Neuroprotection by Physical Activity

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Physical activity is neuroprotective, lowering the risk of neurological diseases, increasing overall brain health, and leading to specific gene expression changes throughout the brain. In particular it upregulates growth factors, immediate early genes, immune genes, synaptic trafficking genes, neurotransmitter systems, and activates the extracellular signal-regulated kinases 1 and 2 (ERK1/2) and protein kinase B (PKB/AKT) signal transduction pathways. The beneficial effects of physical activity are supported in animal models of Parkinson's disease (PD). The unilateral 6-hydroxydopamine (6-OHDA) rat and bilateral 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse PD models show behavioral and biochemical sparing in the striatum after forced limb use, and forced treadmill running.

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PHYSICAL ACTIVITY BENEFICIALLY AFFECTS THE BRAIN

A growing body of evidence suggests that mild[1], moderate, and vigorous physical activity[2] are neuroprotective, decreasing the risk of many brain disorders including ischemic stroke[3,4], Alzheimer's disease[1,5], and Parkinson's disease (PD)[2]. Many clinicians routinely recommend physical activity for those suffering from the effects of these diseases. In PD patients physical activity has been shown to improve gait, tremor, grip strength, balance, and motor coordination[6,7]. Regardless of disease presence physical activity can improve sleep[8], cognition[9,10], and decrease depression[11-13]. Supporting animal data show that exercise and environmental enrichment enhance learning and memory, increase neuronal survival, increase resistance to brain insults, trigger synaptogenesis, promote brain angiogenesis, and promote neurogenesis[14,15]. We believe physical activity affects the entire brain and have previously studied the effects of physical activity on the brain alone (unpublished) and in an Alzheimer's disease model[14].

Exercise gene expression changes have been studied largely in the hippocampus, a site of neurogenesis crucial in spatial learning and memory[16-18]. Initial examinations showed increases in nerve growth factor (NGF) and brain derived neurotrophic factor (BDNF) throughout the brain with the most dramatic increases in the hippocampus and posterior cortex[16]. In the hippocampus voluntary wheel running also increases the expression of phosphoinositide kinase 3 (PI3K), protein kinase B (PKB/AKT), BDNF, cAMP response element binding (CREB), and tyrosine kinase B (TrkB, the BDNF receptor)[19]. It is now understood that physical activity modulates the BDNF system through intracellular signaling systems such as AKT and extracellular signal-regulated kinases 1 and 2 (ERK1/2) with endpoint effects on the production, phosphorylation, and function of CREB[20] (**Figure 1**). AKT also phosphorylates forkhead box O3 (FOXO3), a transcription factor, causing its retention in the cytoplasm. When in the nucleus, FOXO3 likely triggers apoptosis by inducing the expression of genes critical for cell death[21]. Keeping FOXO3 in the cytoplasm, therefore, may promote cell survival.

Two DNA microarray studies comparing voluntary running rats to their sedentary counterparts revealed the upregulation of genes involved in neuronal activity, synaptic structure, and neuronal plasticity in the hippocampus[22, 23]. These genes included: neurotrophins, immediate early genes (IEGs), immune genes, and trafficking proteins[22]. The second study also revealed the upregulation of neurotrophic factors (NGF, BDNF, and basic fibroblast growth factor, FGF-2) as well genes involved in synaptic trafficking (syntaxin, synapsin I, and synaptotagmin), neutrotransmitter systems (ionotropic glutamate receptor subunits NR2A and NR2B, excitatory amino-acid carrier 1 (EAAC1), γ-aminobutyric-acid receptor β3 ($GABA_A$ β3), and glutaminic acid decarboxylase (GAD65)), and signal transduction pathways (ERK1/2, and protein kinase C (PKC))[23]. They furthered showed that CaMKIIδ was more highly expressed during acute exercise (3 days) and that ERK1/2 was more highly expressed during chronic exercise (28 days)[23]. CaMKII is activated by increases in Ca^{2+} (**Figure 1**) and phosphorylates many substrates including components of the ERK1/2 signal transduction pathway. **Figure 1** shows the BDNF – TrkB interaction, but most growth factors, including glial derived neurotrophic factor (GDNF), NGF, and FGF-2, activate the same signaling cascades[24-26].

