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Enhancing Neuroplasticity in the Basal Ganglia: The Role of Exercise in Parkinson's Disease

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Abstract: Epidemiological and clinical trials have suggested that exercise is beneficial for patients with Parkinson's disease (PD). However, the underlying mechanisms and potential for disease modification are currently unknown. This review presents current findings from our laboratories in patients with PD and animal models. The data indicate that alterations in both dopaminergic and glutamatergic neurotransmission, induced by activity-dependent (exercise) processes, may mitigate the cortically driven hyper-excitability in the basal ganglia normally observed in the parkinsonian state. These insights have potential to identify novel therapeutic treatments capable of reversing or delaying disease progression in PD. © 2010 Movement Disorder Society

Key words: dopamine; MPTP; animal models; treadmill; glutamate; electrophysiology; PET imaging

INTRODUCTION

Parkinson's disease (PD) is characterized as a progressive neurodegenerative disease with no known cure. The primary pathology of PD is loss of substantia nigra pars compacta neurons accompanied by loss of striatal dopamine. Exercise has been shown to be beneficial in PD, yet the question remains whether exercise leads to central nervous system (CNS) compensatory or neuroprotective changes with potential to alter the natural course of the disease. Studies have demonstrated that the adult brain is altered by experience including exercise.[1–4] This phenomenon termed "activity-dependent neuroplasticity" is defined as modifications within the CNS, in response to physical activity that promotes a skill acquisition process.[5] As such (1) intensity; (2) specificity; (3) difficulty; and (4) complexity of practice appear to be important parameters for driving neuroplasticity and a potential lasting effect on both brain and behavior.[6,7] Although the importance of these parameters have been primarily established in healthy brain and in brain injury secondary to stroke, this framework has more recently been adopted to study activity-dependent neuroplasticity in neurodegenerative diseases, including PD, and to examine its potential to modify disease progression (Table 1).[8–21]

Using a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-(MPTP)-lesioned mouse model of PD, we have examined the effects of intensive treadmill exercise on activity-dependent neuroplasticity within the striatum. Our studies have focused on exercise-induced changes

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TABLE 1. *Practice variables important for evoking activity-dependent neuroplasticity- examples in brain injury (PD, stroke, spinal cord injury)*

Practice variable	Animal study	Human study
Intensity	Petzinger et al., 2007[20]; Tillerson et al., 2001[21]	Liepert, 2006[13]; Liepert et al., 2000[14]
Specificity	Fisher et al., 2004[19]; De Leon et al., 1999[18]; Tillakaratne, 2002[17]	Forrester et al., 2006[12]; Dobkin et al., 2004[11]
Difficulty	Friel and Nudo, 1998[16]	Wittenberg et al., 2003[10]; Johansen-Berg et al., 2002[9]
Complexity	Jones et al., 1999[15]	Winstein et al., 1997[8]

in dopaminergic and glutamatergic neurotransmission. Interactions between these systems are important for normal basal ganglia function. Both dopaminergic neurons from the substantia nigra as well as glutamatergic afferents from the cerebral cortex and thalamus synapse in close proximity on medium spiny neurons (MSN) of the striatum and together dictate the electrophysiological properties of these cells.[22,23] There is compelling data that the loss of nigral dopaminergic neurons is responsible for an increase in glutamatergic corticostriatal drive at the level of the MSNs, contributing to the motor deficits in PD.[24–27] One possible mechanism by which exercise may drive activity-dependent neuroplasticity in PD may be through mitigating corticostriatal hyperactivity (i.e., hyperexcitability), by modulating dopaminergic signaling, and/or diminishing glutamatergic neurotransmission.

