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Research Paper

Cortical slow wave activity correlates with striatal synaptic strength in normal but not in Parkinsonian rats

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ABSTRACT

Urethane-induced cortical slow wave activity (SWA) spreads into the basal ganglia in dopamine (DA)-depleted rat models of Parkinson's disease (PD). During physiological sleep, SWA is powerfully expressed at the beginning of night and progressively reduced during sleep-time reflecting the sleep need. However, its underlying slow oscillations may contribute directly to modulate cortical plasticity.

In order to determine the impact of the SWA on synaptic strength and its interplay with DA, we simultaneously recorded the electrocorticogram (ECoG) and the corticocortical- and corticostriatal-evoked potentials (CC-EPs, CS-EPs) during eight hours of robust urethane-induced SWA in both normal and PD animals. A subgroup of PD rats was assessed with repetitive apomorphine (APO) administrations.

Normal animals showed a progressive reduction of SWA power during urethane-induced SWA. Compared to normal animals, PD animals showed lower SWA power at the start of anesthesia without a significant reduction over time. Accordingly, synaptic strength measured by CC- and CS-EP amplitudes decreased in normal but not in Parkinsonian rats. The PD animals treated with APO showed a CS-EP amplitude reduction comparable to normal animals. Interestingly, SWA power directly correlated with CS-EP amplitude in normal animals.

These data support the hypothesis that cortical SWA is directly associated with the regulation of synaptic efficacy in which DA exerts a crucial role.

1. Introduction

SWA consists of a slow electroencephalogram (EEG) oscillation ranging between 0.1 and 4 Hz, in which the depolarized up-state is sustained by the activity of cortical neurons, while the hyperpolarized down-state is characterized by widespread cortical neuronal silence (Steriade et al., 2001). The number of neurons synchronously engaged in the depolarized and hyperpolarized state determines the amplitude of the SWA (Steriade et al., 2001). Urethane anesthesia is able to induce cortical SWA which is similar to the physiological SWA of non-rapid eye movement (NREM) (Fox and Armstrong-James, 1986; Steriade et al., 1993) and therefore this anesthetic has been used as a model to investigate central mechanisms underlying sleep (Crook and Lovick, 2016; Pagliardini et al., 2013b, 2013a). Particularly, during SWA, cortical neurons show the same electrophysiological characteristics in both urethane anesthesia and NREM sleep (Clement et al., 2008; Steriade et al., 1993). Thus, it has been postulated that urethane most likely promotes unconsciousness by activating the brain mechanisms involved in natural sleep (Clement et al., 2008). In animal models of Parkinson's disease (PD), urethane-induced cortical SWA powerfully spreads within the basal ganglia (Galati et al., 2009; Magill et al., 2001; Tseng et al., 2001) and this evidence has been linked to an excessive synchronization between cortex and basal ganglia in the dopamine (DA) depleted state (Hammond et al., 2007) interfering with motor program selection.

Indeed, DA depletion also alters the corticostriatal synaptic plasticity, as has emerged in in vitro studies (Picconi et al., 2003) but also in in vivo experiments (Charpier and Deniau, 1997). Of note, the corticostriatal-evoked potentials (CS-EPs) change their response in relation to both sleep and DA denervation (Bateman et al., 1999; Galati et al., 2015; Poewe and Hogl, 2000; Rye and Jankovic, 2002; Stefani et al., 2006).

Abbreviations: APO, apomorphine; CC-EP, corticocortical-evoked potential; CS-EP, corticostriatal-evoked potential; DA, dopamine; ECoG, electrocorticogram; I-O, input-output; MFB, medial forebrain bundle; NREM, non-rapid eye movement; PD, Parkinson's disease; SHY, synaptic homeostasis hypothesis; SNc, substantia nigra compacta; SNr, substantia nigra compacta; SWA, slow wave activity; TH, tyrosine hydroxylase; VTA, ventral tegmental area

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In physiological conditions, the amplitude of the SWA during NREM not only reflects the sleep needed (Tononi and Cirelli, 2014) but could also contribute to the modulation of synaptic plasticity (Tononi and Cirelli, 2014). Accordingly, recent evidence has demonstrated that sleep shrinks synapses of sensory-motor cortex in terms of synaptic interface and volume (de Vivo et al., 2017).

