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Research Report

The role of perioral afferentation in the occurrence of spike-wave discharges in the WAG/Rij model of absence epilepsy

K.R. Abbasova[a,*], S.A. Chepurnov[a], N.E. Chepurnova[a], G. van Luijtelaar[b]

[a]Department of Human & Animal Physiology, Lomonosov Moscow State University, Moscow, Russia
[b]Department of Biological Psychology, Donders Institute for Cognition, Brain and Behavior, Radboud Nijmegen University, Nijmegen, The Netherlands

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ABSTRACT

According to the focal cortical theory of absence epilepsy, spike-and-wave discharges (SWDs) have a cortical focal origin in the perioral region of the somatosensory cortex in rats. In the present study the role of peripheral afferents of the perioral (snout) region in the occurrence of spontaneous SWDs was investigated in the WAG/Rij (Wistar Albino Glaxo from Rijswijk) rat model of absence epilepsy in order to examine whether an input from peripheral sources is imperative for the occurrence of SWDs. Twelve male WAG/Rij rats were chronically equipped with cortical EEG electrodes. Peripheral afferents of the perioral region of the snout *nervus trigeminus* were pharmacologically blocked with a local injection of 2% Novocain, a blockade of *nervus facialis* and saline injections were used as controls. ECoGs were recorded before and after bilateral injection of the drug. Blockade of the *n. trigeminus* decreased the incidence and duration of SWD, while similar injections with Novocain near the *n. facialis* had no effect. Injections with saline were also not effective. Our data demonstrate that intact peripheral afferent input may be primarily involved in the initiation of SWDs. It suggests that the cortico-thalamo-cortical circuits need the peripheral stimulations from the snout and vibrissae for an initiation of the spontaneous SWDs.

1. Introduction

Many brain regions and their interconnections are critically involved in the generation of spike-wave discharges (SWDs) typical for absence seizures (Blumenfeld, 2005; Depaulis and van Luijtelaar, 2006). Lesions of the lateral thalamus including the specific relay nuclei of the ventro-basal complex and reticular nucleus of the thalamus (RTN), and also highly selective lesions in the rostral pole of the RTN (Berdiev et al., 2007; Berdiev and van Luijtelaar, 2009) are known to suppress SWD in genetic rodent models (Buzsaki et al., 1988; Avanzini et al., 1992; Meeren et al., 2009). Outcomes of thalamic EEGs and unit recordings confirmed the involvement of the thalamus in the occurrence of SWDs (Inoue et al., 1993; Seidenbecher et al., 1998; Sitnikova and van Luijtelaar, 2007). A specific role of the somatosensory cortex and in particular the perioral region of the S1 in the initiation of SWDs was described (Meeren et al., 2002). A functional inactivation of

* *Corresponding author*. Lomonosov Moscow State University, Vorobjovy Gory, d.1, k. 12, Biological Faculty, Department of Human & Animal Physiology, Moscow 119899, Russia. Fax: +7 495 9392895.
E-mail address: akenul@gmail.com (K.R. Abbasova).

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the whole cortex (spreading depression) or a local inactivation with lidocaine of the perioral zone of the somatosensory cortex suppresses SWDs in cortex and thalamus (Vergnes and Marescaux, 1992; Sitnikova and van Luijtelaar, 2004). Combined intracellular and local field potentials in genetic absence epileptic rats from Strasbourg, (GAERS, another well validated model for absence seizures), have confirmed and extended the results: it seems that cortical layer VI contains cells that are hyperexcitable (Polack et al., 2007, 2009). These studies demonstrate that an intact cortico-thalamo-cortical circuitry is a necessary condition for the occurrence of SWDs and that SWDs in genetic rodent models might have an origin in the deep cortical layers of the perioral region of the S1.

The critical area for the initiation of the SWDs, the perioral projection in the S1, is the terminal station of the corticopetal lemniscal pathway, which arises from the principal trigeminal nucleus (PrV) and it transits through the ventral lateral part of the posterior medial nucleus (VPM) of the thalamus (Chiaia et al., 1991; Pierret et al., 2000). The VPM contains relay cells: anterograde tracer injections showed that it receives input from the brainstem trigeminal complex and that it projects to the S1 (Pierret et al., 2000). These forward projections are matched by feedback projections to the corresponding afferent thalamic nucleus (Jones, 1985) which closes the circuit. In addition, the ascending corticopetal and descending cortico-thalamic pathways give collaterals to the RTN which inhibit the VPM during drowsiness, non-REM sleep, and absence seizures. However, one may wonder where the cortical trigger (Meeren et al., 2002) or another decisive event for the initiation SWDs in the cortical region is coming from.

