Experimental Gerontology 87 (2017) 129–136

Contents lists available at ScienceDirect

Experimental Gerontology

journal homepage: www.elsevier.com/locate/expgero

APOEε4 impacts up-regulation of brain-derived neurotrophic factor after a six-month stretch and aerobic exercise intervention in mild cognitively impaired elderly African Americans: A pilot study

Joanne S. Allard [a], Oyonumo Ntekim [b], Steven P. Johnson [c], Julius S. Ngwa [d], Vernon Bond [c], Dynell Pinder [a], Richard F. Gillum [d], Thomas V. Fungwe [b], John Kwagyan [e], Thomas O. Obisesan [c,*]

[a] Department of Physiology and Biophysics, Howard University College of Medicine, Washington, DC, USA
[b] Department of Nutritional Sciences, School of Nursing and Allied Health Sciences, Howard University, Washington, DC, USA
[c] Division of Geriatrics, Department of Medicine, Howard University Hospital, Washington, DC, USA
[d] Department of Internal Medicine, Howard University Hospital, Washington, DC, USA
[e] Department of Community and Family Medicine, Howard University Hospital, Washington, DC, USA

ARTICLE INFO

Article history:
Received 12 July 2016
Received in revised form 27 October 2016
Accepted 1 November 2016
Available online 15 November 2016

Section Editor: Christiaan Leeuwenburgh

Keywords:
Aerobic exercise
BDNF
APOE
Oxygen consumption
African Americans
Mild cognitive impairment

ABSTRACT

Possession of the Apolipoprotein E (APOE) gene ε4 allele is the most prevalent genetic risk factor for late onset Alzheimer's disease (AD). Recent evidence suggests that APOE genotype differentially affects the expression of brain-derived neurotrophic factor (BDNF). Notably, aerobic exercise-induced upregulation of BDNF is well documented; and exercise has been shown to improve cognitive function. As BDNF is known for its role in neuroplasticity and survival, its upregulation is a proposed mechanism for the neuroprotective effects of physical exercise. In this pilot study designed to analyze exercise-induced BDNF upregulation in an understudied population, we examined the effects of APOEε4 (ε4) carrier status on changes in BDNF expression after a standardized exercise program. African Americans, age 55 years and older, diagnosed with mild cognitive impairment participated in a six-month, supervised program of either stretch (control treatment) or aerobic (experimental treatment) exercise. An exercise-induced increase in VO_2Max was detected only in male participants. BDNF levels in serum were measured using ELISA. Age, screening MMSE scores and baseline measures of BMI, VO_2Max, and BDNF did not differ between ε4 carriers and non-ε4 carriers. A significant association between ε4 status and serum BDNF levels was detected. Non-ε4 carriers showed a significant increase in BDNF levels at the 6 month time point while ε4 carriers did not. We believe we have identified a relationship between the ε4 allele and BDNF response to physiologic adaptation which likely impacts the extent of neuroprotective benefit gained from engagement in physical exercise. Replication of our results with inclusion of diverse racial cohorts, and a no-exercise control group will be necessary to determine the scope of this association in the general population.

1. Introduction

Alzheimer's disease (AD) is associated with many risk factors, advanced age being the strongest, with a doubling of risk every 5 years past the age of 65. African Americans (AAs) are also at higher risk for AD with estimated prevalence ranging from 14% to 100% higher than Caucasians (Gurland et al., 1999; Potter et al., 2009; Barnes and Bennett, 2014; Hall et al., 2009). Despite the disproportionately high incidence of AD within the AA population, this group remains severely underrepresented in clinical trials on AD (Nussbaum, 2013). Importantly, AAs also suffer from higher burdens of several diseases that increase the risk for AD including type-2 diabetes (T2DM) and cardiovascular disease (CVD).