Indeed, the cortical sleep-like oscillations induced through electrical stimulation of the medial lemniscus modulates glutamatergic synaptic plasticity (Chauvette et al., 2012). Accordingly, the corticocortical-evoked potentials (CC-EPs), representative of the global cortical synaptic strength (Rall, 1967), increase with time spent awake and decrease with time spent asleep (Vyazovskiy et al., 2008).

Therefore, SWA might play a dual role in a feedback control loop in which synapses with stronger efficiency produce a larger SWA amplitude that subsequently operates an homeostatic (Nelson and Turrigiano, 2008) reduction of synaptic strength (Olcese et al., 2010). The long-lasting depression of excitatory postsynaptic potentials could be triggered by the oscillatory nature of the SWA (Czarnecki et al., 2007; Nelson and Turrigiano, 2008).

Given these premises, we investigate the effect and time-course of long-lasting urethane-induced SWA on synaptic transmission measured by an input-output (I-O) curve of the CC-EP and CS-EP. Subsequently, we explore the impact of chronic DA depletion and DAergic treatment on these evoked responses and on SWA changes.

We hypothesize that dopaminergic denervation strongly affects SWA and the related evoked potentials. We used the evoked field potentials because they are a reliable tool for studying synaptic communication and especially excitatory post-synaptic potentials in vivo (Galiñanes et al., 2011). Moreover, the monosynaptic connection of the CC-EP and CS-EP lead to a straightforward identification of the evoked response (Galiñanes et al., 2011; Prosperetti et al., 2013; Vyazovskiy et al., 2008) that is linked to synaptic strength (Galiñanes et al., 2011; Rall, 1967; Vyazovskiy et al., 2008). We focused our study on frontal motor cortex evoked responses because the most substantial increase after prolonged wakefulness, as measured by SWA power, has been described within this region (Borbély and Achermann, 1999; de Vivo et al., 2017).

2. Methods

2.1. Animals

Experimental procedures were carried out on 16 adult male Sprague-Dawley rats (Harlan, Udine, Italy) that weighed between 170 and 200 g, corresponding to six weeks of age. The study was conducted at the Laboratory for Biomedical Neurosciences (LBN) in compliance with Swiss laws on animal experimentation and the National Institute of Health's Guide for the Care and Use of Laboratory Animals. The study was approved by Ticino veterinary authorities. All procedures were performed with the intention of minimizing animal discomfort and stress. The rats were kept on a regular light-dark cycle (lights on at 08:00 am, lights off at 08.00 pm; room temperature 20–22 °C) and were given food (Harlan RM Diet, Udine, Italy) and water ad libitum. The study design and the experimental procedures are depicted in Fig. 1A, B.

2.2. Unilateral Parkinsonian 6-OHDA-lesioned model

A unilateral (right hemisphere) DA denervation was performed on 10 rats according to a standard protocol (Galati et al., 2008; Prosperetti et al., 2013; Salvadè et al., 2016). The rats were anesthetized with 1.5–2.5% isoflurane in oxygen and were mounted on a stereotaxic instrument (Stoelting Co., Wheat Lane, Wood Dale, IL, USA). Body temperature was maintained at 37 °C–38 °C with a heating pad (Stoelting Co., Wheat Lane, Wood Dale, IL, USA) that was placed beneath the animal. After a subcutaneous injection of the local anesthetic lidocaine, a midline scalp incision was made and a hole (Ø ~ 1.0 mm) was drilled in the skull on the right side. The neurotoxin was diluted with 30 mM saline solution of 6-hydroxydopamine (6-OHDA) containing 0.03% of ascorbic acid and was injected into the medial forebrain bundle (MFB; coordinates: 4.0 mm posterior of the bregma, 1.3 mm laterally of the midline and 7.0 mm beneath the cortical surface). Injections of 3 µl of 6-OHDA were administered through a 30-gauge cannula connected to a 10 µl Hamilton syringe over a period of 3 min. The injection of the neurotoxin was preceded by a bolus of desipramine (25 mg/kg, i.p.) in order to minimize the uptake of 6-OHDA by noradrenergic neurons. Electrophysiological recordings were carried out two weeks after 6-OHDA injection.

