2022

Skeletal Muscle Induced, BDNF-Mediated Secretions Retrogradely Initiates Pro-Neuroplastic Signaling Cascade That Increases Cognitive Function in Adults with Autism Spectrum Disorder

Julie Dalmolen
Cal Poly Humboldt, jlb77@humboldt.edu

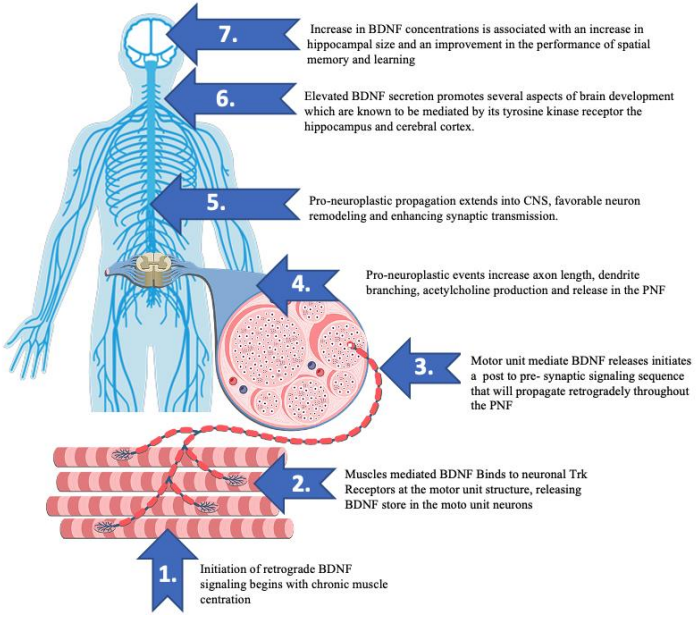
Skeletal Muscle Induced, BDNF-Mediated Secretions Retrogradely Initiates Pro-Neuroplastic Signaling Cascade That Increases Cognitive Function in Adults with Autism Spectrum Disorder

Julie L. Dalmolen, Lukas Coppen,M.S., Maya DiMaio, David Adams Ph.D., Eli Lankford Ph.D., Brian Blackburn Ph.D.
Obesity, Diabetes and Metabolism Lab, Department of Kinesiology, Cal Poly Humboldt, Arcade, CA, USA

Introduction

Autism Spectrum Disorder (**ASD**) is a neuro-cognitive condition associated with pathogenic neuroplasticity (1). This condition critically impacts communication as well as social and cognitive behavior in individuals with ASD. Brain Derived Neurotrophic Factor (**BDNF**) is a growth signaling protein implicated in augmenting neuroplasticity by facilitating axon elongation, synaptic proliferation, and neurotransmitter formation and release by binding to its key receptor Tropomyosin Receptor Kinase B **(Trkb)** (2). Interestingly, human skeletal muscle **(HSM)** has been identified as a BDNF secreting tissue capable of initiating pro-neuroplastic molecular events that support central and peripheral neural remodeling (3). Research conducted on rodents has demonstrated that chronic exercise significantly increases the expression of both proBDNF(**pBDNF**) inactive isoform, mature BDNF(**mBDNF**) active isoform, and cognitive function (4).Thus, HSM may represent a novel mechanism capable of enhancing systemic neural remodeling. Investigations conducted on other neurodegenerative disorders report that exercise favorably influences total BDNF expression and concentration (5), thus promoting retrograded muscle mediated central and peripheral neuro-remodeling. In this study, we intend to use moderate intensity aerobic exercise (**AE**), ≥ 60% heart rate reserve and maximum oxygen uptake ($\mathbf{VO_{2max}}$), as an intervention to induce **BDNF** secretion in HSM. The researchers hypothesize that chronic exercise may be a critical catalyst in inciting contraction-mediated, muscle-induced BDNF proliferation capable of supporting neural remodeling across the peripheral **(PNS)** and central nervous systems **(CNS)**. Further, the researchers believe that these changes may be a key factor in improving social and cognitive deficits associated with **ASD**.

Muscle-induced BDNF Proliferation Sequence



Methods

Participant description

This study will be conducted at a university in Northern California and will include Neurotypical participants **(NT;**n=10) and participants with Moderate **(mASD;**n=10) and Severe **(sASD;**n=10) ASD**.** All Participants will perform a 6-week AE intervention program.
Inclusion criteria require informed consent, participants to be inactive and 18 years of age or older, and 3 months free from BDNF enhancing medication.

Cognitive Assessment

Once inclusion criteria is met, participants will undergo the Woodcock Johnson 4th version cognitive assessment, both pre and post exercise intervention.

Bio fluid Collection/Bio Marker Detection

Three 24- hour consecutive urine samples will be collected during visits 3-5 and 6-8. Visit 5 and 8 will involve one 5mL blood draw after a 12 hour fast.

