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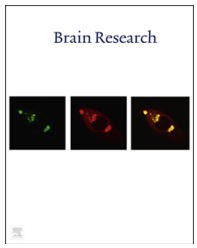

Research Report

Neuroprotective and antidepressant-like effects of melatonin in a rotenone-induced Parkinson's disease model in rats

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ABSTRACT

Parkinson's disease (PD) is a neurodegenerative disorder characterized by a progressive loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc). Systemic and intranigral exposure to rotenone in rodents reproduces many of the pathological and behavioral features of PD in humans and thus has been used as an animal model of the disease. Melatonin is a neurohormone secreted by the pineal gland, which has several important physiological functions. It has been reported to be neuroprotective in some animal models of PD. The present study investigated the effects of prolonged melatonin treatment in rats previously exposed to rotenone. The animals were intraperitoneally treated for 10 days with rotenone (2.5 mg/kg) or its vehicle. 24 h later, they were intraperitoneally treated with melatonin (10 mg/kg) or its vehicle for 28 days. One day after the last rotenone exposure, the animals exhibited hypolocomotion in the open field test, which spontaneously reversed at the last motor evaluation. We verified that prolonged melatonin treatment after dopaminergic lesion did not alter motor function but produced antidepressant-like effects in the forced swim test, prevented the rotenone-induced reduction of striatal dopamine, and partially prevented tyrosine hydroxylase immunoreactivity loss in the SNpc. Our results indicate that melatonin exerts neuroprotective and antidepressant-like effects in the rotenone model of PD.

Abbreviations: DOPAC, 3,4-dihydroxyphenylacetic acid; DHPG, dihydroxyphenylglycol; EDTA, ethylenediaminetetraacetic acid; HVA, homovanillic acid; HPLC, high-performance liquid chromatography; 5-HIAA, 5-hydroxyindoleacetic acid; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; 6-OHDA, 6-hydroxydopamine; PD, Parkinson's disease; SNpc, substantia nigra pars compacta; TH, tyrosine hydroxylase

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1. Introduction

Parkinson's disease (PD), the second most common neurodegenerative disease, is characterized by the progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc) and consequent reduction in dopamine content in striatum, which is responsible for the motor impairment (Long-Smith et al., 2009). The cause of PD is still unknown, but several environmental risk factors have been implicated in the etiology of the idiopathic form, including exposure to pesticides, such as rotenone (Sanders and Greenamyre, 2013).

Rotenone is a natural compound commonly used as an insecticide. It easily crosses the blood–brain barrier and acts as a potent mitochondrial complex I inhibitor (Büeler, 2009). Intranigral and systemic exposure to rotenone in rats reproduces many of the key pathological features of PD, including selective nigrostriatal loss, striatal dopamine depletion, α-synuclein inclusions, hypokinesia, rigidity, hunched posture, depressive-like behavior and cognitive deficits (Betarbet et al., 2000; Moreira et al., 2012; Santiago et al., 2010).

Melatonin is a neurohormone produced by the pineal gland at night, exhibiting a circadian pattern of secretion. This molecule is implicated in the control of various physiological functions such as seasonal reproduction, sleep regulation, control of circadian rhythms and modulation of human mood and behavior (Pandi-Perumal et al., 2013). In addition, melatonin has important antiinflammatory and antioxidant properties, such as free radical scavenging and has been implicated in mitochondrial homeostasis (Hardeland et al., 2011). Because of these functions, melatonin has been studied for its neuroprotective potential in PD models. Indeed, both acute and chronic melatonin administration protects dopaminergic neurons against neurotoxicity induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP; Acuña-Castroviejo et al., 1997; Antolín et al., 2002; Capitelli et al., 2008; Jin et al., 1998; Ma et al., 2009; Patki and Lau, 2011), rotenone (Coulom and Birman, 2004; Lin et al., 2008; Saravanan et al., 2007; Zhou et al., 2012), and 6-hydroxydopamine (6-OHDA; Sharma et al., 2006).

