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The influence of high intensity exercise and the Val66Met polymorphism on circulating BDNF and locomotor learning

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ABSTRACT

Brain-derived neurotrophic factor (BDNF) has been directly related to exercise-enhanced motor performance in the neurologically injured animal model; however literature concerning the role of BDNF in the enhancement of motor learning in the human population is limited. Previous studies in healthy subjects have examined the relationship between intensity of an acute bout of exercise, increases in peripheral BDNF and motor learning of a simple isometric upper extremity task. The current study examined the role of high intensity exercise on upregulation of peripheral BDNF levels as well as the role of high intensity exercise in mediation of motor learning and retention of a novel locomotor task in neurologically intact adults. In addition, the impact of a single nucleotide polymorphism in the BDNF gene (Val66Met) in moderating the relationship between exercise and motor learning was explored. It was hypothesized that participation in high intensity exercise prior to practicing a novel walking task (split-belt treadmill walking) would elicit increases in peripheral BDNF as well as promote an increased rate and magnitude of within session learning and retention on a second day of exposure to the walking task. Within session learning and retention would be moderated by the presence or absence of Val66Met polymorphism. Fifty-four neurologically intact participants participated in two sessions of split-belt treadmill walking. Step length and limb phase were measured to assess learning of spatial and temporal parameters of walking. Serum BDNF was collected prior to and immediately following either high intensity exercise or 5 min of quiet rest. The results demonstrated that high intensity exercise provides limited additional benefit to learning of a novel locomotor pattern in neurologically intact adults, despite increases in circulating BDNF. In addition, presence of a single nucleotide polymorphism on the BDNF gene did not moderate the magnitude of serum BDNF increases with high intensity exercise, nor did it moderate the relationship between high intensity exercise and locomotor learning.

1. Introduction

Animal models suggest that exercise may promote a nurturing environment for the formation of functionally appropriate synaptic connections during learning (Black, Isaacs, Anderson, Alcantara, & Greenough, 1990; Cotman, Berchtold, & Christie, 2007; Klintsova, Dickson, Yoshida, & Greenough, 2004; Xu et al., 2009). Through upregulation of molecular mediators of neural plasticity, exercise strengthens synaptic transmission, thus "priming" the nervous system for encoding of pertinent information (Cotman et al., 2007; Intlekofer et al., 2013; Ploughman et al., 2007). Experiments within animal models corroborate the molecular influences of exercise on enhanced cognitive and motor performance and learning and indicate brain derived neurotrophic factor (BDNF) as a key mediator of these enhancements (Griesbach, Hovda, & Gomez-Pinilla, 2009; Intlekofer et al., 2013; Klintsova et al., 2004; Vaynman, Ying, & Gomez-Pinilla, 2004; Ying et al., 2008).

Brain derived neurotrophic factor has been identified as a requisite for induction of neural plasticity with motor learning and has been evidenced to mediate functional recovery following neurologic insult in the animal model (Ploughman et al., 2009; Schäbitz et al., 2004, 2007). In addition, animal models have shown that BDNF mediates the beneficial effects of exercise in facilitation of spatial learning (Intlekofer et al., 2013) and recovery of motor

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skill function (Griesbach et al., 2009; Ploughman et al., 2007, 2009; Ying et al., 2008). Blockade of BDNF mRNA, via an antisense BDNF oligonucleotide, negates the ability of exercise and rehabilitation to upregulate BDNF gene expression as well as limit recovery of skilled reaching with rehabilitation in the ischemic animal (Ploughman et al., 2009).

In humans, aerobic and anaerobic exercise are thought to promote increases in systemic BDNF (Ferris, Williams, & Shen, 2007; Knaepen, Goekint, Heyman, & Meeusen, 2010; Rojas Vega et al., 2006; Skriver et al., 2014; Winter et al., 2007). However, direct causal evidence of BDNF's moderating role in the relationship between exercise and learning, demonstrated in the animal literature, has not been demonstrated in humans. Converging evidence has linked exercise with improved cognitive function in healthy individuals as well as those post stroke (Colcombe & Kramer, 2003; Kluding, Tseng, & Billinger, 2011; Quaney et al., 2009; Rand, Eng, Liu-Ambrose, & Tawashy, 2010; Winter et al., 2007). Evidence citing the effects of aerobic exercise on *motor* learning, however, is sparse in comparison to studies of cognitive performance and learning (Roig, Skriver, Lundbye-Jensen, Kiens, & Nielsen, 2012; Skriver et al., 2014; Statton, Encarnacion, Celnik, & Bastian, 2015).

Roughly thirty percent of humans (Shimizu, Hashimoto, & Iyo, 2004) possess a single nucleotide polymorphism (SNP) on the BDNF gene (Val66Met) (Egan et al., 2003). This polymorphism has been linked to decreased activity dependent release (Chen et al., 2004; Egan et al., 2003) of BDNF within the animal model. In healthy humans, presence of the polymorphism has been associated with altered cortical activation and short term plasticity (Beste et al., 2010; Cheeran et al., 2008; McHughen et al., 2010) as well as altered skill acquisition and learning (Beste et al., 2010; Joundi et al., 2012; Kleim et al., 2006; McHughen et al., 2010). In addition, presence of the polymorphism has recently been shown to influence the rate of motor learning in individuals post-stroke (Helm, Tyrell, Pohlig, Brady, & Reisman, 2015). It is currently unknown whether presence of the Val66Met polymorphism would attenuate release of BDNF in response to exercise in humans and if this attenuation would impact motor learning.