An experiment was performed in which the afferents from the snout that project to the somatosensory cortex, were temporary blocked in order to investigate whether peripheral input is imperative for the occurrence of SWDs. Novocain, a local anesthetic and a sodium channel blocker, and saline were injected subcutaneously on both sides of the snout near the *n. trigeminus* under the foramen infraorbitalis, other control conditions were bilateral novocain and saline injections near the *n. facialis*.

Experiments were carried out in WAG/Rij rats, one of the well described genetic models for non-convulsive genetically controlled absence epilepsy (van Luijtelaar and Coenen, 1986; Coenen and van Luijtelaar, 2003).

2. Results

The effect of Novocain on number and duration of SWDs after the injections near the *n. trigeminus* and *n. facialis* is presented in Fig. 1.

There were no differences in the number of SWDs between the four conditions before injections. In contrast, the three-way ANOVA on the number of SWDs obtained after the injection showed a significant main effect for Novocain: it reduced the number of SWDs ($F=314.7$, df1,10, $p<.0001$, eta .91), it mattered whether the trigeminus or facialis was affected ($F=394.9$, df 1,10, $p<.0001$, eta .89); the number was lower after injection near the *n. trigeminus*, and also a large interaction effect between nerve and drug ($F=297.4$, df 1,10, $p<.0001$, eta >.9). The latter outcomes suggest that Novocain

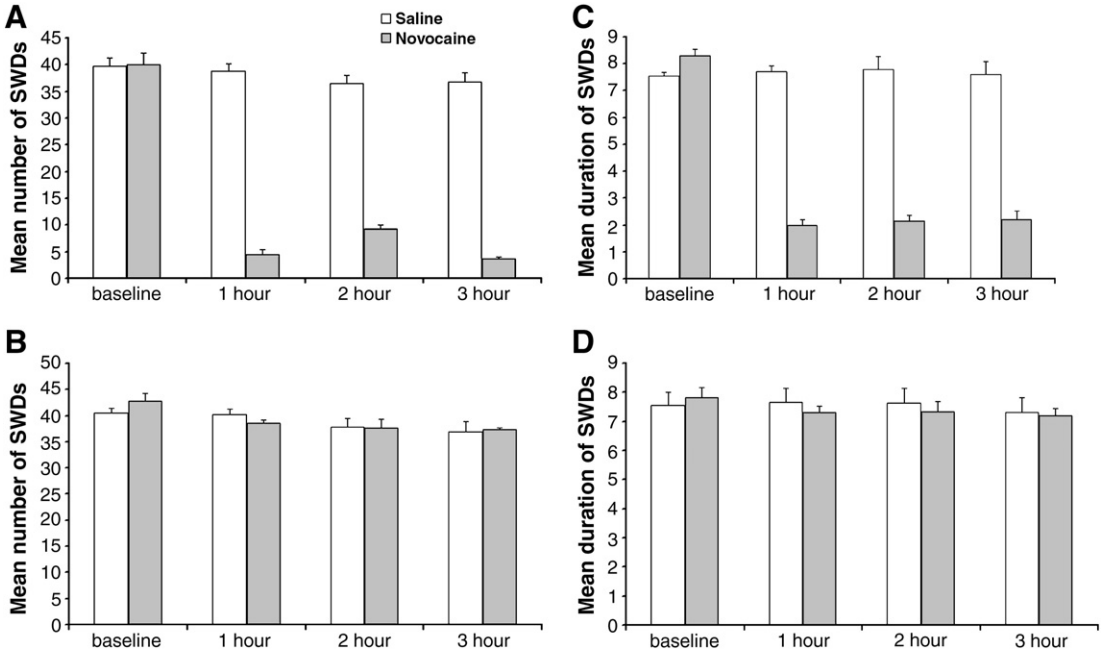

Fig. 1 – (A) Hourly (mean + s.e.m.) number of SWDs before (1 h) and after (3 h) peripheral injection of *n. trigeminis* with 2% Novocain or saline. (B) Hourly (mean + s.e.m.) number of SWDs before (1 h) and after (3 h) peripheral injection of *n. facialis* with 2% Novocain or saline. (C) Mean Duration of SWDs (mean + s.e.m.) before (1 h) and after (3 h) peripheral injection of *n. trigeminis* with 2% Novocain or saline. (D) Mean duration of SWDs (mean + s.e.m.) before (1 h) and after (3 h) peripheral injection of *n. trigeminis* with 2% Novocain or saline. Group size is always $n=6$.