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Editorial

Exercise as a Buttress against Parkinson's Disease

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Abstract

The integrity of the nigrostriatal dopaminergic system underpins the capacity to initiate and control movement with loss of dopamine a central aspect of inability to express activity. Effective strategies for enhancing physical exercise provide both preventional and interventional ingredients for maintaining movement and/or reinstating movement among patients with Parkinson's disease, as well as improving the performance of non-motor behaviors. The relative loss or availability of striatal dopamine correlates directly with the expression of locomotor behavior in mice. Regular and persistent maintenance of exercise programs ensures a plethora of lasting benefits that include enhanced or repaired functional connectivity, and elevations of mood, cognitive performance, sleep quality and motor ability concurrent with reductions in pain, apathy and weight problems.

Keywords: Motor; Dopamine; Exercise; Activity; Intervention; Prevention; Performance.

Taking into account, the burgeoning proportion of individuals presenting more-or-less sedentary occupations/lifestyles, physical exercise, defined as a planned, structured physical activity with the purpose of improving one or more aspects of physical fitness and functional capacity, presenting a useful and non-invasive, non-pharmacological health strategy, renders a lifestyle encompassing perhaps the most effective health-promoting behavior available to individuals with positive outcomes for ageing as well as both neurologic and psychiatric conditions. Since ageing-related disorders may be expected to increase and the relative benefits of new and improved chemotherapies will probably not develop apace, it seems necessary that preventional and interventional measures focus upon lifestyle suitability. Taking into account the prolonged prodromal stage of PD, in most cases, renders it a risky notion to decide whether or not insidious disease expression leads to a reduction of physical activity years before motor symptom onset and PD diagnosis (Ascherio and Schwarzschild, 2016). Physical exercise/activity improves neuroimmune functioning, ensures the prevention/intervention of chronic heart disease, cardiovascular problems, type II diabetes, obesity and psychological Ill-health, e.g. depressiveness and apathy, all of which may exacerbate the severity of Parkinson's disease (PD), and provide a buttress to guard against the risk for developing future parkinsonism in different populations. Thus, despite limited success reflected by longitudinal studies for assessing the its efficacy in PD patients, exercise is recommended to restore and reinstate functionality in the dopamine (DA) system and promote better performances to improve motor functions in individuals (Fisher et al., 2013, 2014; Goodwin et al., 2008, 2011, 2015; Petzinger et al., 2015). In this context, it has emerged that all types of physical activity, and not just exercise regimes, may decrease the risk for PD or decelerate the rate of disorder progression (Ellis et al., 2013; Paul et al., 2016; Yang et al., 2015), not just with regard to symptom-profiles but also affecting accidents due falls, and cognition, mood and sleep domains (Reynolds et al., 2016; Sparrow et al., 2016). Nevertheless, there is meagre support for the contention that any particular type of exercise, e.g. the superiority of progressive resistance training, in comparison with other physical training for rehabilitation in PD ought to prevail (Saltychev et al., 2016). Sedentary lifestyles are implicated in several neurodegenerative conditions that may or may not co-occur with PD through the shared propensities for neuroinflammation, oxidative stress and/or metabolic syndrome at cellular levels (Jang et al., 2016; La Hue et al., 2016).

The necessity for establishing and promoting strategies and tactics for embracing physical activity and reducing the time spent dwelling/retreating within sedentary behaviors among elderly populations with mild to moderate PD has never been greater (BenkaWallen et al., 2015). It is important also to be aware that PD patients often present a concatenation of non-motor symptoms, such as cognitive impairment and dementia (Chen et al., 2016), sleep problems (Pagano et al., 2016), depression and anxiety (Taylor et al., 2016), apathy (Alzahrani et al., 2016), pain (Young Blood et al., 2016) and fatigue (Martino et al., 2016). Non-exercise physi-

cal activity, with positive effects upon functional performance, has been shown to be related to the severity of motor symptoms in PD autonomous from the magnitude of nigrostriatal degeneration depicting an inverse relationship between motor UPDRS severity scores and duration of non-exercise physical activity (Snider et al., 2015). Under laboratory conditions utilizing the MPTP mouse model of PD, physical exercise has been found to alleviated akinesia and DA deficits (Archer and Fredriksson, 2010, 2012, 2013; Archer and Kostrzewa, 2016; Archer et al., 2014; Fredriksson et al., 2011) and ameliorate several parameters of regional and cellular neurodegeneration/neuroinflammation by promoting synaptic plasticity (Shin et al., 2016), neural precursor cell proliferation in the hippocampus (Klein et al., 2016; Sung, 2015), activations of antioxidant systems (Tsou et al., 2015) and mitochondrial functioning (Cheng et al., 2016; Gonçalves et al., 2016; Marques-Aleixo et al., 2016), as well as providing improved cognitive performan and DA integrity (Aguiar et al., 2016). In order to derive a more stringent test of parkinsonism in the laboratory, Hood et al. (2016) administered aged mice (16 month-old mice) with progressive doses of the selective DA neurotoxin, MPTP, that induced a 55% loss of striatal tyrosine hydroxylase (TH), and a somewhat higher loss of dopamine transporter (DAT). Exercise, performed on a treadmill at 18 cm/sec over 1 hour, 5 days/week, over 4 weeks, did not alter the loss of TH or DAT in the MPTP-denervated mice although spontaneous locomotion was elevated in these mice. Nevertheless, despite this latter observation a strong relationship between sedentary or exercise conditions – MPTP-lesioned or intact (vehicle-treated) mice – high or low levels of DA and high or low levels of spontaneous locomotor behavior in a correlational analysis among 50 individuals mice (see Figure 1, below).

