicillin*

Local administration of some antibiotics such as cephalosporin and penicillin onto the cortex or systemically (250000-600000 unit/kg) at high doses can induce a seizure in cats and rodents. Penicillin acts as a GABA agonist (De Deyn, D'Hooge, Marescau, & Pei, 1992; Tang & Loke, 2011) and has limited effect in rodents rather than cats. Because of the unstable penetration of penicillin through the blood-brain barrier, produces multifocal spikes with only occasional bursts of bilaterally synchronous SWDs associated with the deficit of attention. In fact, seizures initiated through parenteral penicillin have minor similarity to clinical absence seizures in rats.

*L-PTZ*

PTZ, a tetrazole derivative, is the most commonly used epileptic induced agent for systemic convulsive epilepsy. PTZ is a GABAA receptor antagonist and interacts with GABAA receptors at the picrotoxine binding site. The extensive use of PTZ in different types of epilepsy is caused by this model as an identifier of anticonvulsants and proconvulsants. The low dose of PTZ (20–30 mg/kg) intraperitoneally (IP) or subcutaneously produce freezing and used to induce absence-like seizures from 3 weeks of age. L-PTZ produces twitching of vibrissae at the frequency (6-7) Hz SWD on the EEG in rodents. Generally, seizure initiates 2-10 min after injection depends on the dose and species. SWDs duration is about 2-3 sec. in rodents (De Deyn et al., 1992; MacDonald & Barker, 1977; Tang & Loke, 2011).
**GHB and g-butyrolactone (GBL) models**

GHB is a GABA metabolic substance that produces naturally in the mammalian brain. Endogenous GHB is in little concentration in different areas of the nervous system. Autoradiographic studies have shown the presence of GHB receptors in the cortex, thalamus, striatum, hypothalamus, substantia nigra and hippocampus. The affinity of GHB for GABAB receptors has been shown especially in the thalamocortical network. Following the IP administration of GHB, electrographic and behavioral events occur similarly to generalized absence seizures in the cats, rats, and monkeys (De Deyn et al., 1992; Pitkänen et al., 2005). Intravenous administration (200mg/kg) of GHB induces absence epileptic attacks in the same frequency of human SWDs (2.5Hz) and clinical symptoms such as head drops, behavioral immobility, pupillary dilation, staring, rhythmic eye movements and, stereotypical automatisms. This model is considered as a valid model because it is predictable, reproducible, and produces electrographic and behavioral symptoms similar to the human condition. In addition, as the kinetics of the GHB is detected well then it is a good model for the study of some drugs with unknown pharmacokinetic features (Cortez & Snead, 2006).

Furthermore, GBL as a pro-drug of GHB increases the reproducibility and predictability of the GHB model of absence seizures. GBL is more common usage because of the consistency and rapidity of onset of its effect (Bearden et al., 1980) and has been shown to produce exactly the same EEG and behavioral effect as that of GHB. The single dose application of GBL generates absence seizures through the activation of the GHB-related neuromodulation or interaction with GABAergic inhibitory and excitatory
neurotransmission in the cortical-thalamocortical circuit (Bearden, Snead III, Healy, & Pegram; Pitkänen et al., 2005).

Administration of GHB (240mM) changes the rhythmicity of EEG in the GHB models. The peak components of GBL rise up 1 minute after GBL injection and fell rapidly to undetectable levels within 5 minutes. GBL-induced SWDs can be quantitated as cumulative duration (in seconds) per 20-min cycle or as a percent of control SWDs duration. This pharmacological rat model is a very appropriate experimental model for the study of the mechanisms of bilaterally synchronous SWDs production and screen for the anti-seizure activity of antiepileptic drugs in generalized absence seizures (Depaulis, Snead, Marescaux, & Vergnes, 1989; Karamahmutoğlu et al., 2013; Tang & Loke, 2011).

