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David D. Church

Jay R. Hoffman

Gerald T. Mangine
Kennesaw State University, gmangine@kennesaw.edu

Adam R. Jajtner

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Comparison of High Intensity versus High Volume Resistance Training on the BDNF Response to Exercise

David D. Church[1], Jay R. Hoffman*[1], Gerald T Mangine[2], Adam R. Jajtner[1], Jeremy R. Townsend[3], Kyle S. Beyer[1], Ran Wang[1], Michael B. La Monica[1], David H. Fukuda[1], Jeffrey R. Stout[1].

[1]Institute of Exercise Physiology and Wellness, Sport and Exercise Science, University of Central Florida, Orlando, FL, [2]Department of Exercise Science and Sport Management, Kennesaw State University, Kennesaw, GA, [3]Exercise and Nutrition Science, Lipscomb University, Nashville, TN

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Send correspondence to:

Jay R. Hoffman, Ph.D.

Institute of Exercise Physiology and Wellness

Sport and Exercise Science

University of Central Florida

12494 University Blvd

Orlando, FL 32816-1250

407-823-1272

Jay.Hoffman@ucf.edu

Abstract

This study compared the acute and chronic response of circulating plasma brain-derived neurotrophic factor (BDNF) to high-intensity low-volume (HI) and low-intensity high volume (HV) resistance training. Twenty experienced resistance trained men (23.5±2.6 y, 1.79±0.05 m, 75.7±13.8 kg) volunteered for this study. Prior to the resistance training program (PRE), participants performed an acute bout of exercise using either the HI (3-5 reps; 90% of one repetition maximum [1RM]) or HV (10-12 reps; 70% 1RM) training paradigm. The acute exercise protocol was repeated following 7-weeks of training (POST). Blood samples were obtained at rest (BL), immediately- (IP), 30-min (30P) and 60-min (60P) post exercise at PRE and POST. A 3-way repeated measure ANOVA was used to analyze acute changes in BDNF concentrations during HI and HV resistance exercise, and the effect of 7-weeks of training. No training x time x group interaction in BDNF was noted ($p=0.994$). Significant main effects for training ($p=0.050$) and time ($p<0.001$) in BDNF were observed. Significant elevations in BDNF concentrations were seen from BL at IP ($p=0.001$), 30P ($p<0.001$), and 60P ($p<0.001$) in both HI and HV combined during PRE and POST. BDNF concentrations were also observed to increase from PRE to POST when collapsed across groups and time. No significant group x training interaction ($p=0.342$), training ($p=0.105$), or group ($p=0.238$) effect were noted in the BDNF area under the curve response. Results indicate that BDNF concentrations are increased after an acute bout of resistance exercise, regardless of training paradigm, and are further increased during a 7-week training program in experienced lifters.

Key Words: Neurotrophin, resistance exercise, muscle, training status

New and Noteworthy

There have been a number of investigations examining the BDNF response to exercise, however our understanding of changes in the BDNF response to resistance training has been primarily limited to frail, older adults. This is the first study that has compared two different resistance training paradigms in experienced, resistance trained adults and have demonstrated that training, independent of resistance training paradigm, can modify the BDNF response to an acute bout of resistance exercise.

Introduction

Brain-derived neurotrophic factor (BDNF) is a neurotrophin of the nerve-growth factor protein family, whose downstream effects are mediated through tropomyosin-related kinase (Trk) receptors (38). BDNF is present throughout the nervous system, and a crucial mediator in the formation of neuronal circuits throughout the brain where it promotes neuronal survival, neurite outgrowth, and synaptogenesis (12). BDNF associated adaptations to hippocampal architecture have been associated with positive changes in memory and learning (11, 30, 31, 41) and has been reported to ameliorate the response to stressful stimuli (20, 22). Despite its notable role in the central nervous system, expression of BDNF and its high affinity receptor TrkB are broad, being found in skeletal muscle, cardiac, liver, and adipose cells (26). While its role in the skeletal muscle is less clear, increased expression of skeletal muscle BDNF has been shown to increase fat oxidation in an AMP-activated protein kinase-dependent mechanism (28). However, BDNF synthesized in the skeletal muscle does not appear to contribute to systemic circulating levels, but rather acts in a paracrine or autocrine fashion (28). Preliminary data indicates that the brain is the primary source, providing approximately 80%, of circulating plasma BDNF in response to exercise (34).

Elevations in circulating BDNF concentrations have been demonstrated following an acute bout of both aerobic and resistance exercise (13, 27, 35, 43). A 4-fold increase in resting BDNF secretion rates (58 $ng \cdot 100g^{-1} \cdot min^{-1}$ to 206 $ng \cdot 100g^{-1} \cdot min^{-1}$) were reported following three months of endurance training at ~65% of VO_{2max} (37). In addition, increases in circulating BDNF concentrations observed during exercise and in the recovery period appear to be associated with both duration and intensity of exercise (4, 13, 27, 35, 37). Ferris and colleagues (13) demonstrated that 30 minutes of cycling at 10% above subjects' ventilatory threshold

resulted in higher concentrations of BDNF than when cycling at 20% below. However, the total amount of work performed was greater during the higher intensity protocol. In addition, Cho and colleagues (4) reported greater elevations in circulating BDNF concentrations during a maximal aerobic capacity test with greater duration of exercise. These data suggest that the greater volume, or the combination of greater volume and/or higher intensity, may have provided the stimulus for a greater BDNF response to exercise.