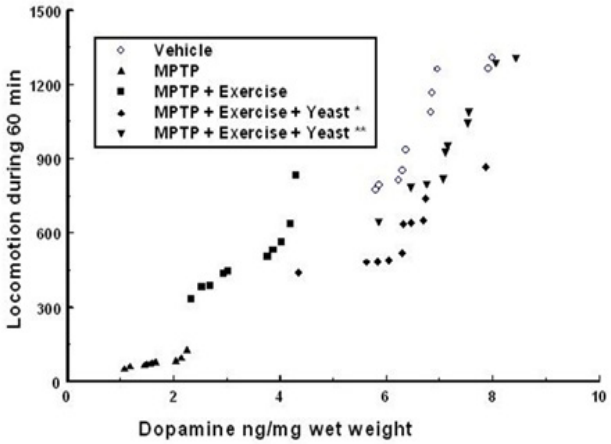

Figure 1: Mean locomotion counts in the Spontaneous Motor activity test during Week 10 (Friday test) in relation to mean striatal dopamine concentration (ng/mg) by each of the five groups: Vehicle, MPTP, MPTP+Exercise, MPTP+Exercise+MilmedI (MPTP+Exercise+Yeast*) and MPTP+Exercise+MilmedII (MPTP+Exercise+Yeast**) groups, and by all 50 mice studied. Pearson's correlation coefficient, r = 0.914, (N = 50) $p < 0.00001$. Yeast* = MilmedI; Yeast** = MilmedII. Methods and Procedures for MPTP and Milmed treatments as well as the exercise (running-wheels) protocols were carried out and maintained as detailed previously (Archer and Fredriksson, 2010, 2012, 2013; Archer et al., 2014; Fredriksson et al., 2011).

This correlational analysis implies that a sufficiency of locomotor behavior is dependent upon the integrity of DA neurons. Loss of DA due to MPTP treatment accompanied by sedentary conditions leads to low levels of activity. As hypothesized (Kravitz et al., 2016) deficits in DA signaling contribute to a sedentary state leading to obesity. This notion is underpinned by: (i) impairments in DA synthesis, release and receptor function relate to obesogenicdiets, and (ii) since movement initiation and control requires intact striatal DA, loss of DA is central to sedentary behavior.

Human studies of PD patients point to marked improvement of gait, balance and mobility due to the organization of supervised exercise programs using fMRI to promote improvements in functional connectivity (Alberts et al., 2016; Beall et al., 2013; Shah et al., 2016). In a study of 19 early PD patients and 20 healthy controls who took part in a supervised, high-intensity, stationary recumbent bicycle exercise program (3 occasions/week over 12 weeks) utilizing maximal aerobic power, Duchesne et al. (2016) employed brain scanning to examine changes related to performance of an implicit version of the serial reaction time task before and after the learning task. Pre-post implicit motor sequence learning-related escalations of functional activity were observed in the hippocampus, striatum and cerebellum of the PD patients; these functional activity increments were correlated with increases in aerobic fitness with regard to the hippocampus but not the cerebellum which presented a negative relationship to aerobic fitness. They concluded that exercise induced alterations in brain regions associated with motor learning accompanied by improved motor performance in PD patients. Despite the prolonged prodromal stage of PD, there is a sufficiency of evidence to maintain that sports activity/physical training combined with high levels of overall physical activity by youth and young adults provide protective measures unless pre-existing markers for biologic or genetic factors that lower PD risk are present (Shih et al., 2016). Motor training exercises involving 'coordination and manipulation therapy' improved mobility, balance and cardiac function in PD patients over the course of a 12-month period (Zhao et al., 2016). Furthermore, exercise programs designed for PD patients alleviated non-motor symptoms over several domains that included depression, cognition, fatigue, apathy, anxiety, and sleep (Cusso et al., 2016). Lauze et al. (2016) found that physical exercise/activity interventions induced positive effects upon physical and functional capacities whereas effects upon disease symptoms and psychosocial aspects, although present, were to a lesser extent and with greater variability. One aspect for concern is that exercise studies in PD and dementia consistently exclude Lewy Body dementia patients (Inskip et al., 2016), despite preliminary indications regarding exercise-induced improvements.

Conclusions

Excepting for hereditary predispositions and/or neurotoxicological environmental accidents, regular physical exercise that encompass a sufficient degree of physical effort and energy expenditure will serve as a proactive, preventional buttress against symptoms and biomarkers for

any forthcoming PD. Once a PD diagnosis has been assigned, it has been found to be essential that PD patients invest both intention and endeavor in maintain, or even increasing, exercise frequency, duration and intensity. The retroactive, self-destructive step of retreating into a sedentary, apathetic lifestyle presents the most debilitating and self-damaging scenario that may be contemplated; it should come as no surprise that the 'inactivity' complacence is associated with a myriad of non-motor symptoms to add to disorder progression.

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