**THIP**

THIP, as a GABA agonist, induces bilaterally synchronous SWDs in rats. THIP is a selective GABA agonist for the extra synaptic delta-subunits of GABAA receptors. Delta-subunits of GABAA receptors were found in the thalamus and neocortex abundantly. The optimum dose of THIP to induce bilaterally synchronous SWDs is 5-10 mg/Kg and lasted 7 to 9 seconds. The dose of THIP to elicit SWDs is 7.5mg/kg (IP). The model is quantitated similar to GHB model (Depaulis et al., 1989; Fariello & Golden, 1987; Fisher, 1989; Pitkänen et al., 2005).
Chemical Models of atypical absence epilepsy

**AY-9944**

AY-9944 is a common compound for atypical absence seizure induction. Subcutaneous administration of AY-9944 (7.5 mg/kg), inhibits the reduction of 7-dehydrocholesterol to cholesterol and leads to an abnormal cognitive outcome. It causes seizure onset in the prepubescent and maximum peak in the adult period. Anti-absence drugs decrease these seizures and phenytoin and GABA agonist’s drugs exacerbate them. The AY-treated rat can be used to investigate the pathogenesis and treatment of this malignant disorder (Chan et al., 2004; Cortez, Cunnane, & Snead, 2002; Cortez et al., 2001).

In some atypical absence epilepsy studies antimitotic agent MAM with AY-9944 was used to produce seizures. The MAM-AY Model (Double-Hit Model) rats display bilaterally synchronous SWDs with a frequency of 4 to 6 Hz. The MM-AY-induced atypical absence seizures and ethosuximide, as well as sodium valproate, suppress the induced seizures. The histopathologic assessment showed the MAM-treated rat brains have hippocampal heterotopias, atrophy, and abnormalities of cortical lamination. The MAM-AY-treated rat is a reproducible model for studying refractory atypical absence seizures in children with brain mal-development (Pitkänen et al., 2005; Serbanescu, Cortez, McKerlie, & Snead, 2004).

**Genetic models of absence epilepsy**

During recent decades it has been revealed that genetic factors play a critical role in the idiopathic generalized epilepsies, including absence epilepsy. Some evidence emphasizes the role of genes in the pathogenesis of CAE. It has been reported that monozygotic twins suffered more frequently from CAE than pairs of dizygotic twins (Berkovic, Howell, Hay,
& Hopper, 1994; Marini et al., 2003). Although there are several types of chemical animal models for CAE, genetic models are more valid to research. Spontaneous absence seizures and reproduced symptoms in the genetic models could be considered as the most important advantages compared to chemical models and reliable to clarify the pathophysiology of the human condition.

Some genetically models of rats and mutant mice are currently used in most experiments. There are six mutant mice which are suitable models for absence epilepsy including lethargic, tottering, mocha, stargazer, slow-wave-epilepsy and ducky.

*Genetic mutant mouse models*

Spontaneous mutations in mice, associated with other epilepsy models that, generated by genetic engineering approaches, are very important models to comprehend the pathogenesis of human epilepsies. They were considered as a reproducible biological model for experimental strategies to prevent or reverse the onset of seizures. Spontaneous SWDs have also been observed in mutant mouses, which are usually accompanied by other neurological disorders (Ataxia). A Mendelian basis underlies epileptic phenotype in the most of mice models. Since epileptic mutants mouse is favored models in neurobiology and neuropharmacology for the study of abnormal brain synchronization, but they have pioneer role in the neurogenic analysis of seizure disorders: these models were the key role to figure out the significance of single genes in the hereditary transmission of epilepsy in the mammalian nervous system. Yet there are several absence epileptic mutants mouse (tottering, lethargic, stargazer, mocha, slow-wave-epilepsy and ducky), but their number are restricted by the rate of mutations, feasible dysfunctions (Crunelli & Leresche, 2002; Pitkänen et al., 2005).
**Tottering mouse**

The phenotype of tottering mice includes motor seizures and ataxia (Tokuda et al., 2007). There were no abnormalities in their electroencephalographic (EEG) recordings associated with motor seizures (Tokuda et al., 2007). The mutation in these mice is the tottering locus on chromosome 8 (Campbell & Hess, 1996; Green, 1981). This chromosomal mutation leads to create an abnormal α1A subunit of voltage-gated Ca$^{2+}$ channel. This subunit forms the core of P/Q Ca$^{2+}$ channels and this malformation decrease the Ca$^{2+}$ current (Bourinet et al., 1999). It has been believed that a decrease of the Ca$^{2+}$ current in Purkinje cells has been involved in the pathophysiology of ataxia in (Rhyu, Abbott, Walker, & Sotelo, 1999). Tottering mice are the best model for ataxia.