Bio marker detection

Commercially available ELISA kits will be used to determine the presence and concentration levels of total BDNF (proBDNF & mBDNF) in bio fluids collected in the study. Urine samples will undergo gas spectrometry analysis for identification of additional biomarkers. Blood BDNF analyses will require a collection of venous blood collected from participants following an overnight fast. Blood samples will be allowed to coagulate at room temperature for 30 min. Real Time PCR will also be employed to determine BDNF gene expression.

Intervention

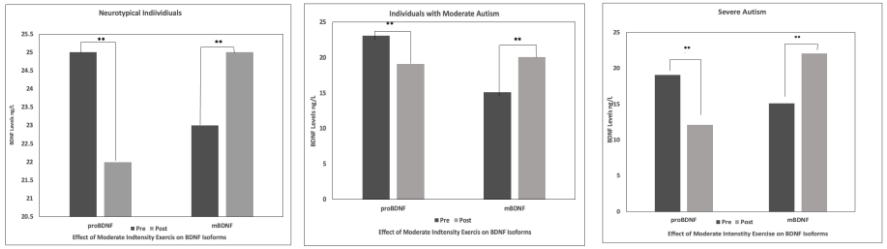
Baseline aerobic fitness will be determined by a treadmill test to establish VO_{2max}, an index of the maximum capacity to transport and utilize oxygen during incremental AE. A modified VO_{2max} algorithm will be used to predict the ≥ 60% maximum heart rate and VO_{2max} of the exercising participants. Post assessments will assume participants to be exercising at an intensity ≥ 60% of either their maximum heart rate or VO_2 max. Exercise sessions will be monitored by an exercise physiologist and or personal trainer. Participants will have a choice of a treadmill, elliptical, row machine, stationary bike, and active-play video games (Xbox 360 Kinect) and traditional AE equipment.

Proposed Results

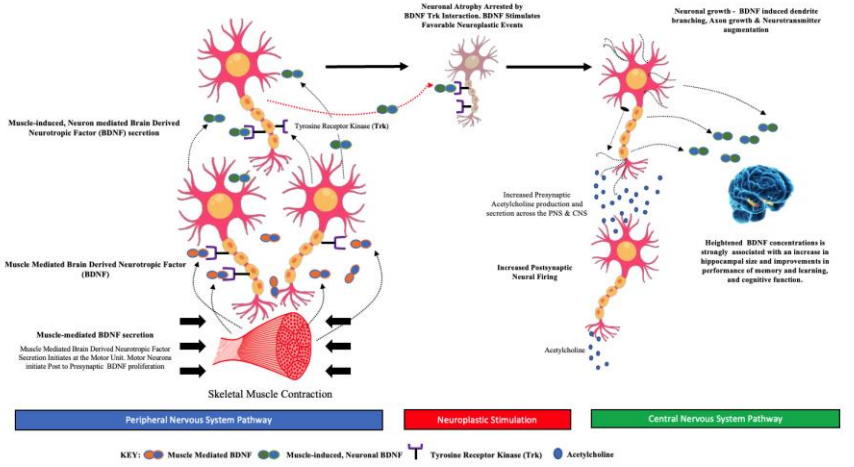
In NT individuals, we anticipate that exercise will result in a decrease in proBDNF and an increase in mBDNF, suggesting BDNF activation will induce normal physiological neuro-remodeling and maintenance.

Previously reported investigations have indicated that individuals with mASD exhibit higher levels of serum and urinary BDNF than their NT counterparts. Although concentrations of the BDNF protein levels were elevated, there is a void in the literature concerning whether the BDNF levels are active or inactive. In the mASD group, we anticipate exercise will increase proBDNF gene expression, and protein levels and moderately increase mBDNF. These conjectures suggest that exercise not only provokes gene expression but also enhances the catalytic activity of the enzyme Intercellular Furin Convertase **(IFC).**

In the sASD group, both pBDNF and mBDNF will be blunted compared to mASD and NT groups. We predict that exercise will produce a robust response in both the inactive and active forms of BDNF. These results suggest that exercise increases gene expression, upregulates BDNF protein levels, and augments IFC activity.



Mechanism of Action



Discussion

The objective of this study is to identify exercise as an effective therapy for improving cognitive function in individuals with ASD. Moderate intensity AE is one activity that is known to up-regulate BDNF, with synthesis and release into the peripheral nervous system that increases in a dose-response manner (3). Exercise as a therapy for individuals with ASD is important as a sedentary lifestyle is associated with this community (6) In addition to weight-management, cardiovascular and other physical health benefits, AE could partially ameliorate neurocognitive deficits in individuals with ASD and serve as a safe and side-effect free intervention. The researchers predict that the results of this study will demonstrate that moderate intensity AE improves cognitive function through an increase in BDNF through the collective cellular pathways of the PNS and CNS which are genetically driven by the stimulus of chronic skeletal muscle contraction elicited by AE.

For references and additional information such as study protocol and participant activities within this investigation, contact **Julie Dalmolen at jlb77@humboldt.edu**