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Thalamic stimulation in absence epilepsy

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Summary
Purpose: The site specific effects of two different types of electrical stimulation of the thalamus on electroencephalic epileptic activity as generated in the cortico-thalamo-cortical system were investigated in genetic epileptic WAG/Rij rats, a well characterized and validated absence model.
Methods: First, 12 male rats received low frequency (double-pulse pairs of 2.5 Hz, 150 μA intensity and 30 s inter-pair-interval) open-loop stimulation to either the Ventral-Postero-Medial (VPM) or the Anterior Thalamic Nucleus (ATN) for 8 h. Second, rats received high frequency (130 Hz, pulse train of 1 s) closed-loop stimulation applied to either VPM or ATN whenever a spike-wave discharge (SWD) was automatically detected.
Results: Low frequency stimulation induced 8 Hz SWD-like afterdischarges (AD). AD were frequently seen in VPM but rarely in ATN stimulated rats. AD, recorded in cortex and thalamus, showed a strong temporal coherence (visually assessed) and opposite spike polarities. Properties of AD and spontaneous SWD were equally affected by the stimulation. Closed-loop high frequency stimulation disrupted spontaneous SWD with no difference between ATN and VPM stimulated rats. 89% of SWD could be disrupted leading to a decrease in average SWD duration from 9 to 1.5 s.
Conclusion: Low frequency stimulation induced AD, which strongly mimic SWD. Moreover, the effects were site-specific. High frequency thalamic stimulation disrupts ongoing SWD probable by interfering with the slow firing pattern of cortico-thalamo-cortical neurons seen during SWD cycle. The absence of stimulation site specificity for high frequency stimulation might be due to the fact that stimulation only started on average 1 s after SWD onset when SWD are already fully expressed in the bidirectional cortico-thalamo-cortical resonance system.

Introduction

The generation of generalized spike and wave discharges (SWD), the electrophysiological hallmark of absence epilepsy, is known to rely on an intact cortico-thalamo-cortical network (Crunelli and Leresche, 2002; Danober

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et al., 1998; Onat et al., 2012; van Luijtelaar and Sitnikova, 2006; van Luijtelaar et al., 2011b). Pathophysiological mechanisms of SWD generation are commonly studied in two well described and validated genetic animal models, WAG/Rij and GAERS, which show spontaneous periods of reduced responsiveness, accompanied by SWD (Coenen and Van Luijtelaar, 2003; Depaulis and van Luijtelaar, 2006). In these models an epileptic-focus, located in the deep layers of the somatosensory-cortex, was identified as the site of SWD origin (Meeren et al., 2005, 2002; Polack et al., 2007, 2009).

Recently it was shown that low-frequency electrical stimulation of this epileptic-focus in WAG/Rij and GAERS rats could induce afterdischarges (AD), which strongly resembled SWD (Lüttjohann et al., 2011; Zheng et al., 2012). Like SWD, local-field-potential recordings of AD, measured in the deep somatosensory and on the motor-cortex, showed a rhythmic spike and wave pattern with a frequency of 8 Hz. Furthermore, AD were most frequently induced during drowsiness and only seldom during deep sleep and active-wakefulness, indicating the same vigilance preference known for SWD occurrence (Drinkenburg et al., 1991; Lüttjohann et al., 2011; Smyk et al., 2011). Given this strong similarity between SWD and AD, the authors assumed that these AD, like SWD reflect a cortico-thalamo-cortical phenomenon, and that based on characteristics of AD, network properties relevant for the generation of SWD could be inferred. However, the recordings in our previous study were restricted to the cortex and it needs to be established whether AD are indeed mimicking SWD as far as the involvement of the thalamus is concerned. Therefore, it is investigated whether AD, similar to SWD, can be measured in both cortex and thalamus and whether thalamic stimulation is able to affect characteristics of SWD and AD similarly.