The manifestation of tottering seizures (behavioral arrest, assuming a fixed staring posture) is the same as CAE in human. The frequency of SWDs in these mice is higher (6-7 Hz) than human and absence seizures are suppressed by anti-absence drugs (Heller, Dichter, & Sidman, 1983; Kaplan, Seyfried, & Glaser, 1979).

**Lethargic mouse**

The lethargic mouse has a spontaneous mutation on chromosome 2 in the gene encoding of the β4 subunit of voltage-gated calcium channels (Frankel, 1999). This subunit is an auxiliary part of voltage-gated calcium channels that regulate Ca$^{2+}$ influx (Burgess, Jones, Meisler, & Noebels, 1997). The phenotype of a lethargic mouse appears after 15 days of age by ataxia and lethargic behavior accompanied to focal motor seizures. Generalized cortical SWDs are the second seizure type which is recorded in their EEG (Pinault et al.,...
The characteristic of their absence seizures is the same as human CAE and tottering absence seizures (Pinault et al., 1998).

There were no structural and pathological changes in the brain and spinal cord but some immunological discrepancies such as splenic and thymic degeneration and lymphocytopenia were seen (Dung, 1977). Interestingly, after two months of age, their immune function and loss of body weight would be recovered but their fertility reduced (Devanagondi, Egami, LeDoux, Hess, & Jinnah, 2007).

**Stargazer mouse**

This mutant was named stargazer because of mutation in stargazing protein (γ2 subunit of T-type or Cav3.1 calcium channel). A single mutation has been occurred in the gene encoding stargazing on mouse chromosome 15 (Letts et al., 1997; J. Noebels, Qiao, Bronson, Spencer, & Davisson, 1990). This protein has a modulatory role in voltage-gated calcium channels (Burgess & Noebels, 1999). In addition, the γ2 subunit is necessary for AMPA (a-amino-3-hydroxy5-methyl-4-isoxazole propionic acid) receptor for synaptic targeting in the ionotropic glutamate receptors (Chen et al., 2000).

An increase of calcium currents in thalamic relay neurons may have a crucial role in absence of seizure initiation in stargazer mice (Snead, 1995). The phenotype of stargazer is similar to the other mutant mice including ataxia, paroxysmal dyskinesia, absence seizure and head tossing (Sharp et al., 2001).

**Mocha mouse**

The characteristic of absence seizures in mocha is the same as a stargazer mouse. The frequency of SWDs is 6-7 Hz and phenotype accompanied to ataxia, tonic-clonic seizures,
pigment dilution, and increased the bleeding time (Sarkisian, 2001). The gene encoding the AP-3δ protein on chromosome 10 has been mutated in these mice (J. L. Noebels, 2003). The AP-3 complex is a heterodimer which regulates lysosomes trafficking and other related organelles (Di Pietro et al., 2006; Kanheti et al., 1998).

**Slow-wave-epilepsy mouse**

SWDs in this mutants appear with a frequency of 3 - 4.5 Hz during absence seizures (Cox et al., 1997). It has been considered as a valid model for absence epilepsy due to seizure phenotype and anti-absence-drug responses (Blumenfeld, 2005). The main mutation underlying SWDs generation in the spike-wave-epilepsy mice has been occurred in the gene encoding the ubiquitous sodium hydrogen exchanger on chromosome 4 (Papale et al., 2009). This exchanger regulates the hemostasis, cell volume and mitogenic responses to growth factors.

These mutants have some extra phenotype as the same as the other mice models for absence epilepsy. Ataxia, tonic-clonic seizures and cerebellum degeneration are some phenotypes that appeared in these mutants beside of absence seizures (Qiao & Noebels, 1993).

**Ducky mouse**

The frequency of SWDs in ducky mice the same as the most of mice model of absence epilepsy is 6 Hz (Barclay et al., 2001). Ataxia, limb dyskinesia and developmental dysgenesis of some brain areas like cerebellum, medulla and spinal cord are some additional phenotypes that exist in these mice. The gene encoding α2 and a δ2 subunit of high-voltage activated Ca^{2+} channels on chromosome 9 has been mutated (Porter et al.,
These channels are extremely permeable to Ca^{2+} in excitable and non-excitable cells and have a critical role in the absence seizures genesis (Zhang, Mori, Burgess, & Noebels, 2002).

