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Review article

# Pathophysiology of absence epilepsy: Insights from genetic models

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## HIGHLIGHTS

- Rodent genetic models share many similarities with human absence epilepsy.
- Spike-and-wave discharges are initiated in the primary somatosensory cortex.
- Deep layer pyramidal neurons of somatosensory cortex are ictogenic neurons.
- These pyramidal neurons acquire their ictogenic properties during cortical maturation.

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## ABSTRACT

Absence Epilepsy (AE) is a prototypic epileptic syndrome that develops during brain maturation but cannot be fully explored in human patients. Genetic animal models, especially rats with spike-and-wave discharges recorded on the electroencephalogram, the hallmark of absence seizures, offer strong face validity with the human pathology that allows precise exploration of the pathophysiology of this form of epilepsy. Using an array of different methods, recent studies have demonstrated that spike-and-wave discharges are initiated in the primary somatosensory cortex and then rapidly propagate to motor cortices and thalamic nuclei. More specifically, *in vivo* electrophysiological intracellular recordings showed that the pyramidal neurons of the deep layers of this cortex exhibit fast activation, hyperexcitability and hypersynchronizing characteristics in favor of their role as ictogenic neurons in absence seizures. Furthermore, longitudinal studies during brain maturation suggest the progressive development of these features. Exploration of the different key players in the maturation of the primary somatosensory cortex should determine the anomalies that lead to the development of the cortical generator of absence seizures.



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## 1. Introduction

Absence Epilepsy (AE) is a particular epileptic syndrome characterized by generalized non-convulsive seizures concomitant with a cessation of activity and associated with a transient alteration of consciousness. These absence seizures are often accompanied in human patients by mild automatisms or moderate tonic or clonic components affecting the limbs, eyeballs or eyelids [1]. Typical absences seizures are associated with bilateral, synchronous and regular 3-Hz spike-and-wave discharges (SWDs) on the electroencephalogram (EEG; Fig. 1), which start and end abruptly without postictal depression. These seizures first occur around the age of 5–7 years and then regularly during quiet wakefulness, inattention and at transitions between sleep and awakening. They generally last less than 10–20 s but may occur frequently in some patients. The pharmacological sensitivity of absence seizures is quite unique: they are suppressed by ethosuximide, which is ineffective in most other forms of epilepsy [2], but also by some large-spectrum antiepileptic drugs (*e.g.*, valproate and, to a lesser efficacy, lamotrigine) [3,4]. By contrast, they are aggravated by carbamazepine and phenytoin that are rather effective against generalized convulsive and partial seizures [1]. Beside absence seizures, cognitive and affective comorbidities have been described but no other neurological disorders are associated [5]. In typical childhood absence epilepsy, remission is observed during adolescence in about 70% of the patients.

## 2. Animal models of absence epilepsy

Understanding the pathophysiology of AE is critical to improve our general understanding of generalized idiopathic epilepsy as well as the concomitant lack of responsiveness during generalized seizures. Indeed, AE is often considered as a prototypic form of generalized epilepsy with many EEG and behavioral features that are shared with other forms of epilepsy. However, studying AE in the clinic is rarely a priority due to the young age of most patients, the fact that it is well controled by current antiepileptic drugs and its remission in most cases. Therefore, our current mechanistic knowledge on AE has been mainly collected from experiments performed in animal models and more specifically, genetic models in mice and rats (see [6] for a recent review). However, the possibility for some patients to develop more severe phenotypes (*e.g.,* cognitive deficits, no remission) and the need to better understand the mechanisms of associated brain functions *(e.g.,* consciousness) make the study of AE quite relevant. Because they are genetic, these models offer the unique opportunity to study individuals with a natural history close to clinical situations and therefore provide ideal conditions to understand the pathophysiology of human AE and its evolution throughout life. Different genetic models have been described in mice and rats based on EEG recordings demonstrating the occurrence of spontaneous SWDs associated with behavioural arrest. Three main features confer to these models a considerable value to the understanding of AE: (i) the possibility to record SWDs regularly, over a life-time period, in either freely moving or immobilized animals; (ii) the comparison of data between epileptic and non-epileptic lines and, (iii) the possibility to explore epileptic animals before the onset of seizures. This is in particular the case in the two rat models which have been described and mostly studied, the WAG/*Rij* [7,8] and the GAERS rats [9,10]. Mice models in which monogenic mutations have been described are also commonly used to understand the pathophysiology of AE, although electrophysiological methods have been less often used in these species (see [6] for a recent review).

In all genetic models of AE, animals exhibit bilateral and synchronized SWDs that start and end abruptly on a desynchronized background activity when EEG is performed over the parietal and frontal cortices [6] (Fig. 1). As in human patients, there is no postictal depression. In these models, whatever the species, SWDs have a frequency between 5 and 9 Hz and a duration of 1 s to 60 s. Their recurrence can be very variable from 1 to 260 SWDs/h depending on the model, the age of the animals and test conditions. In some models (*e.g.,* GAERS, WAG/*Rij*, Stargazer), the spike frequency is higher at the beginning of SWDs (up to 11 Hz in rat models) whereas a frequency of about 7–9 Hz is generally observed, a few seconds after the beginning of the SWDs [9,11–15]. This may reflect the dynamics in fire pattern of neurons underlying SWDs and suggests that different circuits may be rapidly recruited within the first few seconds of SWDs.

SWDs are always associated with an interruption of the animals' activity often called "behavioural arrest" [7,9,15–17]. Rhythmic twitching of the vibrissae and/or jaw muscles in both mice and rats are also often observed. In both GAERS and WAG/*Rij*, EMG measures showed that neck muscle tone is diminished during the course SWDs and resumes at the end [7,9,12,18]. In some animals, light chewing with occasional tongue protrusions can sometimes be also observed [10]. Disconnection with the environment during SWDs, one of the key features of AE, was addressed in both GAERS and WAG/*Rij* rats by training rats to press on a lever to obtain food reward or using a positively motivated discrimination test [19]. During SWDs, animals interrupted their pressings and resumed them upon cessation of the seizures. Other data indicated that WAG/*Rij* do not evaluate correctly the time that has passed during SWD, in line with clinical data in children with AE [20,21].

## 3. The somatosensory cortex as a brain region of SWD initiation

Although absence seizures are still classified as 'generalized seizures' in the clinic [22], EEG [23–26] and magnetoencephalographic [27] investigations in young AE patients have shown that the onset of brain paroxysms is often associated with early activation of discrete, often unilateral, frontal or orbital cortical areas. These findings have led to the hypothesis that absence seizures are not truly 'generalized', with immediate and global cortical involvement, but are rather initiated from specific cortical networks and then propagate [25]. Children with typical AE have

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