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Acute and chronic pharmacological models of generalized absence seizures

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ABSTRACT

This article reviews the contribution of pharmacologically induced acute and chronic animal models to our understanding of epilepsies featuring non-convulsive generalized seizures, the typical and atypical absence seizures. Typical absences comprise about 5% of all epilepsies regardless of age and the atypical ones are even more common. Although absence epilepsy was thought to be relatively benign, children with childhood epilepsy (CAE) turn out to have a high rate of pretreatment attention deficits that persist despite seizure freedom. The phenomenon of the absence seizure has long attracted research interest because of the clear temporal relationship of the conspicuous EEG rhythm of 3 Hz generalized spike and wave discharges (GSWD) and the parallel transient "loss of consciousness" characterizing these seizures which is time-locked with the GSWD. Indeed, clinical epileptologists, basic scientists and neurophysiologists have long recognized in GSWD a unique electrographic and behavioral marker of the genetic predisposition to most types of epilepsy. Interestingly, the subject is still controversial since it has recently been proposed that both classification terms of CAE currently in use: idiopathic and primary generalized, be abandoned – a point of debate. Both issues – underlying mechanisms and focal origin of absence seizures – may be further enlightened by observations in valid animal models.

Contents

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1. Introduction

The multifactorial and compounding causes of epilepsies expectedly result in their multimodal and dynamic expression and differing treatments, natural histories, and outcomes (NCGC, 2012). The prevalence of generalized seizure types is very high and in some countries it is estimated as clearly the highest, i.e. in China it is 3.12% compared to 0.57% of partial seizure types (Gu et al., 2013). Furthermore this vast seizure type, recently redefined simply as seizures occurring in and rapidly engaging bilaterally distributed networks (Berg et al., 2010; see also Panayiotopoulos, 2012; Korff and Scheffer, 2013) is a very diverse group including convulsive seizures (myoclonic, clonic, tonic, tonic–clonic) as well as non-convulsive seizures (typical and atypical absences). Consequently, the experimental animal models used to investigate the generalized seizures ought to be equally versatile in order to recapitulate and elucidate as best as possible the human condition, i.e. the semiology, abnormal electrographic discharges, medical refractoriness. Where possible, the animal models should reflect the known underlying neuroanatomical, biochemical and genetic factors that underpin the seizures being modeled.

As early as the 4th century BC, Hippocrates made the first proposal of trying to explain epilepsy through experimentation in animal models (suspecting as a culprit some fluid in the brain of the epileptic goat, Temkin, 1945). The fundamentally shared propensity of animals for developing seizures was next appreciated in 1869 when John Hughlings Jackson called for greater attention to spontaneously arising seizures in dogs. Jackson's colleague David Ferrier demonstrated that direct electrical stimulation of cortex in several mammals generated clonic seizure events that resembled human epilepsy (Grone and Baraban, 2015). Experimentation with chemical convulsants began soon thereafter (Wiedeman, 1877). Some of these convulsants, like absinth and strychnine, have long since been abandoned, and others, like penicillin, are being gradually replaced and only few, like pentylenetetrazole remain as widely used models today. Recently developed models of pharmacologically induced seizures tend to exploit the accumulated knowledge on neurotransmitter systems, like GABA (Cortez and Snead, 2006). The subject of animal models of seizures has been extensively reviewed (Pitkänen et al., 2006; Kandratavicius et al., 2014; Barker-Haliski et al., 2015; Löscher, 2011; Simonato et al., 2014; Dedeurwaerdere et al., 2014; McCandless, 2012).

This article reviews the contribution of pharmacologically induced acute and chronic animal models to our understanding of epilepsies featuring non-convulsive generalized seizures, the typical and atypical absence seizures. Typical absences comprise about 5% of all epilepsies regardless of age and the atypical ones are even more common (Panayiotopoulos, 2010) Although absence epilepsy was thought to be relatively benign, children with CAE turn out to have a high rate of pretreatment attention deficits that persist despite seizure freedom (Masur et al., 2013). The phenomenon of the absence seizure has long attracted research interest because of the clear temporal relationship of the conspicuous EEG rhythm of 3 Hz generalized spike and wave discharges (GSWD) and the parallel transient "loss of consciousness" characterizing these seizures which is time-locked with the GSWD. Indeed, clinical epileptologists have long recognized in GSWD a unique electrographic and behavioral marker of the genetic predisposition to most types of epilepsy (Metrakos and Metrakos, 1966; Avoli et al., 1990). Interestingly, the subject is still controversial since it has recently been proposed that both classification terms of CAE currently in use: idiopathic and primary generalized, be abandoned – a point of debate (Berg et al., 2010; Panayiotopoulos, 2012; Korff and Scheffer, 2013). Both issues – underlying mechanisms and focal origin of absence seizures (Tenney et al., 2013) – may be further enlightened by observations in valid animal models.