CHANGES IN DOPAMINERGIC NEUROTRANSMISSION WITH EXERCISE

Our MPTP model consisted of administration of four intraperitoneal injections of 20 mg/kg (free-base) at 2-hour intervals for a total administration of 80 mg/kg, which leads to 60–70% of nigrostriatal dopaminergic neuronal death. Five days post-lesioning, when cell death is complete, mice were subjected to exercise on a motorized treadmill for 30 days (5 days/week). Task specific benefits were observed as improvements in both running velocity and endurance. Improvement was also observed on a motor task that was designed to assess balance.[20] These benefits were accompanied by increased dopamine availability, revealed as an increase in stimulus-evoked release and a decrease in dopamine decay as measured by fast-scan cyclic voltammetry. Interestingly this exercise effect of dopamine release was most pronounced within the dorsolateral striatum. Since the primary role of this area is in motor function, use-dependent forms of neuroplasticity may explain this regional specificity in an exercise-induced effect. Additionally, we observed an increase in expression of dopamine D2 receptor mRNA and down regulation of the dopamine transporter (DAT) protein within the striatum, changes that are consistent with increased dopaminergic signaling.[19] A primary role of DAT is to clear dopamine from the extracellular space. Down-regulation of DAT protein leads to increased synaptic dopamine availability for dopamine receptor binding.[28] The binding of dopamine to both the D1 and D2 receptors are required in the normal brain to elicit a motor response. After basal ganglia injury, however, this synergy is lost and dopamine binding to either D1 or D2 may elicit a motor response.[29] In addition, dopamine binding to the D2 receptor alone may elicit a robust response that may be attributed to its heightened sensitivity after lesioning.[30] Thus, an exercise-induced increase in D2 receptor expression coupled with an increase in the synaptic availability of dopamine may be sufficient to elicit increased dopaminergic neurotransmission and improved motor function. Preliminary Positron Emission Tomography (PET) imaging studies in our lab using 18F-Fallypride, a benzamide ligand with high affinity for the D2 receptor, have demonstrated an exercise-induced increase in binding affinity within the striatum, confirming our D2 receptor findings. Interestingly, we observed no exercise-induced changes in either the total level of striatal dopamine, as measured by HPLC in tissue homogenates, or the number of dopaminergic substantia nigra neurons, measured by immunohistochemistry. These findings suggest that high intensity exercise leads to compensatory changes in dopamine handling and neurotransmission.[20]

CHANGES IN GLUTAMATERGIC NEUROTRANSMISSION AND EXERCISE

Studies in our laboratory also suggest that exercise-induced neuroplasticity of the glutamatergic system may diminish corticostriatal hyperexcitability and underlie the motor improvement observed in our exercised mice. Specifically, using immuno-electron microscopy, we have observed that treadmill exercise reversed the MPTP-induced increase level of *presynaptic* glutamate immunolabeling within striatal terminals, suggesting that exercise reduced the amount of glutamate available for release.[19] In addition, new studies in our lab demonstrate that treadmill exercise modulates postsynaptic AMPA receptor (AMPAR) subunit expression through an increase in both GluR2 and phosphorylation of GluR2 at serine 880.[31] The poten-

tial process by which these changes may lead to decreased glutamatergic hyperexcitability could involve a general reduction in glutamatergic neurotransmission and synaptic strength (i.e., long-term depression). We have been interested in examining exercise induced changes in the AMPAR, as it is responsible for the majority of fast excitatory neurotransmission in the CNS and it mediates activity-dependent processes that alter synaptic strength.[32,33] Located on the postsynaptic MSN, the AMPAR is an ionotropic channel that converts the chemical signal of presynaptically released glutamate into a postsynaptic electrical signal through the mobilization of cations such as Na^+ and Ca^{2+}.[34] The AMPAR is a heteromeric tetramer consisting of four subunits GluR1–4; the most abundant in the striatum are GluR1 and GluR2.[32,35] Alterations in GluR2 expression and phosphorylation have been associated with diminished synaptic strength (i.e., long-term depression).[32,36–38] Increased expression of the GluR2 subunit within the tetrameric complex of the AMPAR, as seen in our exercised mice, creates an additional positive charge within the channel pore, which impedes cation flow, lowers calcium conductance and thus diminishes synaptic strength.[34,39] Another means of regulating AMPAR transmission occurs via trafficking and removal of the AMPAR from the membrane. This may be regulated through phosphorylation of AMPAR subunits, including GluR2. Specifically, phosphorylation of serine 880 on the GluR2 subunit leads to internalization of the entire receptor and decreased synaptic strength (i.e., long-term depression).[33,40] Studies in our laboratory reveal that treadmill exercise increases the phosphorylation state of GluR2 at serine 880 in MPTP-lesioned mice. Additional electrophysiological studies indicate that exercise-induced changes in the expression of GluR2 subunit lead to decreased excitability in the MSNs, demonstrated by reduced EPSCs generated by cortical stimulation. They have also shown reduced polyamine sensitivity and loss of rectification in AMPAR conductance at depolarized membrane potentials of MSNs. These findings provide further evidence that changes in GluR2 expression are the basis for the exercise-induced reduction in the EPSCs of MSNs.[34,39] Finally, consistent with an exercise mediated attenuation of corticostriatal hyperexcitability, we have also observed an exercise induced decrease in cerebral blood flow in corticostriatal regions using cerebral perfusion studies in rats with basal ganglia injury.[41] Collectively our data in both mouse and rat models of basal ganglia injury indicate that exercise training attenuates the over-activation in basal ganglia-cortical circuits.

