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Research Report

Chronic low-dose melatonin treatment maintains nigrostriatal integrity in an intrastriatal rotenone model of Parkinson's disease

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ABSTRACT

Parkinson's disease is a major neurodegenerative disorder which primarily involves the loss of dopaminergic neurons in the substantia nigra and related projections in the striatum. The pesticide/neurotoxin, rotenone, has been shown to cause systemic inhibition of mitochondrial complex I activity in nigral dopaminergic neurons, with consequent degeneration of the nigrostriatal pathway, as observed in Parkinson's disease. A novel intrastriatal rotenone model of Parkinson's disease was used to examine the neuroprotective effects of chronic low-dose treatment with the antioxidant indoleamine, melatonin, which can upregulate neurotrophic factors and other protective proteins in the brain. Sham or lesioned rats were treated with either vehicle (0.04% ethanol in drinking water) or melatonin at a dose of 4 μg/mL in drinking water. The right striatum was lesioned by stereotactic injection of rotenone at three sites (4 μg/site) along its rostrocaudal axis. Apomorphine administration to lesioned animals resulted in a significant ($p<0.001$) increase in ipsilateral rotations, which was suppressed by melatonin. Nine weeks post-surgery, animals were sacrificed by transcardial perfusion. Subsequent immunohistochemical examination revealed a decrease in tyrosine hydroxylase immunoreactivity within the striatum and substantia nigra of rotenone-lesioned animals. Melatonin treatment attenuated the decrease in tyrosine hydroxylase in the striatum and abolished it in the substantia nigra. Stereological cell counts indicated a significant ($p<0.05$) decrease in dopamine neurons in the substantia nigra of rotenone-lesioned animals, which was confirmed by Nissl staining. Importantly, chronic melatonin treatment blocked the loss of dopamine neurons in rotenone-lesioned animals. These findings strongly support the therapeutic potential of long-term and low-dose melatonin treatment in Parkinson's disease.

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1. Introduction

Parkinson's disease is the most common neurodegenerative movement disorder which is characterized by a marked loss of dopamine-producing neurons within the substantia nigra pars compacta and a depletion of postsynaptic dopamine within the striatum (Shimohama et al., 2003). This deficit in dopaminergic function results in motor behavioral abnormalities including postural imbalance, rigidity, uncontrollable tremor and bradykinesia (Lotharius and Brundin, 2002). The severity of these motor symptoms has been linked to the loss of dopaminergic neurons in the substantia nigra (Grealish et al., 2010; Iancu et al., 2005). Oxidative stress is thought to be a major contributing factor to the neurodegeneration associated with Parkinson's disease, as dopamine neurons are particularly prone to an imbalance between the generation of free radicals versus antioxidant defense activity (Coyle and Puttfarcken, 1993; Jenner, 1992; Taylor et al., 2013). This involves the continuous production of reactive oxygen species via autoxidation and monoamine oxidase-mediated metabolism of dopamine, and the presence of increased iron and lower total glutathione levels in the substantia nigra, as compared with other brain regions (Berg et al., 2004; Jenner, 2003).