**Genetic Rat models of absence epilepsy**

In the mutant mousses models generally, a single gene underlie the epileptic phenotype (SWDs), however, in humans, a polygenetic mode of inheritance occurs then it seems that polygenic rat models are more valid in comparison to other models (Sarkisova & van Luijtelaar, 2011). Genetic absence epileptic rats from Strasbourg (GAERS) and WAG/Rij rats for the first time about 25 years ago represented spontaneous absence seizure attacks. It is believed that a single gene might be responsible to appear absence seizure attacks (Rudolf et al., 2004) but different genes involve in the characteristics of absence seizures and SWDs (Rudolf et al., 2004). Different study with different approaches revealed that these two rats have a similar feature to human absence epilepsy, statistic data showed fabulous information about absence epilepsy that published with use of these two rats (more than 500 articles, see Fig.2).

**GAERS rats**

In France (Strasbourg), a fully inbred strain of rats was derived from an outbred Wistar colony. It is notable that, 100% of animals show the EEG and behavioral characteristics of absence seizures in three-month-old rats. However, the first detectable SWDs appear around 30 days of age. In the first seizures, the SWDs appear rarely and in short duration (1-3 seconds).
During life time the severity of seizures (duration and frequency) increase gradually. The most SWDs occur at around 4 to 6 months. There are not any different in the characteristics of SWDs in the males and females, that represent genetic transmission autosomal (Coenen & Van Luijtelaar, 2003; Crunelli & Lerescue, 2002).

The frequency of SWDs in these rats is 7-10 Hz (Seidenbecher & Pape, 2001). The behavioral manifestation is the same as a typical absence seizure such as loss of cautiousness, and some chewing motion during the seizure. It has not been reported any pathological and structural abnormalities in these rats (Avanzini, Vergnes, Spreafico, & Marescaux, 1993). Anti-Absence drugs are able to suppress seizure attacks. The most important difference of absence seizures in GEARS and human is the higher frequency of SWDs (Avanzini et al., 1993).

It is believed that polygenetic mutation involves in the absence seizures genesis in this rat model (Rudolf et al., 2004). A polygenic mutation on the chromosomes of 4, 7 and 8 seems that regulate the SWDs initiation in the GAERS (Rudolf et al., 2004). Single nucleotide mutation in the gene encoding T-type Ca\textsuperscript{2+} channel has occurred in GAERS. Future studies are necessary to determine the exact chromosomal mutations (Powell et al., 2009).
**WAG/Rij rats**

The WAG/Rij strain is a subline of the WAG strain that was derived from Wistar supply by A. L. Bacharach at the Glaxo Laboratories in London (UK) in 1924. In fact, WAG/Rij is an inbred strain in which brother-sister mating has been carried for more than 130 generations. The behavioral study showed WAG/Rij rats have a short latency to move out from the home cage into familiar and new environments (Coenen & Van Luijtelaar, 2003; Sarkisova & van Luijtelaar, 2011). It is believed most similarity in the cognitive deficits as well as behavioral disturbances have been shown in the WAG/Rij rats to CAE patients (Karson, Utkan, Balci, Aricoglu, & Ates, 2012).

SWDs are emerged at around 60 to 80 days in WAG/Rij (Vergnes et al., 1986; Schridde and van Luijtelaar, 2004). At the age of 3 months, half of the WAG/Rij display fully developed SWDs, and at 6 months of age all of the animals show SWDs and it occurs alternatively until the death of the animals (Pitkanen et al., 2005). SWDs in the WAG/Rij rats are very age dependent. In 6-month-old rats, the number of SWDs is about 16–18 discharges per hour.

Sex differences are very little (Coenen & Van Luijtelaar, 1987). Generally, burst activities last of 1–30 s and a spike-wave frequency of 7–11 Hz in the cortical EEG of adult WAG/Rij rats (Sarkisova & van Luijtelaar, 2011). The behavioral manifestation of seizures (facial myoclonic jerks, eye twitching, and head tilting) is the same as GAERS rats (Sitnikova & Van Luijtelaar, 2007). It is noticeable that besides of high frequency of SWDs, the age of SWDs initiation is different from human. The pharmacological responses to anti-absence drugs in these rats are the same as human (Karimzadeh et al.,...
A polygenetic mutation (chromosome 5 and 9) control the SWDs in these rats (Gauguier et al., 2004).