Along-side investigations into putative treatments for AD, there is growing interest in the mechanisms underlying the health benefits of lifestyle adaptation, especially in light of its demonstrated impact on T2DM and CVD (Gielen et al., 2015; Lin et al., 2015). In particular, aerobic exercise has been shown to improve cognitive function, in both young and elderly populations (Baker et al., 2010; Colcombe et al., 2006; Hillman et al., 2008). While exercise-induced upregulation of brain-derived neurotrophic factor (BDNF) is well documented (Coelho et al., 2014; Erickson et al., 2012; Erickson et al., 2011; Griffin et al., 2011; Schmolesky et al., 2013; Neeper et al., 1996), there are inconsistencies, with a few studies reporting either no change or lowered serum BDNF levels in exercised subjects (Babaei et al., 2014; Goda et al., 2013; Swift et al., 2012). These inconsistencies are poorly understood. Regardless, BDNF is critically important for neuronal

* Corresponding author at: Division of Geriatrics, Department of Medicine, Howard University Hospital, 2041 Georgia Ave. NW, Washington, DC 20060, USA.
E-mail address: tobisesan@howard.edu (T.O. Obisesan).

http://dx.doi.org/10.1016/j.exger.2016.11.001

differentiation, synaptic plasticity and neuron survival (Mariga et al., 2015; Vilar and Mira, 2016). In humans, increased BDNF levels have been linked to increased hippocampal volume and spatial memory performance (Erickson et al., 2010), whereas decreased BDNF is linked to AD and other psychiatric disorders (Erickson et al., 2010; Driscoll et al., 2012; Lommatzsch et al., 2006; Ziegenhorn et al., 2007; Holsinger et al., 2000; Weinstein et al., 2014). Thus, BDNF upregulation is a supported, proposed mechanism for the cognitive-enhancement triggered by lifestyle adaptation from physical exercise.

Recent evidence suggests that BDNF expression is differentially affected by variants of the apolipoprotein E (APOE) gene (Alvarez et al., 2014; Liu et al., 2015; Sen et al., 2015). The APOE gene is polymorphic with three major alleles: ε2, ε3 and ε4. These gene variants produce proteins with differing physiologic properties and variable associations with health risk (Liu et al., 2013). APOE is responsible for trafficking of lipoproteins, fat-soluble vitamins and cholesterol (Zhang and Liu, 2015). The ε4 allele has been associated with the development of atherosclerosis (Altenburg et al., 2007) and cardiovascular disease (Lopez et al., 2014), both of which increase AD risk. In fact, hetero- and homozygosity for the ε4 allele incurs a 3 fold and 12 fold increased risk for AD, respectively, compared to those homozygous for the ε3 allele (Verghese et al., 2011). Though AAs are at higher risk of AD compared to Caucasian Americans, whether the APOE gene differentially influences exercise training-induced changes in BDNF levels in older AA, mild cognitively impaired (MCI) subjects has not be examined.

The aim of this pilot study was to examine the effects of a 6-month supervised and standardized exercise program, on serum levels of BDNF, in mild cognitively impaired elderly AAs. We hypothesized that an increase in aerobic capacity would result in a parallel increase in BDNF levels. Although, there was an expectation of baseline differences in serum BDNF levels based on APOE genotype, we anticipated an exercise-induced increase in serum BDNF across all APOE genotypes. Through our analyses, we identified an unexpected association between APOEε4 status and 6-month changes in serum BDNF levels.

2. Methods and materials

The protocols used in this investigation were approved by the Howard University Institutional Review Board. As required for studies involving human subjects, all participants completed a signed informed consent form prior to enrollment in the study. Participants were recruited mostly through newspaper advertisement, direct mailing, health fairs and hospital clinics.

