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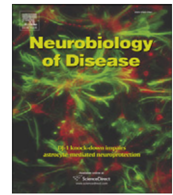

A role for the preoptic sleep-promoting system in absence epilepsy

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ABSTRACT

Absence epilepsy (AE) in humans and the genetic AE model in WAG/Rij rats are both associated with abnormalities in sleep architecture that suggest insufficiency of the sleep-promoting mechanisms. In this study we compared the functionality of sleep-active neuronal groups within two well-established sleep-promoting sites, the ventrolateral and median preoptic nuclei (VLPO and MnPN, respectively), in WAG/Rij and control rats. Neuronal activity was assessed using c-Fos immunoreactivity and chronic single-unit recording techniques. We found that WAG/Rij rats exhibited a lack of sleep-associated c-Fos activation of GABAergic MnPN and VLPO neurons, a lower percentage of MnPN and VLPO cells increasing discharge during sleep and reduced firing rates of MnPN sleep-active neurons, compared to non-epileptic rats. The role of sleep-promoting mechanisms in pathogenesis of absence seizures was assessed in non-epileptic rats using electrical stimulation and chemical manipulations restricted to the MnPN. We found that fractional activation of the sleep-promoting system in waking was sufficient to elicit absence-like seizures. Given that reciprocally interrelated sleep-promoting and arousal neuronal groups control thalamocortical excitability, we hypothesize that malfunctioning of sleep-promoting system results in impaired ascending control over thalamocortical rhythmogenic mechanisms during wake–sleep transitions thus favoring aberrant thalamocortical oscillations. Our findings suggest a pathological basis for AE-associated sleep abnormalities and a mechanism underlying association of absence seizures with wake–sleep transitions.

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Introduction

The sleep–waking cycle is a key factor influencing the expression of absence epilepsy (AE). EEG hallmarks of absence seizures, spike-wave discharges (SWDs), are strongly inhibited during alert wakefulness and rapid eye movement (REM) sleep and predominantly occur during transitory decreases in the level of vigilance in wakefulness, during light non-REM sleep (NREM) and transitions from NREM to REM sleep (Halasz et al., 2002). AE and other forms of idiopathic generalized epilepsy are associated with a number of abnormalities in sleep architecture including longer latencies to sleep and REM sleep onset, increased percentage of drowsiness and awakenings, reduced REM sleep percentage and decreased sleep efficiency (Baldy-Moulinier, 1992; Barreto et al., 2002; Maganti et al., 2005; Sun et al., 2005; Huang et al., 2007). AE patients also have increased daytime somnolence (Maganti et al., 2006, Byars et al., 2008). Similar changes in sleep parameters were found in Wistar Albino Glaxo/Rijswijk (WAG/Rij) rats, an accepted genetic model of human absence epilepsy, including prolonged transitional periods from wakefulness to sleep, lengthened intermediate stage of sleep, more frequently followed by arousals, and decreased REM sleep percentage (Gandolfo et al., 1990; Coenen and van Luijtelaar, 2003; van Luijtelaar and Bikbaev, 2007). These changes in sleep architecture suggest a hypothesis that AE is associated with insufficiency of the sleep-promoting mechanisms. Neuronal groups putatively involved in sleep initiation and maintenance via inhibitory control over multiple arousal neuronal groups were identified within two preoptic area subregions, the ventrolateral preoptic area (VLPO) and the median preoptic nucleus (MnPN) (Sherin et al., 1996; Gong et al., 2000). Malfunctioning of the preoptic sleep-promoting neuronal populations may be implicated in the mechanisms associating SWDs with transitional periods from wakefulness to sleep.

Like rhythms typical of normal NREM sleep, SWDs are generated within the thalamocortical circuitry (Crunelli and Leresche, 2002; Huguenard and McCormick, 2007). Aberrant thalamocortical oscillations may result from excessive neocortical excitability (Gloor and Fariello, 1988) and/or increased thalamic synchronization (Huguenard and McCormick, 2007) caused by impaired neurotransmission (Pumain et al., 1992; Avanzini et al., 1996; Luhmann et al., 1995;

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Hosford et al., 1997; D'Antuono et al. 2006; Merlo et al., 2007; Tan et al., 2008) and/or dysfunctional ion channels (Crunelli and Leresche, 2002; Talley et al., 2000; Budde et al., 2005; Strauss et al., 2004; Kole et al., 2007; Broicher et al., 2008). However, thalamocortical rhythmogenic mechanisms are highly controlled by cholinergic, monoaminergic and hypocretinergic/orexinergic neuronal groups, which affect both excitability and firing mode of thalamocortical cells by modulation of the membrane and synaptic properties of neurons involved in rhythmogenesis (McCormick, 1992; Steriade, 1999; Govindaiah and Cox, 2006). Imbalance in the ascending control of the thalamocortical circuits caused by pathological impairments within multiple arousal system has been suggested as one of the mechanisms underlying SWDs generation (Snead, 1995; Danober et al., 1998). However, arousal neuronal groups are under inhibitory control from the preoptic sleep-active neuronal groups (Saper et al., 2001; Szymusiak and McGinty, 2008). Therefore, imbalance in the ascending control of the thalamocortical circuit may result from abnormal functioning of preoptic sleep-promoting neuronal groups.

The aims of this study were (1) to assess functionality of preoptic sleep-promoting neuronal groups in WAG/Rij rats via comparison of sleep- and wake-related c-Fos protein expression and neuronal discharge within the VLPO and MnPN in WAG/Rij and control non-epileptic rats; (2) to study EEG and behavioral effects of interventions simulating incomplete activation of the sleep-promoting mechanisms in non-epileptic rats. The results demonstrate (1) insufficiency of the sleep-promoting mechanisms in genetically epilepsy-prone rats and (2) induction of absence seizures in response to incomplete activation of the sleep-promoting mechanisms during waking using electrical stimulation and chemical manipulations restricted to the MnPN. We hypothesize that insufficiency of the sleep-promoting system results in abnormal ascending control over thalamocortical excitability during transitions from wakefulness to sleep, favoring aberrant thalamocortical oscillations.