Immediately following both voluntary wheel running and treadmill running in rodents there is an increase of corticosterone (indicative of the stress response) along with a decrease in phosphorylated CREB (pCREB) with treadmill running animals displaying a higher elevation of corticosterone and

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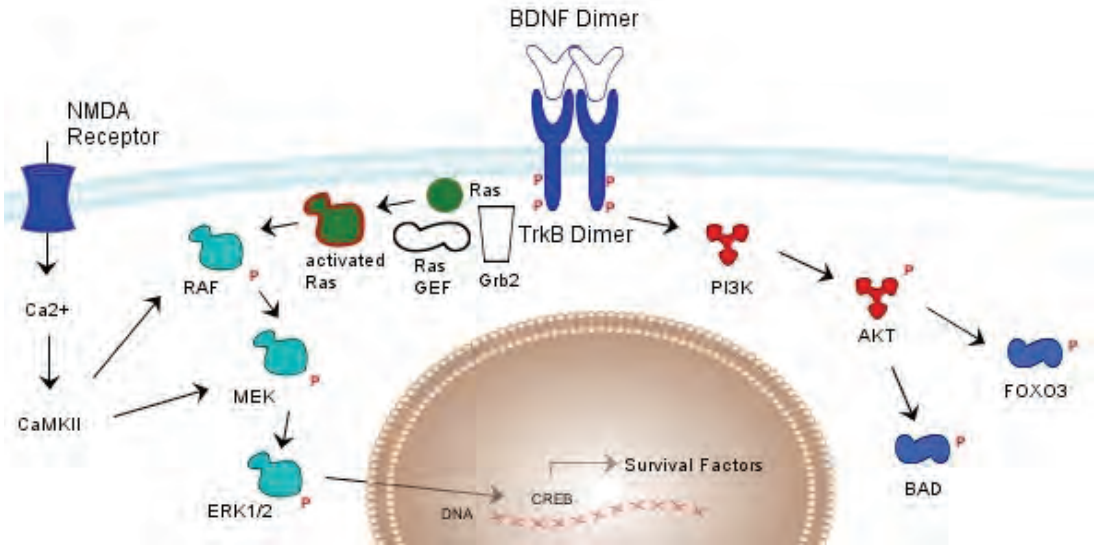

Figure 1 | **BDNF Signaling Pathways**. BDNF activates the AKT and ERK1/2 pathways. PI3K indirectly causes the phosphorylation of AKT, which phosphorylates and inhibits death proteins (FOXO3 and BAD). ERK1/2 is phosphorylated by a kinase cascade (RAF to MEK to ERK1/2) that is activated by RAS, which is activated by RAS-GEF binding to Grb2 bound to phosphorylated TrkB dimers. This pathway also can be phosphorylated by CaMKII[19, 21-23].

decrease in pCREB[27]. Though of small effect, corticosterone is known to decrease the expression of BDNF in the dentate gyrus (DG) of the hippocampus[28]. If corticosterone is administered subcutaneously to adrenalectomized animals, there is a transient decrease in BDNF at 4 and 6 hours and an increase in its TrkB receptor at 6 and 12 hours[29]. This immediate stress response, however, is likely specific to acute exercise and may diminish with repeated exercise exposures[27]. Studies have shown that the increases in corticosterone do fall off over time[30,31]. After five weeks of wheel running, there is no difference in corticosteroid response in a 20 minute restraint stress test between exercised and sedentary animals[31]. Lastly, in a study that standardized the distance ran between rats, it was shown that voluntary exercisers ran more rapidly for a shorter time than forced exercisers and had less bromodeoxyuridine (BrdU) incorporation into the DNA of hippocampal slices (an indication of neurogenesis)[32]. These studies show that although forced exercise may transiently activate the stress response, long term forced exercise may be more beneficial.

PARKINSON'S DISEASE MODELS

After extensive investigation of the hippocampus our attention has turned to brain areas related to PD. PD is characterized by tremor at rest, muscle rigidity, postural instability, and a slowing of physical movement (bradykinesia) that can progress to a complete loss of movement (akinesia)[33]. As disabling motor symptoms are managed with medications (such as L-3, 4-dihydroxyphenylalanine, L-DOPA), other symptoms become more apparent. These include depression, high level cognitive dysfunction, and subtle language problems[34,35]. It is thought that symptoms emerge from the progressive loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc). At the onset of motor symptoms dopaminergic neuron loss is already 60-80%. These neurons normally project to the striatum forming the nigrostriatal dopaminergic pathway[33]. Insufficient action of dopamine (DA) on the striatum is believed to lead to decreased stimulation of the motor cortex and PD symptoms[34-38].