2.1. Initial eligibility screening

Eighty-nine of the volunteers that were screened for eligibility met initial criteria and were tested for MCI and cardiovascular disease. All eligible participants fulfilled the following inclusion criteria: age >55 years; ability to exercise vigorously without causing harm to self (as determined by the cardiovascular disease screening, treadmill test and history of cardiovascular disease); diagnostic designation as MCI according to Petersen criteria (Petersen, 2004) using education adjusted scores; have a committed study partner; be in good general health; and ability to undergo required medical and study related assessments. Based on the initial evaluation of medical history, volunteers with a history of the following conditions were excluded: head trauma, uncontrolled diabetes mellitus and hypertension; current chronic renal, liver, respiratory, musculoskeletal, or neurologic disorders; recent myocardial infarction (within the previous 6 months), unstable angina, and chronic alcohol or drug abuse. Persons using hormone replacement therapy (HRT) or medications that may affect memory (e.g., anticholinergics, sedative hypnotics, narcotics, and antiparkinsonian agents), and those starting new medications within 6 weeks of enrollment, were also excluded from the study.

2.2. MCI diagnosis

Diagnosis of MCI was made using the following criteria: memory complaints, performance scores on the Wechsler Memory Scale Logical Memory II (adjusted for education), Clinical Dementia Rating Scale (CDR) rating of ≤0.5, Modified Hachinski Ischemic Score of ≤4, Geriatrics Depression Scale (GDS) rating of <6, and education adjusted Mini-Mental State Examination (MMSE) scores (adjusted MMSE = raw MMSE − (0.471 × [education − 12]) + (0.131 × [age − 70])) of between 24 and 30 (Mungas et al., 1996). Subjects with probable dementia according to National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's disease and Related Disorders Association (NINCDS/ADRDA) criteria; and those having memory loss from medical, neurological or psychiatric conditions, medication effects, or delirium were excluded from the study.

2.3. CVD screening

Qualified volunteers underwent a maximal treadmill exercise test using the Bruce protocol (Bruce and Hornsten, 1969) to screen for cardiovascular disease (CVD). Blood pressure, heart rate, and ECG were recorded before the test, at the end of every exercise stage, and every 2 min for 6 min after discontinuing the test. Testing was discontinued when the subject unable to continue the required movement, or CVD signs and symptoms occurred. Signs of CVD included >2-mV ST-segment depression, significant ST segment elevation, extra systole, chest pain, arrhythmias, hypotension or dizziness (White and Evans, 2001; American College of Sports Medicine Position Stand, 1998a; American College of Sports Medicine Position Stand, 1998b). Those showing signs of CVD were not continued in the study.

2.4. Blood collection and processing

Participants were instructed to fast (consume only water), refrain from smoking, and avoid use of any anti-inflammatory medications during the 24-hour period prior to the blood draw for baseline and 6-month testing. Additionally, subjects were instructed to refrain from exercise for 72 h prior to testing, and to confirm that they had no infection in the week prior to testing. All blood samples were drawn using sterile techniques by personnel trained in phlebotomy. Blood samples were taken between 9:30 am and 11:00 am in order to minimize any possible circadian variations. Blood was drawn from the median cubital or cephalic vein.

For serum collection, blood samples were incubated at room temperature and allowed to coagulate for 45 min. After centrifugation at1000 ×*g* for 10 min, in a refrigerated centrifuge, the overlying serum was collected, aliquoted and stored at −80 °C until used for BDNF assays. For plasma and buffy coat collection, blood samples were collected in tubes containing anticoagulant. Samples were then centrifuged at 200 ×*g* for 20 min (without brake). Plasma and buffy coat layers were then collected into cryotubes and stored at −80 °C.

2.5. Dietary guidelines and randomization

Study partners and subjects were instructed that subjects should maintain their usual caloric intake during the study period. Participants were requested to maintain an American Heart Association Step 1 diet: consisting of <30% of energy from fat, approximately 55% from carbohydrate, approximately 15% from protein, and a cholesterol intake of <300 mg/day. After baseline measurements, 29 subjects randomized into stretch ($n = 12$) and aerobic ($n = 17$) exercise groups began exercise training intervention.