Although the role of the cortex and thalamus in SWD initiation and spreading is widely recognized, the exact interactions between a cortical focus and different thalamic nuclei and their contributions in these processes still need to be elucidated (van Luijtelaar et al., 2011b). The VPM (ventral-postero-medial) thalamic nucleus is thought to be part of the key-network of SWD generation. It sends sensory information to and receives information from the somatosensory-cortex via direct thalamo-cortical and cortico-thalamic connections. These cells project collaterals to the caudal reticular-thalamic-nucleus (RTN), which in turn sends GABAergic projections to the VPM (Deschenes et al., 1998; Lu and Lin, 1993; Pinault and Deschenes, 1998). The anterior-thalamic-nucleus (ATN), by contrast, does not have any direct connections to the epileptic-focus. It is part of the limbic-loop and predominantly projects to the cingulate and the retrohippocampal cortex (Shibata, 1993a,b; Van Groen and Wyss, 1995). Furthermore, the ATN sends and receives projections to the rostral RTN (Gonzalo-Ruiz and Lieberman, 1995; Pinault and Deschenes, 1998). The sensitivity of stimulation to induce AD can be compared between VPM and ATN. If AD are indeed a type of SWD (Lüttjohann et al., 2011; Zheng et al., 2012), they should be recorded in the VPM and more readily induced via stimulation of the VPM than via ATN.

While low-frequency thalamic stimulation is expected to induce epileptic activity in the form of AD, high-frequency thalamic stimulation (130 Hz) has antiepileptic effects and should abort ongoing SWD (Vercueil et al., 1998). The location specificity/sensitivity (VPM, ATN) of this type of stimulation will be investigated in the second part of the study. It is hypothesized that it is easier to disrupt SWD by VPM as compared to ATN stimulation. Whereas in the first part of the study low-frequency stimulation will be applied in an open-loop fashion, i.e. is continuously applied, high-frequency stimulation will be applied in a closed-loop fashion, i.e. only in reaction to SWD.

Method

Subjects

12 male WAG/Rij rats, age 6 months, were used as experimental subjects. They were born and raised at the department of Biological Psychology, Donders Centre for Cognition, Radboud University Nijmegen, The Netherlands. Prior to surgery rats were housed in pairs (High Makrolon® cages with Enviro-Dri® bedding-material and cage-enrichment) with free access to food and water and were kept at a 12—12 h light—dark cycle (light off at 8.30 A.M.). After surgery rats were housed individually. The experiment was approved by the Ethical Committee on Animal Experimentation of Radboud University Nijmegen. Efforts were made to minimize the amount of discomfort and restrict the number of animals.

Surgery

Stereotactic surgery was performed under isoflurane anesthesia: WAG/Rij rats were divided in two groups, which differed with respect to the location of the stimulation electrodes (Group 1: local stimulation in the VPM; Group 2: local stimulation in the ATN).

In both groups two tripolar electrode sets (Plastic-One MS333/2a) were implanted. Each tripolar electrode set consisted of three stainless steel wires, isolated with polyimide, with a diameter of 0.2 mm. Only the tip of each electrode wire was un-isolated.

In group 1 ($n = 7$) the three electrode wires of the first tripolar assembly were implanted in the VPM, right hemisphere (A/P: −3.3 mm, M/L: −2.5 mm, H: −7.2 mm). Wires were oriented in an anterior—posterior direction and had the following configuration: stimulation anode, stimulation cathode, active recording electrode. Tip distance between electrode tips was 0.3 mm to ensure localized stimulation and recording within the VPM. The first wire of the second electrode set was implanted epidurally on the motor cortex (A/P: +2 mm, M/L: −2 mm), right hemisphere and was used as active recording electrode. The second and third wire of this set were implanted on top of the cerebellum and functioned as ground and reference electrode respectively.

In group 2 ($n = 5$) two electrode-wires of the first tripolar-assembly were implanted in the ATN right hemisphere (A/P: −1.4 mm, M/L: −1.5 mm, H: −6.4 mm) and functioned as stimulation anode and cathode. Again, wires were oriented in an anterior—posterior direction and had a tip distance of 0.3 mm to ensure localized stimulation. The third wire of this electrode set was epidurally implanted on the motor cortex (A/P: +2 mm, M/L: −2 mm), right hemisphere, and

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