2.3. Tyrosine hydroxylase immunohistochemistry

After completing the recordings, the 10 rats were sacrificed with an i.p. overdose of urethane. The brains were removed immediately, and then frozen at − 20 °C. We measured the degree of dopaminergic damage within the substantia nigra compacta (SNc), the ventral tegmental area (VTA) and the ipsilateral striatum by tyrosine hydroxylase (TH) immunostaining (Fig. 1C), as reported elsewhere (Galati et al., 2008, 2010, 2015; Prosperetti et al., 2013). Briefly, coronal brain 40-µm-thick sections were cut with an Oxford vibratome across the entire rostrocaudal extent of the striatum and midbrain. Free-floating sections were washed three times with Tris-buffered saline, pH 7.4, and endogenous peroxidase activity was inactivated by Tris-buffered saline containing 2% H_2O_2. The sections were rinsed with Tris-buffered saline (0.1% Triton X-100 and 2% normal goat serum) and incubated with 2% normal goat serum followed by overnight incubation at 4 °C with mouse anti-TH primary antibodies (1:2000; anti-TH Chemicon, Millipore). Primary antibodies were detected using a secondary antibody (goat anti mouse IR800, Rockland, Gilbertsville). Sections were then rinsed with Tris-buffered saline, mounted on gelatin-coated slides, dehydrated, and cover-slipped with Permount, observed and photographed with a light microscope. All histological samples showed absence of TH reaction with a preserved VTA ipsilateral to 6-OHDA injection.

2.4. Electrophysiological recordings

The electrophysiological recordings were performed under urethane anesthesia injected at the same hour of the day (8.00 am, 1.4 mg/kg, i.p.) maintaining the body temperature at 37 °C–38 °C with a heating pad (Stoelting Co., Wheat Lane, Wood Dale, IL, USA) that was placed beneath the animal. We continuously recorded the ECoG for ~8 h (7.77 ± 1.53 h in all animals, n = 16) and performed the I-O curves of the CC-EP and the CS-EP starting at the same hour in the morning (at 10.00 am), and then every 2 h during six consecutive hours in normal (n = 6) and untreated Parkinsonian rats (n = 5; Fig. 1A, B). An additional group of Parkinsonian animals (n = 5) was injected with the DA-agonist apomorphine (APO, 0.05 mg/kg, s.c.) 10 min before each I-O curve. APO is able to produce an improvement of motor function 5 min after s.c. bolus administration lasting from 30 to 90 min (Gancher et al., 1989). Two 1 mm diameter golden screw electrodes (gold plated screws, conical cross S1, Svenska Dentorama AB) were implanted in the frontal right and left cortices (coordinates: 2 mm anterior of the bregma, 3 mm laterally to the midline) under urethane anesthesia (Salvadè et al., 2016). Furthermore, a tungsten recording electrode with an impedance of ~0.1 MΩ (TM33B01, World Precision Instruments, FL, USA) was implanted into the striatum (coordinates: 0.48 mm anterior of the bregma, 3.5 mm lateral to the midline and 4 mm ventral to the cortical surface) (Galati et al., 2015). One reference epidural screw electrode was placed over the right cerebellar hemisphere.

2.5. Data acquisition and stimulation protocol

The signal was amplified (gain: 1 K, band-pass filter: 1 Hz–3 kHz;