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INTERVENTION WITH EXERCISE RESTORES MOTOR DEFICITS BUT NOT NIGROSTRIATAL LOSS IN A PROGRESSIVE MPTP MOUSE MODEL OF PARKINSON'S DISEASE ☆

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Abstract—Many studies have investigated exercise therapy in Parkinson's disease (PD) and have shown benefits in improving motor deficits. However, exercise does not slow down the progression of the disease or induce the revival of lost nigrostriatal neurons. To examine the dichotomy of behavioral improvement without the slowing or recovery of dopaminergic cell or terminal loss, we tested exercise therapy in an intervention paradigm where voluntary running wheels were installed half-way through our progressive PD mouse model. In our model, 1-methyl-4-phenyl-1,2,3,6-tetra hydropyridine (MPTP) is administered over 4 weeks with increased doses each week (8, 16, 24, 32-kg/mg). We found that after 4 weeks of MPTP treatment, mice that volunteered to exercise had behavioral recovery in several measures despite the loss of 73% and 53% tyrosine hydroxylase (TH) within the dorsolateral (DL) striatum and the substantia nigra (SN), respectively which was equivalent to the loss seen in the mice that did not exercise but were also administered MPTP for 4 weeks. Mice treated with 4 weeks of MPTP showed a 41% loss of vesicular monoamine transporter II (VMAT2), a 71% increase in the ratio of glycosylated/non-glycosylated dopamine transporter (DAT), and significant increases in glutamate transporters including VGLUT1, GLT-1, and excitatory amino acid carrier 1. MPTP mice that exercised showed recovery of all these biomarkers back to the levels seen in the vehicle group and showed less inflammation compared to the mice treated with MPTP for 4 weeks. Even though we did not measure tissue dopamine (DA) concentration, our data suggest that exercise does not alleviate motor deficits by sparing nigrostriatal neurons, but perhaps by stabilizing the extraneuronal neurotransmitters, as evident by a recovery of DA and glutamate transporters. However, suppressing inflammation could be another mechanism of this locomotor recovery. Although exercise will not be a successful treatment alone, it could supplement other pharmaceutical approaches to PD therapy. Published by Elsevier Ltd. on behalf of IBRO.

Key words: exercise, motor behavior, MPTP, Parkinson's disease, glutamate transporters, tyrosine hydroxylase.

INTRODUCTION

In the clinic and in animal models, exercise has been consistently shown to alleviate some of the motor deficits associated with Parkinson's disease (PD). PD is a common neurodegenerative disorder caused by the loss of dopaminergic neurons in the nigrostriatal pathway. This loss of dopamine (DA) also results in changes in striatal glutamate (Klockgether et al., 1991; Meshul et al., 1999; Robinson et al., 2003; Walker et al 2009) which creates an imbalance between DA and glutamate neurotransmitters. Whether this imbalance of DA and glutamate is a cause or a result of PD is unknown, and unfortunately, as the degeneration progresses over time so does the impairment of basal ganglion-stimulated motor behaviors (Meshul et al., 1999; Touchon et al., 2004; Holmer et al., 2005; Smith et al., 2011). As seen clinically and in animal models, exercise has shown to attenuate motor deficits in PD, but it does not seem to provoke recovery of the lost neurons nor prevent the progressive nature of the disease (Fisher et al., 2004; Fisher et al., 2008; Al-Jarrah et al., 2007; Petzinger et al., 2007; Pothakos et al., 2009; Petzinger et al., 2010; Vučković et al., 2010; Petzinger et al., 2013). This suggests that the behavioral recovery observed must be due to exercise inducing other

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Abbreviations: BDNF, brain-derived neurotrophic factor; DA, dopamine; DAT, dopamine transporter; DL, dorsolateral; EAAC1, excitatory amino acid carrier 1; GFAP, glial fibrillary acidic protein; GLAST, glutamate aspartate transporter; GLT-1, glutamate transporter 1; IHC, immunohistochemistry; ir, immunoreactive; NFATc3, nuclear factor of activated T-cells cytoplasmic 3; PD, Parkinson's disease; pTrkB, phosphorylated tyrosine kinase receptor B; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; SN, substantia nigra; SNpc, substantia nigra pars compacta; TBST, tris-buffered saline tween 20; TH, tyrosine hydroxylase; TrkB, tyrosine kinase receptor B; VGLUT1, vesicular glutamate transporter 1; VGLUT2, vesicular glutamate transporter 2; VMAT2, vesicular mono amine transporter 2.

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