In summary, these findings suggests that alterations in both dopaminergic and glutamatergic neurotransmission through activity-dependent processes modulates cortical hyper-excitability of the basal ganglia. Modulation of cortical hyper-excitability may be what underlies exercise-induced behavioral improvement. An important next step is to translate these findings to humans, and to investigate whether high intensity exercise has similar benefits in PD.

ACTIVITY-DEPENDENT NEUROPLASTICITY AND PARKINSON'S DISEASE

As our studies in animal models suggested that high intensity is a characteristic of exercise that may be specifically important in promoting activity-dependent neuroplasticity, we designed a study to the use of Body-weight supported treadmill training (BWSTT) to drive intensity of practice in individuals with PD. BWSTT involves the use of an overhead harness that allows exercise intensity to be safely escalated by increasing treadmill velocity. Thus, subjects are able to walk at higher gait speeds than they are able to obtain over-ground. They also experience high repetition of stepping, are actively engaged in the training, and have the sensory experience of normal gait kinematics. Patients with PD, no more than 3 years from initial diagnosis were asked to exercise at high intensity, 3 times per week for 8 weeks using body-weight BWSTT. Outcomes consisted of measures of motor performance, including gait kinematics, sit-to-stand, and stair climbing. Unique to this human trial, and directly related to our animal finding, was the inclusion of measures of cortical excitability using transcranial magnetic stimulation (TMS). TMS is a noninvasive method of stimulating the brain and provides a tool for assessment of excitability of the corticospinal motor system. Single TMS pulses are applied over the motor cortex while recording surface electromyography (EMG) responses over a contralateral target muscle. If the target muscle is preactivated (contracted), the TMS pulse induces a characteristic transient period of EMG silence called the cortical silent period (CSP). Importantly for this study, single pulse TMS studies have shown systematic abnormalities of CSP and other corticoexcitability measures in individuals with PD. In general, these abnormalities reflect cortical hyper-excitability in PD compared to non-PD control subjects.[42,43] As CSP represents inhibitory influences on cortical excitability, higher excitability would be evident as a shortened CSP duration. In fact, shortened CSP durations are among the most consistent and widely repro-

duced TMS finding amongst PD patients.[44] Further, symptomatic treatment of PD with surgical or pharmacological interventions is associated with lengthening of the CSP towards levels seen in control subjects.[45,46] Thus, CSP duration could underlie symptomatic improvement, such as improved motor performance. Thus, not only is TMS an excellent tool to measure CSP duration and to examine possible exercise-induced changes in PD, but more importantly TMS may be used to support the existence of CNS changes in response to different exercise parameters including intensity. After 24 sessions of BWSTT subjects demonstrated improved walking performance including increased gait velocity, stride length, step length, and hip and ankle joint excursion, and improved weight distribution during sit-to-stand. More importantly, these subjects also showed reversal of cortical hyper-excitability indicated by increased CSP. In fact, every subject undergoing BWSTT showed exercise-induced lengthening of CSP. To our knowledge, this was the first demonstration of exercise-induced cortical changes in the brain in individuals with PD.

FUTURE DIRECTIONS

We have shown that exercise may influence activity-dependent processes in the basal ganglia through alterations in dopaminergic and glutamatergic neurotransmission. In addition, we demonstrate that exercise-induced behavioral benefits may be in part due to changes in cortical hyper-excitability normally observed in the dopamine depleted state, as in PD. Although we have demonstrated the potential impact of BWSTT on the human condition, a critical next step is to determine whether exercise induces or is associated with a disease modifying effect in PD. The implications for our understanding of the impact of exercise in PD are broad. Not only is there potential to develop new insights into mechanisms of neuroplasticity and motor recovery in PD, but also the study of exercise may lead to the development of novel therapeutics, perhaps even nonpharmacological approaches to delay or reverse disease progression in PD.

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