The vast majority of research investigating the BDNF response to physical activity has primarily examined endurance exercise. The BDNF response during resistance exercise has not been studied to the same extent. In a limited number of investigations, some investigators have reported no change in the acute BDNF response to resistance exercise (18, 35), while others have suggested that training can augment the BDNF response to resistance exercise in previously untrained college-aged men (43). Most of the studies examining the BDNF response to resistance training have been performed in older and frail adults. These studies have generally reported that limited resistance training (3 times per week for 10 - 12 weeks) may be sufficient to increase BDNF concentrations in older adults (5, 15, 31). The majority of these studies have examined serum BDNF, which includes platelets that store and release BDNF in response to exercise. In consideration that plasma is free of platelets, and BDNF turnover in the plasma is approximately 6 minutes (33), changes in plasma BDNF would be more indicative of an acute response to a training stress. Furthermore, ~60-80% of plasma BDNF is thought to be produced in the brain (34). To the best of our knowledge no studies have been performed on the plasma BDNF response to resistance training in experienced, resistance trained men. Thus, the primary purpose of this investigation was to compare the acute BDNF response to two common resistance training paradigms before and following 7-weeks of training in experienced, resistance trained

adults. We hypothesize that resistance exercise will increase BDNF concentrations to both training protocols. In addition, we further hypothesize that 7-weeks of training will augment the BDNF response to exercise.

Methods

Experimental Design

Prior to the onset of the study, all participants were required to complete a 2-week preparatory base resistance training program. Subsequently, participants were then randomly assigned to one of two training groups: a high intensity, low-volume training group (HI; n = 10; 22.6 ± 2.3 years; 87.0 ± 15.1 kg; 1.80 ± 0.05 m; 15.9 ± 7.2% body fat) or a high-volume, moderate intensity training group (HV; n = 10; 24.5 ± 2.6 years; 89.5 ± 12.9 kg; 1.66 ± 0.34 m; 20.6 ± 6.0% body fat). All groups completed an 8-week resistance training program using a 4-day split routine. Blood samples were collected during the first training session of week 1 (PRE) and week 8 (POST). These visits constituted the acute training protocols, during which, participants performed the HI (3-5 reps; 90% of one repetition maximum [1RM]) or HV (10-12reps; 70% 1RM) training paradigm.

Participants

Twenty physically active, resistance-trained men agreed to participate in this study. Following an explanation of all procedures, risks, and benefits, each participant provided his informed consent to participate in the study. This investigation was approved by the New England Institutional Review Board, and all procedures were in accordance with the ethical standards of the 1964 Helsinki Declaration and its later amendments. All participants were free of any physical limitations (determined by medical history questionnaire and PAR-Q) and had

been regularly participating (at the time of recruitment) in resistance training for a minimum of 2 years (5.7 ± 2.2 years).

Prior to the present investigation, all participants described their training habits to be different from the present training regimen in terms of exercise order and groupings. Approximately 82% of the participants described their normal repetition range to be either lower (VOL = 77%) or higher (INT = 87%) than what they were assigned to in the study, with about 43% typically using a 6–10 RM range and another 21% using an alternating (or pyramid) structure for specific multiple joint structural and assistance exercises. Additionally, 50% of the participants reported using either longer (VOL = 54%) or shorter (INT = 47%) rest periods, while approximately 29% did not track their rest times previously. The remaining participants employed a similar training scheme (i.e., intensity, volume, and rest) to what they were assigned to in the study.

Preparatory Phase of Training

All participants completed a preparatory resistance training protocol during the 2 weeks prior to the training intervention (see Table 1). This phase encompassed a total of six workouts: four workouts (Monday, Tuesday, Thursday, and Friday) during the first week and two workouts (Monday and Tuesday) during the second week. The purpose of the preparatory training program was to instruct proper lifting technique, familiarize participants with all exercises, and ensure the participants initiated the study with a comparable training base. In comparison to the training intervention groups, the exercises (and their order) were identical but the volume (6–8 RM) and rest intervals (1–2 min) differed. Participants were instructed not to participate in any other form of physical activity throughout the duration of the study.

142 *Anthropometric Assessments*

143 Anthropometric measurements for all participants were conducted approximately 24 h
144 prior to all strength measures. Height (±0.1 cm) and body mass (±0.1 kg) were determined using
145 a Health-o-Meter Professional scale (Model 500 KL, Pelstar, Alsip, IL) with the participants
146 standing barefoot, with feet together, and in their normal daily attire. Body fat percentage was
147 determined using whole body-dual energy x-ray absorptiometry (DXA) scans (Prodigy TM;
148 Lunar Corporation, Madison, WI). All measurements were performed by the same certified
149 radiological technician using standardized subject positioning procedures.

