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Invited review

The genetic absence epilepsy rat from Strasbourg as a model to decipher the neuronal and network mechanisms of generalized idiopathic epilepsies

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HIGHLIGHTS

- We review several years of data on a genetic model of absence epilepsy in the rat.
- This model recapitulates many features of absence epilepsy and is quite predictive.
- It allows to record intracellular neuronal activity during spontaneous seizures.
- Multimodal methods showed that seizures are initiated in the somatosensory cortex.
- Neurons in the cortical deep layer appear to initiate spike and waves.
- This model allows to test new therapeutic strategies for idiopathic epilepsies.

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ABSTRACT

First characterized in 1982, the genetic absence epilepsy rat from Strasbourg (GAERS) has emerged as an animal model highly reminiscent of a specific form of idiopathic generalized epilepsy. Both its electrophysiological (spike-and-wave discharges) and behavioral (behavioral arrest) features fit well with those observed in human patients with typical absence epilepsy and required by clinicians for diagnostic purposes. In addition, its sensitivity to antiepileptic drugs closely matches what has been described in the clinic, making this model one of the most predictive. Here, we report how the GAERS, thanks to its spontaneous, highly recurrent and easily recognizable seizures on electroencephalographic recordings, allows to address several key-questions about the pathophysiology and genetics of absence epilepsy. In particular, it offers the unique possibility to explore simultaneously the neural circuits involved in the generation of seizures at different levels of integration, using multiscale methodologies, from intracellular recording to functional magnetic resonance imaging. In addition, it has recently allowed to perform proofs of concept for innovative therapeutic strategies such as responsive deep brain stimulation or synchrotron-generated irradiation based radiosurgery.

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1. Introduction

Genetic animal models offer the possibility to study individuals that have a natural history close to the clinical conditions and therefore provide robust conditions to understand the pathophysiology of human diseases and their evolution throughout life. In the case of epilepsy, genetic models offer a similar ontogeny and regular occurrence of spontaneous seizures that constitute a preparation of choice and are strongly recommended by the ILAE task force on animal models of epilepsy (Simonato et al., 2014). Because most idiopathic epilepsies mainly affect children and teenagers, invasive study of their pathophysiological mechanisms cannot be conducted in the clinic for ethical reasons. Therefore, animal models are mandatory to understand these forms of epilepsy and the mechanisms underlying the generation and control of seizures. Absence epilepsy represents a prototypical form of childhood idiopathic epilepsy and different models displaying the electrical, behavioral and pharmacological characteristics of absence seizures have been developed in various species, including rodents, cats or primates by injection of pentylenetetrazol, penicillin, gamma-hydroxybutyrate or GABA agonists (see Snead, this volume). However, although these models have contributed to our understanding of absence seizure generation, the lack of recurrence and the forced induction of seizures in these preparations severely limited the study of the development of the disease, i.e., epileptogenesis. In 1982, we first reported the existence of Wistar rats with spontaneous absence seizures (Vergnes et al., 1982) and rapidly developed the *Genetic Absence Epilepsy Rats from Strasbourg* or GAERS, as well as a control strain. Since then, this model has been used in many studies to understand the pathophysiology of absence epilepsy and is one of the most predictive model for generalized idiopathic epilepsy. Here, we review the principal advantages of this model and present how the use of recent methodologies has allowed to better understand the genetic, cellular, network and molecular mechanisms of absence epilepsy and to develop innovative therapies. In this review a special focus is put on the methods applied to study the GAERS model.

2. What does GAERS model?

Absence epilepsy is a particular epileptic syndrome where the patients show generalized non convulsive seizures characterized by a transient alteration of consciousness evidenced by a loss of responsiveness to environmental stimuli concomitant with a cessation of activity. This may be accompanied by automatisms or moderate tonic or clonic components affecting the limbs, the eyeballs or the eyelids (Panayiotopoulos, 1999). Typical absences seizures are associated on the electroencephalogram (EEG) with bilateral, synchronous and regular 3 c/s spike-and-wave discharges (SWD) which start and end abruptly. In contrast to generalized convulsive or partial seizures, there is no postictal depression or slowing following typical absences. Absence seizures generally last 10–20 s and can occur frequently in some patients, as several hundred times per day, mainly during quiet wakefulness, inattention and at transitions between sleep and awakening. The pharmacological sensitivity of absence seizures is also specific: they are suppressed by several large-spectrum antiepileptic drugs (e.g., valproate, lamotrigine, levetiracetam) but also ethosuximide, which is ineffective in all other forms of seizures. By contrast they are aggravated by carbamazepine and phenytoine that are quite effective against generalized convulsive and partial seizures (Panayiotopoulos, 1999). Absence seizures are found in five non lesional idiopathic generalized epileptic syndromes (Porter, 1993): childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy, myoclonic absence epilepsy and eyelid myoclonia with absences. Beside absence seizures, these patients do not present any other neurological or neuropsychological disorders. In childhood absence epilepsy, remission is observed during adolescence in about 70% of the patients.

2.1. The development of GAERS and its control strain

More than 30 years ago, we reported in Strasbourg the spontaneous occurrence of SWDs evocative of absence seizures following cortical local field potential (LFP) recordings (Vergnes et al., 1982). Breeding of selected pairs of rats displaying such pattern over 3–4 generations led us to obtain a strain with 100% of rats with SWDs. In parallel, we also bred rats from the same outbred Wistar colony in Strasbourg that were free of SWDs and over 5–6 generations we obtained the Non-Epileptic Control (NEC) strain where none of the animals display any seizures (Marescaux et al., 1992a). Both inbred strains have been maintained in Strasbourg and, since 2003, in Grenoble, as well as in Paris, Melbourne, Istanbul and Cardiff (Powell et al., 2014). The GAERS model shares a lot of similarities with another genetic model of absence epilepsy in the rat, the WAG/Rij which was inbred in the United Kingdom, then kept in Rijswijk and later at Nijmegen (The Netherlands) (Depaulis and van Luijtelaar, 2005). However, the number, cumulative total duration and mean duration of SWDs were significantly higher in GAERS compared to WAG/Rij, while the discharge frequency was higher in