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Unraveling a new circuitry for sleep regulation in Parkinson's disease

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ABSTRACT

Sleep disturbances are among the most disabling non-motor symptoms in Parkinson's disease. The pedunculopontine tegmental nucleus and basal ganglia are likely involved in these dysfunctions, as they are affected by neurodegeneration in Parkinson's disease and have a role in sleep regulation. To investigate this, we promoted a lesion in the pedunculopontine tegmental nucleus or substantia nigra pars compacta of male rats, followed by 24 h of REM sleep deprivation. Then, we administrated a dopaminergic D2 receptor agonist, antagonist or vehicle directly in the striatum. After a period of 24 h of sleep-wake recording, we observed that the ibotenic acid infusion in the pedunculopontine tegmental nucleus blocked the so-called sleep rebound effect mediated by REM sleep deprivation, which was reversed by striatal D2 receptors activation. Rotenone infusion in the substantia nigra pars compacta also blocked the sleep rebound, however, striatal D2 receptors activation did not reverse it. In addition, rotenone administration decreased the time spent in NREM sleep, which was corroborated by positive correlations between dopamine levels in both substantia nigra pars compacta and striatum and the time spent in NREM sleep. These findings suggest a new circuitry for sleep regulation in Parkinson's disease, involving the triad composed by pedunculopontine nucleus, substantia nigra pars compacta and striatum, evidencing a potential therapeutic target for the sleep disturbances associated to this pathology.

1. Introduction

Sleep disturbances drastically affect the quality of life of individuals with Parkinson's disease and they often precede the motor impairments (Fahn, 2003; Lang and Lozano, 1998a, b). They are represented by the restless legs syndrome, rapid eye movement (REM) sleep behavior disorder, sleep fragmentation, insomnia and excessive daytime sleepiness (Lima, 2013).

Different factors contribute for these sleep disturbances: motor manifestations from the disease during sleep time, pharmacological treatment, depression, anxiety, age-related sleep disturbances and, most importantly, the neurodegeneration that occurs during the disease (Diederich and McIntyre, 2012). Structures associated with sleep regulation such as the locus coeruleus, lower raphe nuclei and pedunculopontine tegmental nucleus (PPT) are affected before substantia nigra pars compacta (SNpc) (Braak et al., 2004), which may lead to early sleep disturbances. However, recent questions have been raised regarding the exact role of the dopaminergic system in the sleep-wake cycle regulation (Lima, 2013; Monti and Monti, 2007). Observations of a higher dopaminergic level in the medial prefrontal cortex and nucleus accumbens during wakefulness and rapid eye movement (REM) sleep compared to non-rapid eye movement (NREM) sleep and a prominent burst firing of dopaminergic neurons in the ventral tegmental area during REM sleep indicate a role for dopaminergic neurotransmission

Abbreviations: ChAT, Choline Acetyltransferase; DHPG, 3, 4-dihydroxyphenylethyleneglycol; DMSO, Dimethylsulfoxide; DOPAC, 3,4-dihydroxyphenylacetic acid; GPe, External globus pallidus; GPi, Internal globus pallidus; HVA, Homovanillic acid; NREM, Non-rapid eye movement sleep; PPT, Pedunculopontine tegmental nucleus; REM, Rapid eye movement sleep; REMSD, Rapid eye movement sleep deprivation; SN, Substantia nigra; SNpc, Substantia nigra pars compacta; SNpr, Substantia nigra pars reticulata; STN, Subthalamic nucleus; TH, Tyrosine hydroxylase.

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in regulating some aspects across the sleep-wake cycle (Dahan et al., 2007; Lena et al., 2005). Concerning the nigrostriatal pathway, studies show a significant reduction in the time spent in REM sleep after lesions in SNpc and by the blockade of striatal D2 dopaminergic receptors (Lima et al., 2007, 2008).

The basal ganglia and the PPT share a diversity of similarities. Anatomically, both entities have a similar pattern of inputs and outputs including the cortex, thalamus, amygdala and brainstem (Mena-Segovia et al., 2004). Remarkably, electrical stimulation of the PPT evokes an efflux of striatal dopamine that seems to be accomplished via cholinergic and glutamatergic afferents to dopaminergic cells of SNpc (Forster and Blaha, 2003). Also, the burst firing pattern of ventral tegmental area dopaminergic neurons during REM sleep seems to be promoted by the PPT (Dahan et al., 2007). Additionally, the basal ganglia and the PPT share similar functions concerning locomotion, some aspects of memory consolidation and, as suggested recently, sleep regulation (Lazarus et al., 2012; Mena-Segovia et al., 2004).

Since the PPT and the basal ganglia share this diversity of features and are affected by the neurodegeneration during Parkinson's disease, we proposed a physiological association of these structures in sleep regulation, especially in the context of Parkinson's disease. To investigate this, we promoted a PPT lesion with ibotenic acid and a SNpc lesion with rotenone. Both situations were associated to striatal D2 receptors modulation and REM sleep deprivation. Our hypothesis was that these structures were indeed associated to sleep disturbances, especially in the animal model of Parkinson's disease, and that a modulation of striatal D2 receptors could either potentiate or reverse the damaged promoted by ibotenic acid or rotenone. Also, rotenone lesion in SNpc could be more deleterious when compared to PPT, considering the symptomatology when the neurodegeneration reaches SNpc. A better understanding of this issue is of great importance for the elucidation of potential therapeutic targets for sleep disturbances in Parkinson's disease.