Melatonin (N-acetyl-5-methoxytryptamine) is an indoleamine hormone that is secreted by the pineal gland, but also produced in other organs including the gastrointestinal tract, ovaries, testes, bone marrow, and eyes (Esposito and Cuzzocrea, 2010; Singhal et al., 2012). Melatonin has been detected in essentially all biological fluids such as blood, cerebrospinal fluid, bile, and saliva (Acuña-Castroviejo et al., 2014). There are two high-affinity G-protein coupled melatonin receptor subtypes, MT_1 and MT_2, which can couple to multiple signal transduction cascades (Hardeland et al., 2011; Von Gall et al., 2002). A third low-affinity binding site for melatonin, referred to as MT_3, has been identified as the detoxifying enzyme, quinone reductase 2 (Luchetti et al., 2010). Beyond its role in maintaining circadian rhythmicity, homeostasis, and modulation of neuroendocrine and immune function (Acuña-Castroviejo et al., 2014; Hardeland et al., 2011; Macchi and Bruce, 2004), melatonin and its metabolites have antioxidative and free-radical scavenging properties (Borah and Mohanakumar, 2009; Galano et al., 2011; Reiter et al., 2004), and are protective against mitochondrial disease (Martín et al., 2002; Reiter et al., 2008; Srinivasan et al., 2011). Previous studies have demonstrated that melatonin is neuroprotective in the 6-hydroxydopamine (6-OHDA) (Borah and Mohanakumar, 2009; Sharma et al., 2006), 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (Acuna-Castroviejo et al., 1997; Thomas and Mohanakumar, 2004), and systemic rotenone models of Parkinson's disease (Bassani et al., 2014). Researchers have postulated that the neuroprotective effects of melatonin may be due to its actions as an antioxidant and free radical scavenger (Lin et al., 2008; Mayo et al., 2005), as well as its ability to increase the activity of mitochondrial complexes I and IV (Martín et al., 2000). When melatonin is administered at low doses within its endogenous physiological range, it can protect against decreased mitochondrial complex I activity (Dabbeni-Sala et al., 2001) and tyrosine hydroxylase (TH) depletion following 6-OHDA lesioning (Sharma et al., 2006).

Several studies have reported that environmental risk factors such as pesticide exposure may be a major cause of Parkinson's disease. Interestingly, many pesticides can inhibit the mitochondrial electron transport chain, and this dysfunction is thought to be one of the key factors in the development of various neurodegenerative disorders (Berg et al., 2004; Von Bohlen und Halbach et al., 2004; Wallace and Starkov, 2000). Rotenone, which is used as a pesticide and insecticide, has been shown to reproduce many of the behavioral and pathological features of Parkinson's disease by inhibiting mitochondrial complex I activity, with consequent degeneration of dopaminergic neurons within the substantia nigra and striatum (Alam and Schmidt, 2002; Yang et al., 2006). Systemic administration of rotenone has been used as a model of Parkinson's disease, but its deleterious effects including high morbidity and mortality (Betarbet et al., 2000; Cannon et al., 2009; Monti et al., 2010), make it unsuitable for extended studies of neuroprotection. In contrast, the infusion of rotenone into the striatum was found to produce a healthy and useful parkinsonian model, as shown by behavioral, immunohistochemical and biochemical analyses of nigrostriatal function (Carriere et al., 2014; Mulcahy et al., 2011). In the present study, we have examined the neuroprotective effects of chronic low-dose melatonin treatment in this intrastriatal rotenone model of Parkinson's disease.

2. Results

2.1. *Unilateral intrastriatal injection of rotenone is not harmful in rats*

Throughout the duration of this study, a 100% survival rate was observed in both lesioned and control animals. Furthermore, there were no significant differences in either body weight (Fig. 1A) or water consumption (Fig. 1B) between treatment groups.

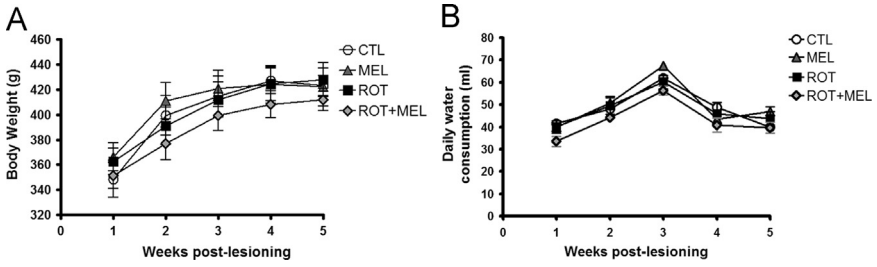

Fig. 1 – Unilateral intrastriatal injection of rotenone does not affect rat health. There were no significant differences in body weight (A) or water consumption (B) between treatment groups.