It seems that channelopathy of slow and fast Ca^{2+} channels has a critical role in the SWDs generation of WAG/Rij rats as well as the other genetic animal models (Gorji, Mittag, Shahabi, Seidenbecher, & Pape, 2011). In addition, some cognitive deficits, as well as pathological changes (neuronal injury and cell death) in several brain areas (hippocampus and neocortex), has been reported in these rats (Jafarian et al., 2015).

**The quantitative comparison of genetic animal models of absence epilepsy**

The articles which used genetic models to study absence epilepsy were counted during 2000 of years to 2018. The number of articles was 293 WAG/Rij, 74 GEARs, 21 stargazers, 19 tottering mice, 7 ducky mice, 3 lethargic, and 3 slow-wave epilepsy. The number of articles which used WAG/Rij rats was significantly more than the others ($p < 0.001$).
Conclusion

Our findings of many diseases have arisen from valid animal models. Although there are several models for the screening, quantification, and evaluation of absence epilepsy but the very important issue is reproducibility of the full clinical syndrome and pathogenesis as well as different etiology of the absence seizures. In this regards, it should be noted how much the existing models are useful for discovering new drugs for 30% medical refractory epilepsy? It seems that current animal models were designed base on the underlying mechanism of seizure, not epileptogenesis. In addition, epilepsy is classified as a chronic disorder and most animal models are not appropriate for long term chronic induction of diseases (Havasimehr, Saffarzadeh, Divanbeigi, & Karimzadeh, 2018). As regards, childhood absence epilepsy has multifactorial genetic etiology; it seems that genetic animal models are more suitable than chemical models, because of the close correlation of EEG features and clinical appearances to the human condition. Among genetic models of mouse and rats, the WAG/Rij and GAERS strains of Wistar rats have asserted to be Valid and predictive models of human absence epilepsy. Although there is some difference in seizure characteristic such as frequency, ontogeny, and the time of seizure developing, the pharmacologic re-activities and the pathogenesis were explained in both strains are very similar to human absence epilepsy. Differences between the two strains could propose the involvement of several genetic mechanisms in the SWDs pathogenesis. Multidisciplinary studies of these two strains, lead to finding trustable information about the role of the cortex and the thalamus, and other subcortical circuits. As statistics show the most published in the absence epilepsy was designed base on the WAG/Rij rats. It should be
mention that pharmacological models such as GHB model are used to assess the mechanisms of receptors in the pathogenesis and new anti-seizure compounds.

As all of these models have some deficits and limitations so researchers should be open mind and enthusiastic to more valid animal models for better understanding of the epileptogenic process and, or discovery of novel therapies for this heterogeneous disorder.

Conflict of interest

The authors declare that there are no conflicts of interest.

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Fig. 1. The cellular and network activity of thalamocortical circuit during absence seizure

During periods of absence seizure activity (like sleep or drowsiness), the neurons are hyperpolarized and show rhythmic burst firing, spreads towards the reticular nucleus and the cortex, the system starts to oscillate in synchrony, which is visible on a large scale EEG as high amplitude and low frequency (3-4 Hz). Under these conditions, the system is incapable of receiving information from the periphery. In wakefulness state, relay neurons receive sensory inputs from the environment and also the brainstem (locus seroluos, raphe Magnus, the reticular nucleus of the pons and hypothalamus nuclei), then project them into 3-5 layers of the somatosensory cortex. After processing it sets a series of nerve branches from the layer 6 neurons of the cortex to relay neurons. Thalamocortical and corticothalamic neurons via excitatory axon collaterals evoke the reticular nucleus of the thalamus. Activation of these neurons leads to thalamic neurons being depolarized and showing tonic single-spike activity. In this state, the conscious perception of our environment appears. (Crunelli & Leresche, 2002; Sejnowski, McCormick, & Steriade, 1998; Steriade, 2005)

Fig. 2. The number of related articles to each genetic models of absence epilepsy since the years of 2000

The bar graphs show the high number of articles that were focused on the WAG/Rij rats to study of absence epilepsy. *** indicates $p < 0.001$.

Table 1. Characteristic of experimental animal models for absence seizures.
Table 2. Special Features of each model. ND: Not significant, CAAS: chronic atypical absence seizure, CRAAS: chronic refractory atypical absence seizures, TAS: typical absence seizures.