PD is also often characterized by the presence of Lewy bodies. These proteinaceous cytoplasmic inclusions composed of α-synuclein, are present in the locus ceruleus, nucleus basalis of Meynert, dorsal motor nucleus of the vagus, hypothalamus, and other sites of some PD patients, but 20-40% patients with neuronal loss in the SNpc have no Lewy bodies raising the question of whether Lewy bodies are markers of presymptomatic PD or a feature of normal aging[39]. Common treatments aim to replace and stabilize dopamine. The most common is L-DOPA, which crosses the blood brain barrier and is converted to DA. Neuroprotective strategies, such as physical activity, however, aim to slow dopaminergic neuron loss and lead to improved functioning of the remaining neurons[33].

It is difficult to model the progressive nature of PD in animals, but two models, 6-hydroxydopamine (6-OHDA) and 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP), are able to model some of the pathology and symptoms. 6-OHDA causes the degeneration of catecholaminergic neurons (DA, norepinephrine, and epinephrine) when applied to the

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brain. For localized dopaminergic degeneration it is stereotactically injected into the SNpc, the nigrostriatal tract (medial forebrain bundle), or the striatum of one brain hemisphere[33]. Dopaminergic neurons start degenerating within 24 hours and striatal DA is depleted 80-90% 2-3 days later corresponding with bradykinesia, impairment of movement initiation, and skilled motor functions on the contralateral side of the body[33,39]. SNpc degeneration also causes the upregulation of post synaptic DA receptors in the striatum. In a unilateral model this upregulation causes contralateral rotations with administration of a DA receptor agonist, apomorphine[36].

MPTP crosses the blood brain barrier and is metabolized by monoamine oxidase B (MAO-B) to 1-methyl-4-phenyl-2, 3-dihydropyridinium ion (MPP+). MPP+ is selectively taken up by the DA transporter (DAT) where it inhibits complex I of the mitochondrial electron transport chain, which mirrors the 30-40% decrease in mitochondrial electron chain complex I activity in the SNpc of PD patients[33]. Increased reactive oxygen species (hydrogen peroxide, superoxide, peroxyl radicals, nitric oxide, and hydroxyl radicals) caused by a dysfunctional complex I react with nucleic acids, proteins, lipids, and other molecules altering their structure, causing damage, and eventually leading to axon degeneration and neuron loss[40].

Acute bilateral MPTP exposure leads to 50-93% loss of cells in the SNpc and more than 99% loss of DA in the striatum leading to akinesia, rigidity, and in some species tremor[33]. A stable early stage unilateral model of PD (MPTP) was developed in middle-aged monkeys[41]. The most pronounced difference from acute bilateral models is the preservation of dopaminergic fiber projections to the caudate nucleus and putamen. Other studies support the concept that cell bodies of DA neurons can be maintained in the substantia nigra for long periods following axonal loss in the striatum[42]. The early stage model with greater preservation of nigrostriatal projections could be useful for testing neuroprotective strategies, such as exercise, to preserve and restore dopaminergic innervation to the striatum.

PHYSICAL ACTIVITY PROMOTES BEHAVIORAL AND BIOCHEMICAL SPARING

Increases in dendritic arborization and synapse number in the cortex have been associated with motor training[43-45]. Hence, Tillerson et al hypothesized that motor training might retard the loss of dopaminergic neuron projections from the SNpc to the striatum in a unilateral 6-OHDA rat model. After infusing 6-OHDA into the medial forebrain bundle (MFB), they forced the use of the impaired limb by casting the unimpaired limb on days 1-7, 3-9, or 7-13 after lesioning. Apomorphine-induced contralateral rotations and DA levels were used as a measure of SNpc dopaminergic neuron loss. Animals receiving a cast on days 1-7 and 3-9 did not show step or forelimb asymmetry, rotated significantly different from sham animals in response to apomorphine, and had significantly different levels of DA, DOPAC, or HVA from sham animals. Timing of exercise matters; early forced use (days 1-7 and 3-9), but not late forced use (days 7-13), of the impaired limb attenuated movement asymmetry and dopamine loss[45].

Tillerson switched to a forced treadmill running paradigm, as unilateral forced use is an exercise modality not commonly practiced in humans. They believed that treadmill running, like forced use, would attenuate DA loss and behavior. Rats were given either 6-OHDA and mice were given MPTP and forced to run until day 12 or 30 for behavioral tests and sacrificed for biochemical analysis. Moderate forced treadmill running reversed 6-OHDA movement impairments in rats after one day with 450 m/day of treadmill running, reversed MPTP movement impairments in mice after three days with 50 m/day, and attenuated striatal DA loss and DA terminal marker loss (DAT, VMAT, tyrosine hydroxylase (TH)) in both models[46]. Treadmill running, like forced use, attenuated both movement impairments and dopamine loss.