Methods

All experiments were performed in accordance with the National Research Council Guide for the Care and Use of Laboratory Animals. Animal use protocols were reviewed and approved by the Internal Animal Care and Use Committee of the Veterans Affairs Greater Los Angeles Healthcare System.

Animals and experimental environment

Six month old WAG/Rij rats ($n = 35$; Harlan, the Netherlands), age-matched Wistar ($n = 12$) and August Copenhagen Irish (ACI, $n = 12$) control rats (Harlan Sprague Dawley, Indianapolis, IN) were used in this study. At this age absence-like seizures in WAG/Rij rats are fully developed and all animals exhibit hundreds of SWDs/day (Coenen and van Luijtelaar, 2003; van Luijtelaar and Sitnikova, 2006). Less epilepsy-prone outbred Wistar rats (the strain of origin for the inbred WAG/Rij strain) and inbred ACI rats, virtually free of SWDs (Inoue et al., 1990) are commonly used as non-epileptic control animals (Strauss et al., 2004; van de Bovenkamp-Janssen et al., 2004). EEG and behavioral effects of electrical stimulation and chemical manipulations of the MnPN neuronal activity were studied in 6 three month old Sprague–Dawley rats that did not exhibit SWDs during 24 h baseline recordings.

Rats were housed individually in Plexiglas cages or in Stand-alone Raturn Animal Handling System (Bioanalytical Systems, Inc., West Lafayette IN, USA) placed inside an electrically shielded, sound-attenuated chamber. Ambient temperature was maintained at 23 ± 0.5 °C. Rats were kept in a 12 h light/dark cycle with lights on at 7:00 A.M. designated as Zeitgeber time 0 (ZT0). Animals had *ad libitum* access to food and water.

Surgery

Surgical procedures were performed under ketamine/xylazine anesthesia (80/10 mg/kg, *i.p.* respectively) and aseptic conditions.

All rats were surgically prepared for behavioral state assessment and seizure monitoring. Four stainless-steel screw EEG electrodes were placed into the skull symmetrically over the frontal (AP, +2.5; ML, 2.5) and parietal (AP, −2.5, ML, 2.5) cortex. One screw placed in the cranium over the cerebellum served as reference electrode. Four Teflon-coated stainless-steel EMG wires were implanted into the dorsal neck muscles.

To record single-unit activity within the VLPO or the MnPN, a preassembled electrode array was used. It consisted of 10 Formvar-insulated stainless-steel microwires (20 µm) inserted into the 23-gauge guide cannula that was attached to a mechanical microdrive anchored to the miniature electrical connector. The stereotaxic coordinates for the MnPN and VLPO were, respectively: anterioposterior (AP), −0.3; mediolateral (ML), 0; horizontal (H), 6–8 and AP, −0.3; ML, 1; H, 8.5–9.5 (Paxinos and Watson, 1998). The guide cannula was lowered inside the brain to position its tip 3 mm above the target. After fixation of the entire assembly to the skull, the microwires were advanced through the guide cannula to a point corresponding to the dorsal margin of VLPO or MnPN.

To manipulate the MnPN activity, animals were implanted with parallel bipolar Formvar-insulated tungsten electrodes (80 µm, 10–20 kΩ at 1000 Hz) or a guide cannula for subsequent insertion of microdialysis probe as described in detail elsewhere (Suntsova et al., 2007). Briefly, electrode wires targeted the most rostroventral and dorsocaudal portions of the MnPN (*AP*, 0.0; *H*, 7.0 and *AP*, −0.46; *H*, 5, respectively (Swanson, 1998)) to provide stimulation of the entire structure. The guide cannulas were implanted in the midline at a 15° angle from the vertical with tips located 3 mm from the target (*AP*, +0.12; *ML*, 0; *H*, 7.1).

Recording

The rats were allowed to recover from surgery for at least one week, and then were connected to amplifiers through light cables suspended by an overhead counterbalanced cable and slip ring to acclimate them to experimental conditions for 5 days.

Experiments were performed on freely moving animals. EEG and EMG signals were recorded bipolarly using Polygraph model 78 amplifiers (Grass Instruments, Quincy, MA). Passbands were set at 1–30 and 100–1000 Hz, respectively. Neuronal activity was recorded extracellularly using bipolar derivations from microwires (impedance at 1 kHz, 600–750 kΩ). Signals from microwires were first amplified through a miniature headstage preamplifier (MPA-8-I, Multi Channel Systems, Reutlingen, Germany) connected to a differential AC amplifier (model 1700; A-M Systems, Carlsborg, WA) with low and high cutoff filters of 10 Hz and 10 kHz, respectively.

Bioelectrical signals were digitized and stored on hard drive for off-line analysis using Micro 1401 data acquisition interface and Spike2 software package (Cambridge Electronic Design, London, UK). Polygraphic data were digitized at a 256 Hz sampling rate and unit activity data at 10 or 25 kHz for waveform and wavemark data channels, respectively.

Electrical stimulation and reverse microdialysis

Electrical stimulation of the MnPN was performed with 200 µs constant-current square pulses using A-65 Timer/stimulator coupled with SC-100 constant-current monophasic stimulus isolation unit (Winston Electronics Company, USA).

MnPN cellular activity was manipulated using microdialytic application of L-glutamate, the $GABA_A$ receptor antagonist bicuculline

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