Exercise and the brain: a slap on the HAND

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Regular exercise is good for the brain. It improves mood, lessens anxiety, and provides a hedge against depression (Salmon 2001). Exercise can also improve cognitive performance in healthy animals and human subjects, and can delay disease onset and/or slow its progression in animal models of Alzheimer's disease (Cotman and Berchtold 2002; Mattson 2012). The results from epidemiological and interventional studies suggest that regular exercise can reduce the risk of age-related cognitive impairment and dementia (Voss et al. 2011). The mechanisms by which exercise enhances and preserves brain function involve stimulation of dendrite growth, strengthening of existing synapses, and formation of new synapses. In addition, exercise stimulates neurogenesis (the production of new neurons from stem cells) in the dentate gyrus of the hippocampus, and some of the newly generated neurons integrate into hippocampal neuronal circuits as they receive synaptic inputs from entorhinal cortex neurons and basal forebrain cholinergic neurons (Vivar et al. 2012). Interestingly, the new neurons produced in response to exercise appear to play a key role in spatial pattern separation, a type of learning and memory that is mediated by the hippocampus (Creer et al. 2010).

Two studies reported in this issue of the Journal of NeuroVirology provide evidence that exercise can counteract adverse effects of human immunodeficiency virus (HIV) infection on neuronal structural integrity, neurogenesis, and cognitive function. HIV-associated neurocognitive disorders (HAND) has become a major concern for many HIV–AIDS patients and health care providers (Clark and Cohen 2010). While protease inhibitor cocktail therapy has been highly effective in prolonging the lives of HIV patients, the virus

continues to adversely affect the brain. Because HIV does not infect neurons, the current understanding of the pathogenesis of HAND invokes a viral reservoir harbored within glial cells. Neurotoxic HIV proteins are then released from the infected cells and damage synapses and neurons by a mechanism involving disruption of cellular Ca^{2+} homeostasis and “excitotoxicity”; the HIV coat protein gp120 and the HIV transactivator Tat have each been shown to endanger neurons by promoting cellular Ca^{2+} overload (Mattson et al. 2005). HIV also stimulates microglial cells to release pro-inflammatory cytokines, reactive oxygen species, and excitotoxins that likely contribute to neuronal degeneration and cognitive impairment in HAND (Gupta et al. 2010). Moreover, gp120 reduces the production of the active form of brain-derived neurotrophic factor (BDNF), suggesting the possibility of reduced trophic support of neurons in HAND (Bachis et al. 2012).

To directly determine if and how regular exercise affects neuropathogenic processes relevant to HAND, Lee et al. (2013) employed a transgenic mouse model in which gp120 expression is driven by an astrocyte (GFAP) promoter. These gp120 transgenic (gp120Tg) mice exhibit reduced hippocampal neurogenesis and impaired dendrite outgrowth compared to nontransgenic control mice. When gp120Tg mice were provided running wheels in their cages for 3–20 days, there was a significant increase in the proliferation of hippocampal neural progenitor cells and of newly generated neurons, and this effect of exercise was correlated positively with daily running distance. The dendrites of newly generated dentate granule neurons were longer in runners compared to sedentary gp120Tg mice. However, when mice that had run for 10 days were deprived of the running wheels for a subsequent 10 days, neurogenesis was reduced to the same level as gp120Tg mice that had never run. Exercise is known to increase BDNF production in the hippocampus, and Lee et al. (2013) found that exercise increased BDNF levels in gp120Tg mice, which likely contributed to the beneficial effects of exercise on

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neurogenesis and dendrite growth (Lee et al. 2002; Li et al. 2008). Moreover, exercise suppressed the activation of cyclin-dependent kinase 5, a kinase which previous studies had shown mediates neuronal apoptosis in experimental models of Alzheimer's disease (Lee et al. 2000), as well as the neurotoxic effects of supernatants from HIV-infected macrophages (Wang et al. 2007). These new findings provide direct evidence that exercise can counteract adverse effects of a neurotoxic HIV protein on hippocampal plasticity, and suggest that the underlying mechanism involves a bolstering of neurotrophic support and suppression of apoptotic biochemical cascades in neural cells (Lee et al. 2013). However, synaptic plasticity and cognitive function were not evaluated in the runner and sedentary gp120Tg mice, and so it remains to be established whether exercise can reverse cognitive deficits in this animal model of HAND.

Will regular exercise prevent or delay HAND in HIV-infected humans and/or will exercise ameliorate cognitive deficits in those already diagnosed with HAND? In a study in this issue of the journal, Dufour et al. (2013) evaluated the relationship between exercise and cognitive performance in over 300 HIV-infected subjects. Based upon whether they reported that they exercised vigorously or not, the subjects were divided into exercise and sedentary groups. The subjects completed a cognitive test battery that covered domains that are often impaired in HAND patients including working memory, verbal fluency, information processing speed, recall, and executive function. After accounting for several potential confounding factors, the authors found that overall performance of the subjects in the exercise group was significantly superior to the sedentary group. Among the domains tested, exercise was associated with better working memory and information processing speed. Previous studies have provided evidence that, as in other patient populations, exercise can lessen anxiety and depression in HIV patients (Hand et al. 2009). The emerging evidence, therefore, suggests that regular exercise improves overall brain health in HIV-infected individuals. Future exercise intervention trials will be required to determine whether and to what extent exercise programs can slow or reverse cognitive impairment in HAND patients.

Collectively, the findings of Lee et al. (2013) and Dufour et al. (2013) raise several questions regarding cellular and molecular changes that occur in the brain in HAND, and the impact of exercise on the underlying disease process. Does exercise affect viral load and/or levels of the neurotoxic HIV gp120 and Tat proteins in the brain? If so, what are the relative contributions to the beneficial effects of exercise on the brain of reduced exposure of neurons to the neurotoxic HIV proteins versus cellular protection against those proteins? In addition to promoting neurogenesis and dendrite outgrowth, BDNF plays key roles in the formation, maintenance, and plasticity of synapses (Lu et al. 2013). Does exercise increase the number and size of synapses in neuronal circuits in the

hippocampus and other brain regions of HAND patients? Brain imaging studies (fMRI and PET) have shown that patients with mild cognitive impairment, which is often prodromal to Alzheimer's disease, exhibit abnormalities in neuronal network activity and a cellular energy metabolism deficit (Kapogiannis and Mattson 2011). Is resting state activity in the default mode network reduced in HAND patients? Recent reports suggest this may indeed be true (Thomas et al. 2013; Towgood et al. 2012).

Finally, will HAND patients benefit from other interventions that can increase BDNF production, and enhance synaptic plasticity, neurogenesis, and cognitive performance? Two such interventions are intermittent fasting (Mattson 2012) and intellectual challenges (Scarmeas and Stern 2004). Will there be additive benefits when exercise is combined with intermittent fasting, and/or intellectual challenges? Will pharmacological agents that are known to increase BDNF production benefit HAND patients? In this regard, antidepressants that inhibit serotonin and/or norepinephrine reuptake at synapses (Castrén and Rantamäki 2010) could be tested in clinical trials in HAND patients. The new findings pointing to HAND disease-modifying effects of exercise in an animal model and HIV patients provide optimism that effective interventions are currently available, and that future treatments that target the specific pathogenic, neuroplasticity-impairing actions of HIV will be developed.

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