It is believed that mild stress can cancel the effect of neuroprotection. Both voluntary and forced exercise have been associated with mild stress. Howell et al addressed this issue by looking at the effect of stress on voluntary exercise. Animals were placed into three groups: runners allowed access to a running wheel, stressed runners allowed access to a running wheel (stressed with one hour of wheel immobilization a day, food deprivation, and a shift in the light dark cycle), and nonrunners. Both stressed runners and nonrunners had significantly more apomorphine rotations than runners alone with no difference in TH staining suggesting that mild stress can cancel the affect of exercise[47]. Earlier studies indicate that corticosterone, produced immediately following exercise, may diminish neuroprotection; these effects, however, wear off after five weeks[30-31]. Numerous other studies demonstrate that voluntary and forced exercise can ameliorate the behavioral and biochemical consequences of 6-OHDA and MPTP PD models[47-52] though the time, amount, method of exercise, and type of lesion do affect the behavioral and biochemical outcome.

In all of the studies the number of SNpc cells did not change with exercise[47-52]; rather, we believe behavioral and biochemical sparing comes from sparing of SNpc axons and terminals projecting to the striatum[51]. It has been hypothesized that forced use ameliorates the behavioral and biochemical effects of

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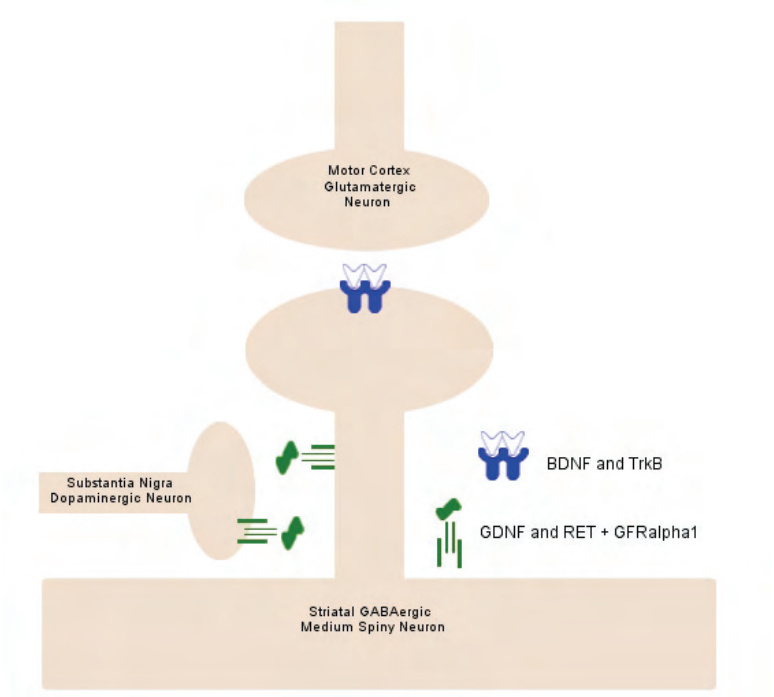

Figure 2 | **Sparing with Exercise.** Exercise results in an increase of neurotrophic factors and their receptors. Both BDNF and GDNF are increased with exercise. In the striatum we believe cortical BDNF increases the survival of striatal spines, while GDNF increases the survival of both SN terminals and striatal spines.

6-OHDA and MPTP through a cascade of events that involves GDNF[53], a potent survival factor for DA neurons[54]. There is a significant increase of striatal GDNF 24 and 72 hours after using a non-impaired limb[55]. In the striatum ERK1/2 activation by GDNF remains elevated up to 1 month afterwards[55,56]. The medium spiny neurons of the striatum receive BDNF from cortical input. They receive and produce GDNF. GDNF homodimers bind two GFRα1 receptors, which then bind two RET (Rearranged during Transfection) receptors, which cross phosphorylate each other in the striatum and SNpc. BDNF increases the survival of striatal spines, while GDNF increases the survival of both SNpc terminals and striatal spines (**Figure 2**). Exercise affects the entire brain with the upregulation of growth factors[16], and it seems most probable that the effects of exercise in PD would emerge at the intersection of the SNpc and motor cortex in the striatum.

CONCLUSIONS

Physical activity in PD has been investigated over the past decades. The 6-OHDA rat and MPTP mouse Parkinson's disease models show behavioral and biochemical sparing in the striatum after voluntary wheel running, forced limb use, and forced treadmill running though the most beneficial time (before or after lesioning), amount, and method (voluntary versus forced) of exercise for neuroprotection are still under investigation. Evidence suggests that reduced nigrostriatal degeneration is due in part to the upregulation of neurotrophic factors, one of the many affects of exercise, acting at the striatum.

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