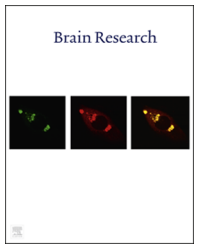
BRAIN RESEARCH 1639 (2016) 47–57

Available online at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/brainres

Brain Research



Research Report

Can physical exercise have a protective effect in an animal model of sleep-related movement disorder?

Andrea M. Esteves[a,*], *Cleide Lopes*[b], *Miriam K. Frank*[a], *Ricardo M. Arida*[c], *Roberto Frussa-Filho*[d,†], *Sergio Tufik*[b], *Marco Túlio de Mello*[e]

[a]*Faculdade de Ciências Aplicadas, Universidade Estadual de Campinas, Brazil*
[b]*Departamento de Psicobiologia, Universidade Federal de São Paulo, Brazil*
[c]*Departamento de Fisiologia, Universidade Federal de São Paulo, Brazil*
[d]*Departamento de Farmacologia, Universidade Federal de São Paulo, Brazil*
[e]*Departamento de Esportes, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil*

ARTICLE INFO

Article history:
Accepted 21 February 2016
Available online 27 February 2016

Keywords:
Sleep disorders
Restless legs syndrome
Limb movement
Physical exercise

ABSTRACT

The purpose of the present study was to determine whether physical exercise (PE) has a protective effect in an experimental animal model of sleep-related movement disorder (A11 dopaminergic nuclei lesions with 6-OHDA). Rats were divided into four groups (Control PE-CTRL/PE, SHAM/PE, A11 lesion/NPE, A11 lesion/PE). Two experiments were performed: (1) the rats underwent PE before (2 weeks) and after (4 weeks) the A11 lesion; and (2) the rats underwent PE only after (4 weeks) the A11 lesion. Electrode insertion surgery was performed and sleep analyses were conducted over a period of 24 h (baseline and after PE) and analyzed in 6 blocks of 4 h. The results demonstrated that the A11 lesion produced an increased percentage of wakefulness in the final block of the dark period (3–7 am) and a significant enhancement of the number of limb movements (LM) throughout the day. Four weeks of PE was important for reducing the number of LMs in the A11 lesion group in the rats that performed PE before and after the A11 lesion. However, in the analysis of the protective effect of PE on LM, the results showed that the number of LMs was lower at baseline in the group that had performed 2 weeks of PE prior to the A11 lesion than in the group that had not previously performed PE. In conclusion, these findings consistently demonstrate that non-pharmacological manipulations had a beneficial effect on the symptoms of sleep-related movement disorder.

*Correspondence to: Faculdade de Ciências Aplicadas, Universidade Estadual de Campinas, Rua Pedro Zaccaria, No.1300, Limeira, SP, Brazil. Fax: +55 19 37016706.
E-mail address: andrea.esteves@fca.unicamp.br (A.M. Esteves).
†In memoriam.

http://dx.doi.org/10.1016/j.brainres.2016.02.036
0006-8993/

1. Introduction

Restless legs syndrome (RLS) is a common sleep-related movement disorder that is characterized by uncomfortable sensations in the limbs. These sensations appear or become worse during the evening/night rest period and are relieved by motor activity (Walters, 1995). Most RLS patients present periodic limb movements (PLMs) in sleep (Thorpy, 2005).

Epidemiologic data have increasingly demonstrated the negative effect of RLS on health. In the Sleep Heart Health Study (Ulfberg et al., 2001), subjects with RLS were found to have a twofold increase in the odds ratios, after adjustment for confounders, for having coronary artery disease and cardiovascular disease in comparison with those without RLS. RLS is significantly associated with diminished quality of life (Allen et al., 2005; Berger et al., 2004) depressed mood, and/or social isolation (Allen, 2004; Berger et al., 2004; Ulfberg et al., 2001). RLS and PLM can negatively affect the quality of sleep, increased sleep latency, number of awakenings and reduced sleep efficiency, thereby resulting in daytime sleepiness (Allen et al., 2003).

Treatment of the idiopathic form of RLS is most commonly pharmacologic (Littner et al., 2004). Specifically, dopamine D2 agonists have become the first-line treatment for this condition (Montplaisir et al., 1999). This is due to association of the dopaminergic system in the pathophysiology of this sleep disorder (Trenkwalder and Paulus, 2010).

As a form of non-pharmacological treatment, the influence of physical exercise on the improvement of RLS symptoms, specifically, PLMs, has also been the subject of clinical research (ASDA, 1992). Studies have demonstrated that acute or chronic physical exercise provides benefits and significantly reduces PLMs in patients with or without spinal cord injury (De Mello et al., 2002; Esteves et al., 2009; Aukerman et al., 2006; Cavagnolli et al., 2013).