2. Materials and methods

2.1. Animals and housing conditions

All of the experiments performed in this study were approved by the ethics committee of Federal University of Paraná (approval ID #655) and conducted according to the guidelines of ethics and experimental care and use of laboratory animals (SBCAL). All efforts were made to minimize animal suffering and to reduce the number of animals used. Male Wistar rats (Supplementary Tables 1 and 2), weighing 280–330 g, were maintained in a temperature controlled room (22 °C ± 2 °C) with a 12 h light-dark cycle (lights on at 7:00 a.m.). The housing consisted in polypropylene cages, where the animals were maintained in groups of 5 animals *per* cage. Bottles of water and pellets of food were available throughout the entire experiment.

2.2. Experimental design

One week before the experiments begin, the animals were maintained in the room described above for habituation. On day zero, the animals underwent stereotaxic surgery for ibotenic acid infusion within the PPT (Experiment 1) or rotenone infusion within the SNpc (Experiment 2). In addition, for both experiments, bilateral guide cannulas were implanted within the striatum as well as cortical electrodes for sleep-wake recording. After a 7 days interval for recovery purposes, the animals were exposed to 24 h of REM sleep deprivation (REMSD), followed by a single striatal infusion of the D2 receptor agonist piribedil (3 μg/μl), the D2 receptor antagonist raclopride (10 μg/μl) or vehicle (Dimethylsulfoxide [DMSO]). Subsequently, part of the animals (4–5 per group) underwent a period of 24 h of sleep-wake recording, corresponding to the sleep rebound period. At the end of this procedure, these animals were decapitated and the brains were removed (for neurochemical analysis). The other set that was not submitted to the sleep recording procedure (4–5 animals per group) had their brains perfused and fixed (for immunohistochemical analysis) (Supplementary Tables 1 and 2).

2.3. Stereotaxic surgery

The animals were initially sedated with intraperitoneal xylazine (10 mg/kg; Syntec do Brasil Ltda, Brazil) and anesthetized with intraperitoneal Ketamine (90 mg/kg; Syntec do Brasil Ltda, Brazil). For ibotenic acid infusion within the PPT (Experiment 1) or rotenone infusion within the SNpc (Experiment 2), the following coordinates were used, bregma as a reference: PPT (AP) = − 7,8 mm, (ML) = ±2,0 mm and (DV) = −7,4 mm; SNpc (AP) = −5,0 mm, (ML) = ±2,1 mm and (DV) = −8,0 mm (Paxinos and Watson, 2005). Ibotenic acid (0.12 M; Tocris Bioscience®, United Kingdom) or saline infusions of 0.2 μl in each hemisphere were made in steps, separated by intervals of 10 s, totalizing 200 s of injection (Blaha et al., 1996). Rotenone (12 μg/μl; Sigma-Aldrich®, United States) or DMSO (Sigma-Aldrich®, United States) infusions of 1 μl in each hemisphere were made at a rate of 0.33 μl/min for 3 min (Noseda et al., 2014; Rodrigues et al., 2014). These infusions were made using an electronic infusion pump (Insight Instruments, Ribeirão Preto, Brazil). For bilateral guide cannulas implantation, the following coordinates were used, bregma as a reference: Striatum (AP) = +1.0 mm, (ML) = ±3.0 mm and (DV) = −6.0 mm (Paxinos and Watson, 2005). Finally, for electrodes positioning, the following coordinates were used, bregma as a reference: (AP) = −1.8 mm, (ML) = −2.0 mm (first electrode) and (AP) = 3.0 mm, (ML) = 1.0 mm (second electrode); Lambda as a reference: (AP) = 1.0 mm, (ML) = −4.0 mm (third electrode) and (AP) = 4.0 mm, (ML) = 1.0 mm (fourth electrode) (Lima et al., 2007; Paxinos and Watson, 2005).

2.4. REMSD procedure

The animals were individually placed in a circular platform (6.5 cm in diameter) inside of a tank (23 × 23 × 35 cm) filled with water up 1 cm below the platform surface for 24 h. Once the animal experiences a REM sleep episode, it loses its muscular tonus and falls into the water, being awakened. This procedure has demonstrated effectiveness in ablation of REM sleep without affecting NREM sleep (Machado et al., 2004). During the experiment, the room was maintained with controlled temperature (22 °C ± 2 °C) and with a 12 h light-dark cycle (lights on 7:00 a.m.). The control group (non-sleep deprived) was maintained in the same room during the period, but isolated in their usual home cages, to mimic a possible effect of isolation caused by the procedure. Water and food were available during the entire experiment.

2.5. Striatal infusions

Striatal infusions of 1 μl of piribedil (3 μg/μl; Tocris Bioscience®, United Kingdom), raclopride (10 μg/μl; Sigma-Aldrich®, United States) or DMSO (Sigma-Aldrich®, United States) were made at the guide cannulas implanted during stereotaxic surgery, at a rate of 0.33 μl/min for 3 min, with the assistance of an electronic infusion pump (Insight Instruments, Ribeirão Preto, Brazil).