Although theorized to moderate the influence of exercise on learning in humans, no studies have concurrently assessed the relationship between exercise induced changes in BDNF, the BDNF Val66Met polymorphism and motor learning. In the current study we utilized the split-belt treadmill paradigm (Reisman, Bastian, & Morton, 2010; Reisman, Block, & Bastian, 2005; Reisman, McLean, Keller, Danks, & Bastian, 2013; Reisman, Wityk, Silver, & Bastian, 2007) to examine the role of BDNF in mediating within session learning and retention of a novel locomotor task following high intensity exercise. We hypothesized that participation in a single session of high intensity upper extremity cycling would elicit increases in peripheral BDNF levels relative to quiet rest. In addition, we hypothesized that high intensity exercise prior to a novel walking task (split-belt treadmill walking) would enhance the rate and magnitude of within-session learning as well as retention on a second day of exposure to split-belt walking. We postulated the benefits of high intensity exercise on motor learning would be greater for subjects without the Val66Met polymorphism.

2. Materials and methods

2.1. Participants

Neurologically intact subjects between the ages of 21 and 35 were recruited as a sample of convenience for participation. All subjects provided written informed consent, with the study protocol approved by the University of Delaware Human Subjects Review Board. To be included, subjects must have demonstrated the ability to walk without assistance and without assistive devices, the ability to understand spoken instruction and communicate with investigators, a resting heart rate between 40 and 100 beats per minute and a resting blood pressure between 90/60 and 170/90. In addition, to be included participants provided written informed consent to supply a saliva sample for genetic testing for the BDNF Val66Met polymorphism. Exclusion criteria included any neurologic condition, intermittent claudication, total joint replacement and orthopedic problems in the lower limbs or spine that limited walking.

2.2. Instrumentation and procedures

Subjects were randomly assigned to an Exercise + Learning or Learning condition. Subjects assigned to the Exercise + Learning condition participated in a short bout of high intensity exercise on an upper body ergometer (UBE) (SCIFIT Systems, Inc., Tulsa, OK) prior to split-belt walking on Day 1. The high intensity exercise consisted of pedaling for 1 min with high resistance immediately followed by 1 min with resistance decreased by half, at speeds sufficient to achieve 80% of the subject's age predicted heart rate maximum. Subjects were provided a timed 1-min rest break, and then repeated the upper-body cycling protocol. Subjects in the Learning group were asked to quietly rest for 5 min prior to treadmill walking to account for time differences between groups (Fig. 1).

All subjects participated in two sessions of split-belt treadmill walking on two consecutive days. Prior to split-belt treadmill walking on Day 1 subjects were asked to walk on the treadmill with the belts tied at a 1:1 ratio at 0.5 m/s for 2 min in order to assess baseline step and limb phase symmetry. All subjects then participated in split-belt treadmill walking for 15 min, consisting of walking at a constant 3:1 speed ratio of 1.5:0.5 m/s. Subjects walked with this speed ratio throughout the entire session (Fig. 1). Subjects returned for a second day of split-belt walking at the same 3:1 ratio for 15 min. Subjects did not participate in acute exercise or treadmill walking with the belts "tied" prior to the split-belt walking session on Day 2.

All participants walked on a split-belt treadmill instrumented with two independent six degree of freedom force platforms (Bertec, Columbus, OH) from which ground reaction force data was continuously collected at 1000 Hz. Kinematic data was continuously collected using an 8-camera Vicon Motion Capture System (Vicon MX, Los Angeles, CA) at 100 Hz. Retro-reflective markers (14-mm diameter) secured to rigid plastic shells were placed on the pelvis, bilateral thighs and bilateral shanks. Single markers were placed on the most prominent superior portion of the bilateral iliac crests, greater trochanters, medial and lateral knee joint lines, medial and lateral malleoli, bilateral heels, and the first and fifth metatarsal heads. During walking all subjects were instructed to gently rest fingertips on the treadmill handrail, and were given verbal cues, as necessary, to avoid excessive use of the handrail while walking.

All subjects wore a safety harness around their chest for fall prevention; however, the harness did not provide body weight support. Blood pressure, heart rate and rating of perceived exertion (RPE) (Borg, 1982) were monitored throughout the treadmill walking sessions.

2.2.1. Genotyping

Each subject provided a 2 mL saliva sample in a DNA Self-Collection Kit (DNA Genotek, Kanata, Canada) containing a DNA stabilizing buffer. The samples were sent to DNA Genotek (GenoFIND Services, Salt Lake City, UT) for processing. Genotek created a set of primers to amplify the region surrounding the SNP (Val66Met: rs6265) of the BDNF gene and then examined the sample for