

● PERSPECTIVE

Skeletal muscle activity and CNS neuro-plasticity

The systemic health benefits of regular skeletal muscle activity are well documented. Increased skeletal muscle activity is associated with an improved systemic metabolic state, reduced incidence of diabetes and obesity, and improved function with age. Despite these known systemic benefits, many healthy people do not meet the recommended daily dose of skeletal muscle activity (exercise) needed to prevent systemic metabolic disease, leading to an increased prevalence of obesity. People with central nervous system (CNS) damage (from a complete spinal cord injury, for example), are even further compromised as they are unable to activate their own musculature. In this perspective paper, we discuss recent findings relating skeletal muscle activity and CNS signaling. A central theme is that appropriately prescribed skeletal muscle activity (rehabilitation) may have important implications for optimizing neural plasticity, enhancing stem cell proliferation and differentiation, and improving the overall environment for regenerative approaches for people with CNS damage (spinal cord injury, stroke, multiple sclerosis, closed cranial trauma, Parkinson's disease, amyotrophic lateral sclerosis, dementia, and psychiatric disorders).

One method to induce skeletal muscle activity in people with paralysis is by activating the skeletal muscle electrically (Petrie et al., 2015). Neuromuscular electrical stimulation directly activates peripheral nerves (not muscle), which consist of the motor and sensory axons that communicate with the muscle from the spinal cord. Many people with traumatic spinal cord injury, for example, have an upper motor neuron injury. A complete upper motor neuron injury prevents any voluntary signal from the motor cortex of the brain to communicate to the muscle; but the lower motor neuron and its associated axons are retained, allowing peripheral communication between the spinal cord and the muscle.

Electrical stimulation *via* skin surface electrodes preferentially activates the peripheral nerves communicating with the muscle, affording an opportunity to exercise the paralyzed muscles. It is important to note that, generally, people with spinal cord injury, stroke, multiple sclerosis, and closed cranial trauma have upper motor neuron lesions, leaving an intact peripheral nervous system to the skeletal muscle. These intact peripheral nerves provide an opportunity to physiologically exercise the skeletal muscle using electrical stimulation. Some classic physiological and molecular responses from repetitive electrical stimulation that resemble volitional exercise include changes in neuromuscular transmission, altered excitation-contraction coupling, long duration low frequency fatigue, metabolic gene regulation, and recovery times following a bout of electrically induced exercise (Petrie et al., 2015). Historically, clinicians electrically stimulated human paralyzed muscle in order to promote motor output; however, recent findings suggest that regular skeletal muscle activity may trigger the release of small compounds into the blood stream (myokines), triggering pleiotropic responses to other tissues. The implication is that CNS neurons above the level of a spinal cord or brain injury may be regulated by muscle activity without direct central communication *via* the spinal cord or subcortical regions. This is an important concept as we search for optimal methods to translate neuro-regenerative responses from animal models to humans (Morgan et al., 2015).

Skeletal muscle and the central nervous system: Over 20 years ago it was discovered that electrically driving human paralyzed muscle induced a systemic increase in β -endorphin levels and improved cortisol regulation. Importantly, there was a dose-response

effect; higher electrical stimulation intensity and duration led to a greater increase in β -endorphin levels. The change in β -endorphin levels was also associated with changes in subjective indexes of depression (Twist et al., 1992). The dose dependent findings supported that the results were likely not due to a placebo effect, however, without a control group this could not be ruled out. Recent animal and human studies more concretely support that a positive correlation exists between skeletal muscle activity and neuronal function in the brain (Wrann et al., 2013); including reduced levels of depression and other mental illnesses (Cotman et al., 2007) enhanced cognition (Cotman et al., 2007; Phillips et al., 2014), neurogenesis (Cotman et al., 2007), and attenuation of neurodegenerative diseases – such as Alzheimer's disease (Bo et al., 2014; Morgan et al., 2015).

The most intriguing findings are from animal experiments that show how compounds directly released from contracting skeletal muscle into the bloodstream trigger brain-derived neurotrophic factor (BDNF) receptors in the hippocampus (Wrann et al., 2013). Irisin is one compound that was recently identified as a small protein that is secreted directly from skeletal muscle after electrical stimulation of the quadriceps muscle of the rat. A model depicting a compound that may trigger systemic communication from the muscle to the CNS is portrayed in **Figure 1**. In those animal studies, irisin crosses the blood-brain barrier and targets specific BDNF receptors in the brain. BDNF is a powerful neuro-protective agent known to promote neuronal proliferation, growth, differentiation and synaptogenesis – key functions necessary for neuronal learning, memory, and regeneration (Thomson et al., 2015). In short, skeletal muscle may act as an important endocrine transducer needed to trigger the release of key compounds that target receptors throughout the CNS; thus promoting an environment conducive to neuronal cellular plasticity following neuro-regenerative interventions. The challenge today is to assess, using accurate methods of measurement, whether these same compounds are regulated by skeletal muscle activity in humans; ultimately establishing a dose of muscle activity that optimizes the factors that promote a healthy environment for the CNS.