However, on the basis of the current hypotheses concerning the pathophysiology of RLS and PLM, some promising attempts have been made to develop procedures for producing an animal model of sleep-related movement disorder. These attempts have involved lesioning (Esteves et al., 2004; Lopes et al., 2012), dietary manipulations (Qu et al., 2007), and pharmacological interventions (Lopes et al., 2012; Luo et al., 2011; Esteves et al., 2013). In particular, lesions in the A11 core result in sleep disturbances in animals. This manipulation is often considered to be an animal model of RLS/PLM (Lopes et al., 2012; Qu et al., 2007). The A11 cell group in the hypothalamus is a major source of descending dopaminergic projections to the spinal cord and the major source of spinal dopamine (DA). It sends projections to the sympathetic preganglionic neurons (SPNs) in the intermediolateral nucleus and directs projections to the suprachiasmatic nuclei (SCNs) (Hokfelt et al., 1979). The neuronal link between the SCNs and the SPNs via A11 neurons suggests that spinal DA actions are under circadian influence. It is believed that some of the diencephalospinal neurons form a sympathetic–excitatory system (Qu et al., 2006).

However, the potential influence of non-pharmacological (physical exercise) treatment in this animal model is seldom studied (Esteves et al., 2013).

The purpose of the present study was to determine whether physical exercise has a protective effect in an experimental animal model of sleep-related movement disorder (A11 dopaminergic nuclei lesion with 6-OHDA).

2. Results

2.1. Physical exercise before and after A11 lesion

Changes from baseline and after physical exercise in sleep patterns that were assessed by recording sleep in light and dark periods (12 h) are presented in Table 1. In the light period (12 h), a repeated-measures ANOVA revealed a significant difference in the group factor for total sleep time (TST) ($F_{(3,20)}=4.937$, $p=0.01$), SE ($F_{(3,20)}=8.284$, $p<0.01$), slow wave sleep (SWS) ($F_{(3,20)}=26.402$, $p<0.001$), paradoxical sleep (PS) ($F_{(3,20)}=6.180$, $p<0.01$) and wakefulness (WK) ($F_{(3,20)}=10.655$, $p<0.01$) and in the time factor for PS ($F_{(1,20)}=4.682$, $p=0.04$). The main results showed that the group CTRL-PE showed an increase in TST, SE and WK ARS in relation to A11 Lesion NPE and PE groups. For SWS, the A11 lesion NPE showed a significant decrease in comparison with all other groups after PE. For LMs, the CTRL-PE, SHAM-PE and A11 lesion-PE groups showed a statistically significant decrease from the A11 lesion-NPE in baseline and after physical exercise (Kruskal–Wallis, $p<0.001$).

In the dark period (12 h), a repeated-measures ANOVA showed a significant difference among groups and an interaction with arousal (ARS) ($F_{(3,20)}=17.718$, $p<0.001$; $F_{(3,20)}=3.309$, $p=0.04$). The A11 lesion-NPE group showed a significant increase in comparison with the other groups in the ARS after four weeks of exercise.

For LMs, the CTRL-PE and SHAM-PE showed a statistically significant difference from the A11 lesion-NPE and A11 lesion-PE in baseline. After exercise, the CTRL-PE, SHAM-PE and A11 lesion-PE groups showed a statistically significant decrease in LMs from the A11 lesion-NPE (Kruskal–Wallis, $p<0.001$).

A repeated-measures ANOVA showed a statistically significant difference for group ($F_{(3,20)}=4.788$, $p=0.01$), time ($F_{(5,100)}=7.372$, $p=0.01$) and interaction ($F_{(15,100)}=2.145$, $p=0.01$) in the percentage (%) of WK in the dark period at both baseline and following exercise that was divided into blocks (7–11 pm, 11 pm to 3 am, 3–7 am). The A11 lesion NPE and PE groups showed an increased %WK in the 3–7 am block in comparison with the CTRL-PE and SHAM-PE groups at baseline. After physical exercise, the CTRL-PE, SHAM-PE and A11 lesion-PE groups showed a significant reduction in comparison with the A11 lesion-NPE (baseline and after physical exercise) group and the a11 lesion-NPE (after physical exercise) group. The results are shown in Fig. 1.

2.2. Physical exercise after A11 lesion

Changes from baseline and after physical exercise in sleep patterns, as assessed by recording sleep in the light and dark period (12 h), are presented in Table 2. During the light period (12 h), a repeated-measures ANOVA showed a significant difference in the group factor for TST ($F_{(3,20)}=8.077$, $p<0.01$)