However, conflicting results have been reported. Some researchers claim that melatonin may exacerbate neurodegeneration (Lin et al., 2013, 2014; Tapias et al., 2010) and suppression of physiological melatonin may relieve motor impairment in animal models (Willis and Armstrong, 1999; Willis and Robertson, 2004, 2005; Willis, 2008). Also, it is important to mention that in clinical trials, melatonin did not improve the motor function of PD patients (Medeiros et al., 2007; Datieva et al., 2013) and reduction of its physiological secretion through bright light therapy enhanced some motor and nonmotor features (Paus et al., 2007; Willis et al., 2012). Because of this controversy, the effects of melatonin need to be better investigated, especially after dopaminergic lesions, because most studies have evaluated melatonin effects by administering it before or concomitantly with a neurotoxin. At the time of diagnosis, approximately 80% of striatal dopamine is depleted and 60% of nigral dopaminergic neurons has already been irreversibly lost (Dauer and Przedborski, 2003).

In addition to the already mentioned motor symptoms, which are the result of nigrostriatal degeneration, patients with PD often present several non-motor symptoms that are very debilitating. Depression is one of the most common of these symptoms, affecting approximately 35% of patients with PD (Aarsland et al., 2012). Melatonin has been studied for potential therapeutic benefits in mood disorders because disturbances in melatonin circadian profile were verified in patients with depression (Micale et al., 2006). Preclinical studies showed that melatonin has antidepressant-like effects in several animal models of depression, such as the forced swim test (Micale et al., 2006; Raghavendra et al., 2000; Shaji and Kulkarni, 1998), chronic mild stress paradigm (Detanico et al., 2009), and tail suspension test (Binfaré et al., 2010; Mantovani et al., 2003). However, melatonin antidepressant effect has never been evaluated in a PD model.

Considering the information above, we decided to investigate the potential antidepressant-like and neuroprotective effects of melatonin in rats previously exposed to rotenone. The animal model employed in this study was developed by our group and tries to mimic the early phase of PD in patients, which is characterized by partial nigrostriatal cell loss, partial striatal dopamine depletion and some non-motor symptoms, such as depression (Morais et al., 2012).

2. Results

2.1. *Open field test*

Locomotion frequency was significantly reduced in the rotenone groups 1 day after the last rotenone exposure compared with controls ($P<0.01$; Fig. 1A), as indicated by the group [$F(3.114)=5.042$; $P=0.0026$] and interaction [$F(3.114)=2.699$; $P=0.0491$] factors, but not by the time factor [$F(3.114)=0.02884$; $P=0.8655$]. Rearing frequency was reduced in the rotenone groups only at the day 1 time-point compared with controls ($P<0.01$; Fig. 1B), as demonstrated by the group factor [$F(3.114)=3.985$; $P=0.0097$], but not by the time [$F(3.114)=0.5292$; $P=0.4684$] and interaction [$F(3.114)=2.268$; $P=0.0843$] factors. A significant increase in immobility was detected in the rotenone groups only at the day 1 time-point compared with controls ($P<0.01$; Fig. 1C), as revealed by the group [$F(3.114)=4.812$; $P=0.0034$] and time [$F(3.114)=5.548$; $P=0.0202$] factors but not by the interaction [$F(3.114)=1.925$; $P=0.1295$] factor.

2.2. *Modified forced swim test*

A significant increase in immobility time was observed in the rotenone group compared with the control group ($P<0.01$) and melatonin group ($P<0.001$; Fig. 2A). Immobility time was similar in the rot+mel and control groups but decreased in the rot+mel group compared with the rotenone group ($P<0.05$) [$F(3.57)=6.194$; $P=0.0010$]. No significant difference in climbing was observed between groups [$F(3.57)=1.093$; $P=0.3593$] (Fig. 2B). Rotenone did not alter swimming time compared with control, but melatonin increased swimming time compared with the control group ($P<0.05$) and rotenone group ($P<0.01$). The rot+mel group exhibited increased swimming time compared with the rotenone group ($P<0.05$) [$F(3.57)=5.354$; $P=0.0026$] (Fig. 2C).