Despite the recent discovery of irisin in animal models, the molecular link between skeletal muscle activity and CNS neuron signaling is in its infancy in humans. In murine animal models, the fibronectin type III domain containing 5 (FNDC5) gene, responding to signaling from the peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC1 α) transcription factor, up regulates BDNF in the brain (Wrann et al., 2013). However, the FNDC5 gene has a mutated start codon (ATA) in humans. Thus, there is a substantially reduced translation of irisin, leading to very low concentrations detected in human cells; less than 1% of the quantity of irisin compared to the rat model (Raschke et al., 2013). Even studies using a downstream ATG start codon yielded only partial translation of the irisin sequence (Raschke et al., 2013). The FNDC5 mutated start codon in humans suggests that irisin is not the sole regulator of neuronal receptors in the brain of humans, but may certainly play some role. The difficulties in measuring irisin are well established in the literature (Elsen et al., 2014; Albrecht et al., 2015), and assays to measure this compound in humans require further development. Interestingly, we recently showed that the FNDC5 gene mRNA is up regulated after a specific dose of neuromuscular electrical stimulation of paralyzed muscle in 5 humans with SCI (**Figure 2**). These findings in humans support that the effects are not a global effect induced systemically or due to placebo; however, the extent that this regulation translates into a known signaling compound remains unknown. Follow-up experiments are currently underway in our laboratory to determine if this regulation leads to measurable changes in compounds released into the blood stream.

Although several of the mechanisms remain elusive, the strength of the relationship between skeletal muscle activity and positive physiological and psychological outcomes remains strong. The challenge is to perform well-designed, controlled trials to better understand the placebo versus the specific physiological and molecular mechanisms

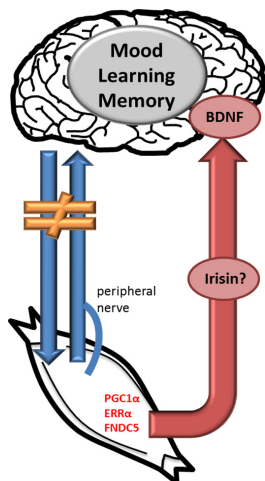


Figure 1 Theorized links between exercise and CNS plasticity.

Central nervous system injury (spinal cord) disrupts one pathway from the exercising muscle to the brain (afferent communication through spinal-thalamic tracts in the spinal cord). Feedback systems mediated by the circulatory system remain intact. Paralyzed muscle activity may regulate PGC1 α , ERR α , and FNDC5 genes, triggering the release of irisin which may target BDNF receptors in the CNS. BDNF: Brain-derived neurotrophic factor; ERR α : estrogen-related receptor alpha; FNDC5: fibronectin type III domain containing 5; PGC1 α : peroxisome proliferator-activated receptor gamma coactivator 1 alpha.

that contribute to the benefits of exercise. Skeletal muscle activity clearly up regulates transcriptional coactivator (PGC1 α) and up-regulates availability of BDNF (Forouzanfar et al., 2015). Overexpression of PGC1 α leads to an increase in orphan nuclear receptor estrogen-related receptor alpha (ERR α) gene and the disruption of ERR α /PGC1 α complex decreases FNDC5 gene availability (Wrann et al., 2013). BDNF signaling is mediated, in part, through the circulatory system which is supported by occlusion studies performed within the brain (Shi et al., 2009).

Neuro-rehabilitation technologies and healthcare: There has been an emergence of methods to enhance skeletal muscle activity in people with CNS injury. While highly complex technologies may offer unique opportunities in neuro-rehabilitation, there needs to be a watchful eye on value (effectiveness/feasibility and cost). If people with CNS compromise are able to engage in a healthy dose of muscle activity, then secondary debilitating complications may be prevented, at a savings to the healthcare industry. Health-minded communities, now classified as “blue zones” in some areas, may move to offer human performance facilities for people who aspire to improve their performance in the home, at work, or in the community. There is an unprecedented growth in community-based “Sports Performance Facilities” to improve performance on the athletic field; however, to date, limited “Human Performance Facilities” are available, at an affordable cost, to improve functional activity of people with paralysis. Indeed, future recognition of “blue zone” communities may want to consider the extent that cost-effective physical activity opportunities are offered to all members of a community.

Conclusion and summary: We assert that neural regenerative processes will require a healthy systemic cellular environment, and that a regular dose of skeletal muscle activity may be a safe and effective means to promote healthful communication between the periphery and the CNS. More work in all areas of neuro-regenerative research is necessary to seamlessly translate research findings from the bench to the bedside. Interdisciplinary collaborations among molecular neuroscientists, rehabilitation specialists, cellular engineers, physical therapists, neurologists, neurosurgeons, healthcare organizations, and community leaders will likely be critical to the ultimate success of future neuro-regenerative enhancement for humans with disability. We recommend a “call to arms” to all stakeholders to engage in the work of translating the exciting neuro-regenerative research findings from basic research into cost-effective and feasible clinical interventions to enhance the health of all people.

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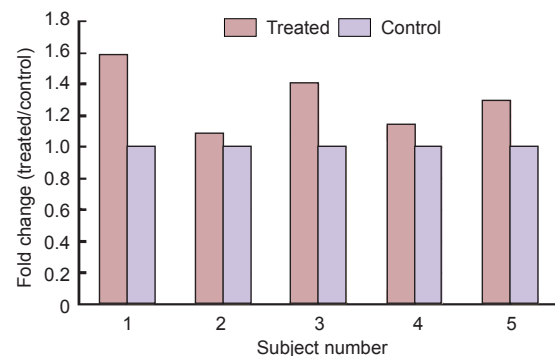


Figure 2 mRNA expression from paralyzed muscle after a single session of electrical stimulation.

Data are fold-change between the control (untreated) limb and the stimulated limb. Values >1.0 represent up-regulation of mRNA transcription. FNDC5: Fibronectin type III domain containing 5.

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