2. Absence seizures

Typical generalized absence seizures in human are characterized by paroxysmal episodes of loss of consciousness that are time-locked in their abrupt onset and offset with that of bilaterally synchronous 3 Hz GSWD as recorded on the electroencephalogram (EEG). Absence seizures typically occur in children between the ages of 4 years and adolescence and they are usually responsive to ethosuximide, valproic acid, or benzodiazepines. Absence seizures are made worse by phenytoin, barbiturates, or carbamazepine (Onat et al., 2013). Ethosuximide has recently been shown in a Class 1 study to be the drug of choice against absence seizures (Glauser et al., 2010).

Atypical generalized absence seizures share the same anticonvulsant drug pharmacology as typical absence seizures, but differ in semiology, associated EEG abnormalities, severity, refractoriness to medical therapy, co-morbid cognitive impairment, and an association with the catastrophic pediatric epilepsy syndrome of Lennox Gastaut (Nolan et al., 2004; Markand, 2003; Table 1). In the respective experimental models these differences between typical and atypical absence seizures appear to be circuitry dependent. While both involve thalamocortical circuitry, they each engage different neuronal networks within that circuitry (Perez Velazquez et al., 2007; Wu et al., 2007; Wang et al., 2009; Onat et al., 2013) (Fig. 1).

In order to understand the fundamental cellular and molecular mechanisms operative in the causation of the epilepsies and to develop novel therapeutic targets for antiepileptic drugs, a number of genetic and pharmacological animal models have been developed (Guillemain et al., 2012; Kandratavicius et al., 2014; Mareš et al., 2012). While animal models have many limitations, animal models of absence epilepsy and absence seizures have been instrumental in elucidating much of what we know about the circuitry and molecular mechanisms of absence epilepsy (Huguenard and McCormick, 2007; Cope et al., 2009a; Crunelli et al., 2011; Paz et al., 2011) and are predictive of anticonvulsant drug efficacy against absence (Guillemain et al., 2012).

The criteria for animal models of typical absence seizures are well established (Snead, 2002; Tables 1 and 2). The unique features of these models represent the circuitry involved and the mechanisms of absence. The novelty of the circuitry and

Table 1
Comparison of features of typical and atypical absence seizures in rodent models and human.

	Rat/mouse		Human	
	(Typical)	(Atypical)	(Typical)	(Atypical)
EEG				
Bilaterally synchronous GSWD	+	+	+	+
GSWD frequency[a]	7–11 Hz	4–6 Hz	2.5–4 Hz	1.5–3 Hz
GSWD from thalamus & cortex	+	+	+	+
GSSWD from hippocampus[a]	–	+	–	+
Ictal behavior				
Staring; myoclonus	+	+	+	+
Move during GSSWD[a]	–	+	–	+
Precise EEG/behavioral correlation[a]	+	–	+	–
Pharmacology				
Blocked by ETO, VPA, TMD	+	+	+	+
Exacerbated by $GABA_{A\&B}R$ agonists	+	+	+	+
Blocked by $GABA_BR$ antagonists	+	+	No data	
Severe cognitive disability[a]	–	+	–	+

[a] Characteristics that separate atypical absence seizures from typical absence seizures. ETO, ethosuximide; VPA, valproic acid; TMD, trimethadione; GSWD, generalized spike-and-wave discharge; GSSWD, generalized slow spike-and-wave discharge; $GABA_BR1bR2$, transgenic hybrid mouse is a mutant mouse over expressing $GABA_B$ receptor subunits R1b and R2 in forebrain neurons; GAERS, Genetic Absence Epilepsy Rats from Strasbourg (with permission from Onat et al., 2013).