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Excercised Muscles and the Brain

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Epidemiological and experimental studies indicate the beneficial effects of regular physical activity in a variety of conditions, including age-related neurodegenerative disorders such as Alzheimer's disease and other dementias as well as brain injury [1-3].Exercised animals performed better in the spatial memory tasks (e.g. Morris water maze or radial arm water maze) compared to sedentary animals [4,5]. Similarly, exercise can improve non-spatial memory as tested in the passive avoidance paradigm and object recognition tasks [4,6,7]. Furthermore, animal experiments showed that treadmill exercise prevented memory impairment in sleep deprivation [8] dementia of the Alzheimer's type [9] and in rats treated with alcohol [10] streptozocin [11] or reserpine [12].

The neuroprotective effect of exercise is thought to be mediated by various molecular mechanisms including upregulation of neurotrophic factors and other molecules associated with learning and memory function, which in turn preserve and strengthen synaptic function leading to memory improvement.

We have shown that regular treadmill exercise reverses memory loss and synaptic plasticity impairment in a rat model of Alzheimer's disease as well as in sleep deprived rats. Additionally, exercise prevented impairment of Long-Term Potentiation (LTP) and normalized levels of the synaptic plasticity- and memory-related signaling molecules in these disorders [8,9,13]. In particular, our studies showed a marked increase in the levels of Brain Derived Neurotropic Factor (BDNF), which supported the prevailing belief that the beneficial effect of exercise may be due to increasing the availability of endogenous neurotrophic factors including BDNF.

How does an Active Skeletal Muscle Communicate with the Brain?

Clearly, there is ample evidence for the beneficial effect of exercise in a variety of brain disorders; however an important question remains unclear. How does muscle activity translate into a beneficial effect on the brain? The contracting muscles may communicate with the brain either through an endocrine mechanism or perhaps through afferent impulses originating from the active muscles. The latter possibility, however, seems unlikely inasmuch as it has been reported that in individuals with severed spinal cord or those under epidural anesthesia (no afferent or efferent impulses), contraction of paralyzed muscles by electrical stimulation produces physiological changes similar to those of normal individuals [14,15]. The alternative, therefore, is that skeletal muscles communicate with other organs through factor(s) released into the circulation during exercise. This possibility has been thoroughly discussed in a number of topical reviews by Pedersen and colleagues [16].

Brain-Derived Neurotrophic Factor (BDNF) is a member of the structurally related family of growth factors known as neurotrophins that affect neurons primarily by activating a number of Tyrosine kinase (Trk) receptors. BDNF and its receptor, TrkB, are most widely expressed in the brain [17]. However, it appears that BDNF is expressed not only in brain tissue but also in skeletal muscle [18]. This neurotrophin is important in regulating survival, growth and maintenance of neurons [19] and may figure prominently in cognitive function as suggested by deficient levels in neurodegenerative diseases [20]. In fact, it has been suggested that that plasma BDNF levels may be used as a biomarker of impaired cognitive function [21].

Exercise enhances BDNF transcription in the brain [22] and increases BDNF blood levels in healthy humans [23-25].The production of BDNF in the brain is activity dependent [26] where it can be stored and released in the dendrites and axons of hippocampal neurons. Like other neurotrophic factors, BDNF regulates activity-dependent protein synthesis and stimulate its own release at synaptic sites allowing for regenerative signaling for extended periods [27]. Since it is known that muscles produce BDNF during exercise, BDNF seems an obvious candidate for a messenger that communicates skeletal muscle activity to the central nervous system. This, however, turned out to be not the case.

Brain-Derived Neurotrophic Factor (BDNF) is Produced in Exercised Muscle

Initial studies showed a significant production of BDNF both at rest and during prolonged exercise in healthy male volunteers and this was thought to be the major source for increased plasma BDNF during exercise [28,29]. Later, however, muscle cell cultures experiments as well as human studies showed that although BDNF was markedly increased in exercised muscle cells, it was not released into the circulation [18] Thus, although BDNF is increased in contracting muscle cells, muscles are not a source of circulating BDNF. Rather, it is postulated, the BDNF produced by muscle during exercise stays in the muscle, perhaps to serve in an autocrine and/or paracrine capacity [16]. If that is the case, then where does BDNF in the circulation come from? It has been reported that at rest, BDNF is released into the internal jugular vein, suggesting that brain tissue is the main contributor to the circulating BDNF [28]. Another contributor to the high levels of BDNF during exercise is blood platelets, which are known to store and release BDNF [30]. It has been suggested that the enhanced levels of circulating BDNF during exercise may, at least in part, due to release of BDNF from activated platelets [18]. This has been confirmed by a study in healthy individuals who show significant increases in BDNF levels in serum, plasma and platelet immediately after the exercise [31].

A Role for Cytokines

Another possible messenger that can be involved in the signaling mechanism between active skeletal muscles and the brain are the cytokines. Cytokines are pro-inflammatory and anti-inflammatory low

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molecular weight glycoprotein molecules, which act as intercellular messengers. Muscles release cytokines into the blood circulation and these may exert specific endocrine effects on distant organs. The levels of Interleukin-6 (IL-6), the first cytokine reported to be secreted into the bloodstream during muscle contractions [32], were markedly increase in response to exercise. Previously, it was thought that the increase in IL-6 levels during exercise was a result of release from macrophages as an immune response to local damage in the contracting muscles [33,34]. It has been shown that labeled IL-6 crosses the blood brain barrier by a saturable transport system and, although only a small fraction of intact IL-6 survives in the cerebrospinal fluid or brain tissue, it may be sufficient to produce biological effects [35,36].It is tempting to speculate that cytokines released during muscle contraction may stimulate the release of BDNF from platelets thus increasing its levels in the cerebral blood circulation and Cerebrospinal Fluid (CSF). In support of this possibility, it has been reported that BDNF expression in the CSF was strongly correlated with IL-6 levels in the CSF and with blood platelet counts [37].

Obviously, more future work is needed to definitively clarify the mechanism of cross-talk between contracting muscle and the brain and how muscle activity translates into beneficial effects on the brain and other organs. Deciphering the molecular mechanism of this pathway will facilitate the discovery of drugs that mimic exercise, which would be greatly beneficial in physically challenged individuals.

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