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REVIEW

Thalamo-cortical mechanisms of sleep spindles and spike—wave discharges in rat model of absence epilepsy (a review)

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Summary According to the most generally accepted cortico-reticular theory of absence epilepsy, sleep spindles and spike—wave discharges (SWD, characteristic hallmarks of absence epilepsy) are closely related. The present review critically evaluates this theory based on the original data obtained in WAG/Rij rat model of absence epilepsy. It is demonstrated that (1) sleep spindles and spike—wave discharges are distinguished in time—frequency domain. (2) EEG waveforms of sleep spindles and SWD are underlain by different synaptic processes, as determined with the aid of computational neuronal model of cortical field potentials. (3) Sleep spindles do not precede SWD. EEG analysis of SWD-precursor activity provides us with a clue to possible prediction of absence epilepsy episodes. Furthermore, by studying Granger causality and EEG coherence at the onset of SWD we gain more insight into the dynamics of the thalamo-cortical neuronal network associations that underlie occurrence of absence seizures. In general, spindle activity and SWD display different time—frequency characteristics as measured in cortex and thalamus, they are accompanied by different neuronal processes and require different involvement of neurotransmitters. Sleep spindles and SWD are considered as autonomous EEG phenomena, and straightforward relationship between them is doubtful.

Contents

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Introduction

Rodents with genetic predisposition to absence epilepsy, such as Genetic Absence Epilepsy Rats from Strasbourg (GAERS) and Wistar Albino Glaxo from Rijswijk (WAG/Rij), have contributed greatly to the understanding of pathophysiology and neuronal mechanisms of human epilepsy (Danober et al., 1998; Coenen and van Luijtelaar, 2003; Depaulis and van Luijtelaar, 2005; van Luijtelaar and Sitnikova, 2006). In all individuals of these rat strains, absence seizures appear spontaneously and accompanied by characteristic spike—wave discharges (SWD) in electroencephalogram (EEG). Behavioral expression of SWD in rats is similar to the clinical manifestation of absence seizures in humans, e.g., immobility, minimal facial myoclonic jerks and twitches (van Luijtelaar and Coenen, 1986; Marescaux et al., 1992). WAG/Rij rat model enables predictions about pharmacotherapy of epileptic patients (i.e., this model fulfills to a criteria of predictive validity) and it is based on theoretical grounds (construct validity), therefore this strain is considered as a valid model of human absence epilepsy (Coenen and van Luijtelaar, 2003).

In the late sixties of the last century, basic mechanisms of generalized epilepsy were extensively studied in feline generalized penicillin epilepsy (Prince and Farrell, 1969, see also, Time—frequency EEG analysis, section for details). Based on experimental data obtained in this model, Gloor and his co-workers introduced a '*cortico-reticular*' theory, which claims that sleep-related natural oscillations can give rise to absence-related SWD (Gloor, 1968, 1969). Further investigations in other animal models have confirmed that sleep spindles and SWD share many common features. It is known that sleep spindles are characteristic EEG hallmarks of sleep stages I—II. Similar to sleep spindles, SWD preferentially occur during drowsiness and light slow-wave sleep (van Luijtelaar and Coenen, 1986; Drinkenburg et al., 1991). Both oscillations are produced in thalamo-cortical neuronal network, which is formed by the neocortex, the specific thalamic and the reticular thalamic nuclei (Steriade and Deschenes, 1984; Steriade et al., 1993; Steriade, 2003; Avanzini et al., 1996; Kostopoulos, 2000; Destexhe and Sejnowski, 2001). Notwithstanding is that sleep spindles are initiated in the thalamus (Steriade and Deschenes, 1984; Steriade et al., 1993; Steriade, 2003), but SWD are triggered by the cortex (Niedermeyer, 1996; Polack et al., 2007),[1] rapidly distributed over the other structures throughout intracortical (ipsilateral and callosal) and descending projections and quickly became generalized (Steriade and Amzica, 1994; Lemieux and Blume, 1986; Sitnikova and van Luijtelaar, 2006). Cortex certainly plays a primary role in the pathogenesis of absence seizures, yet thalamic neurons are also implicated in this process (e.g., Avanzini et al., 1992, 2000; Blumenfeld, 2002; Buzsáki et al., 1988; Buzsáki, 1991). Functional aspects of cortico-thalamic interactions that underlie development of sleep spindle oscillations and SWD are still not fully understood.

The current paper consists of four parts. The first part critically evaluates the cortico-reticular theory of absence epilepsy (Gloor, 1968, 1969) in respect to the relationship between sleep spindles and SWD. The second summarizes results of time—frequency analysis of sleep spindles and SWD. The third part describes neuronal processes underlying occurrence of sleep spindles and SWD that had been retrieved from cortical neuronal model. The fourth part considers EEG features of SWD-precursor activity as recorded in the cortex and in the thalamus and evaluates dynamics of cortico-thalamo-cortical associations at seizure onset.

Relationship between sleep spindles and spike—wave discharges

According to the 'cortico-reticular' theory, '*SWD develops in the same circuit, which normally generate sleep spindles, by an initially cortical transformation of one every two or more spindle waves to a 'spike' component of SWD, while the next spindle wave or waves are eliminated and replaced by a slow negative wave*' (cited by Kostopoulos, 2000).

'*Cortico-reticular*' theory has gained support from the data obtained *in vivo* and *in vitro* in genetic rat models of absence epilepsy (Avanzini et al., 1992, 1993, 2000; Blumenfeld, 2002; Drinkenburg et al., 1993; Kandel and Buzsaki, 1997; van Luijtelaar, 1997). In WAG/Rij rats, it was shown that both sleep spindles and SWD preferably occur during low vigilance states such as drowsiness, light slow-wave sleep, passive wakefulness (Drinkenburg et al., 1991), and characterized by similar EEG characteristics (Drinkenburg et al., 1993). Also distribution of extracellular currents throughout the cortical depth during sleep spindles and during spike—wave discharges[2] is known to be the same[3] (Kandel and Buzsaki, 1997).

More recent studies in WAG/Rij rats cast some doubts as to the probability that SWD derive form spindle oscillations and, therefore, '*cortico-reticular*' theory has been challenged. In particular, it was found that absence seizures are triggered by local area in the somatosensory cortex

[1] More specifically, in WAG/Rij rats SWD are triggered by the local area of perioral projections in the somatosensory cortex (Meeren et al., 2002, 2005).

[2] The authors used the term 'high voltage spindles' (HVS) for what we call SWD.

[3] It follows from the analysis of simultaneous EEG and unit recordings in WAG/Rij rats.