150 *Strength Testing*

151 To determine appropriate training load for both HI and HV, strength in the bench press
152 and squat exercises was assessed. Participants were scheduled for testing at a standard time of
153 day. A general warm up consisting of riding a cycle ergometer for 5 min at a self-selected
154 resistance preceded strength testing. Standardized procedures, as previously described (19) were
155 used for the 1RM barbell bench press and barbell back squat, respectively. Subjects performed
156 two warm-up sets at 40-60% and 60-80% of his perceived 1RM, respectively, before performing
157 3-4 subsequent trials to determine the 1RM. A 3-5 minute rest period was provided between each
158 trial. For all other exercises, the 1RM was assessed using a prediction formula based on the
159 number of repetitions performed to volitional fatigue using a given weight (3). Trials not meeting
160 the range of motion criteria for each exercise or using improper technique were discarded.

161 *Resistance Training Intervention*

162 Participants reported to the Human Performance Lab (HPL) four times per week, at the
163 same time of day, to complete their assigned training program (see Table 1). Both groups

performed the same exercise routine but differed in the intensity of exercise, number of repetitions performed and rest interval between sets. Specifically, the HI training program required participants to perform four sets of 3–5 repetitions with 90% of their 1RM, with 3-min rest period between sets, while the HV group performed four sets of 10–12 repetitions with 70% of their 1RM, with a 1-min rest period between sets. During the resistance training program the load was increased for participants (regardless of group) when the required number of repetitions (for a particular exercise) were achieved on two consecutive workouts. On average three to four participants were being trained by study personnel at one time during the course of the resistance training program. All study personnel were certified strength and conditioning specialists.

Insert Table 1 Here

Blood Sampling

Blood samples were obtained at four time points: baseline (BL), immediately post-exercise (IP), 30 minutes post-exercise (30P), and 60 minutes post-exercise (60P). Participants reported to the Human Performance Lab (HPL) 3 hours post-prandial, at a standardized time of day consistent with their normal training schedule. All blood samples at POST were taken at the same time of day as PRE to avoid the confounding influence of diurnal variations. All blood samples were obtained using a Teflon cannula placed in a superficial forearm vein using a three-way stopcock with a male luer lock adapter and plastic syringe. The cannula was maintained patent using an isotonic saline solution (Becton Dickinson, Franklin Lakes, NJ, USA). Blood samples at BL were obtained following a 15-minute equilibration period. Participants were instructed to lie in a supine position for 15 min prior to the 30P and 60P blood draws.

All blood samples were collected into a Vacutainer® tube containing no containing K_2EDTA. The Vacutainer® tube was kept cold throughout processing in an attempt to reduce the variations in BDNF concentrations during processing. A small aliquot of whole blood from the tube was removed and used for determination of hematocrit and hemoglobin concentrations. The blood was centrifuged at 3,000×g for 15 minutes. The resulting plasma was placed into micro-centrifuge tubes and frozen at −80°C for later analysis.

Blood Analyses

Hematocrit concentrations were analyzed from whole blood via microcentrifugation (CritSpin, Westwood, MA, USA) and microcapillary techniques. Hemoglobin concentrations were analyzed from whole blood using an automated analyzer (HemoCue, Cypress, CA, USA). Coefficient of variation for each assay was 1.53% for hematocrit and 0.55% for hemoglobin. Plasma volume shifts were calculated using the formula established by Dill & Costill (9).

Multiplex ELISA was used to quantitate plasma BDNF concentrations using MAGPIX® (Luminex, Austin, TX, USA) and a commercially available kit (EMD Millipore, Billerica, MA, USA) according to manufacturer's guidelines. To eliminate inter-assay variance, all samples were analyzed in duplicate by a single technician. The coefficient of variation for BDNF was 7.84%.

Nutrient Intake and Dietary Analysis

Participants were instructed to maintain their normal kilocaloric intake habits throughout the investigation. Kilocaloric and macronutrient intake were monitored via weekly food diaries. Consequently, all participants were required to record all food and beverage intake over the course of 3 days (two weekdays and one weekend day) during the initial and final week of

(weeks 1 and 8) of the training program. The FoodWorks Dietary Analysis software version 13 (The Nutrition Company, Long Valley, NJ) was used to analyze dietary recalls.

Statistical Analysis

Prior to hypothesis testing, the Shapiro-Wilk test was used to evaluate the assumption of normality for dependent variables. As our data was not normally distributed we opted to log-transform BDNF measurements (using the natural logarithm). To examine group and training differences in the BDNF response to exercise before and following the 7-week training program, a three-way [training (PRE, POST) x time (BL, IP, 30P, 60P) x group (HI, HV)] repeated measures analysis of variance (ANOVA) was performed. The effect of training on AUC measures, calculated using the trapezoidal methods, was examined using a two-way [training (PRE, POST) x group (HI, HV)] repeated measures ANOVA. In the event of a significant interaction or main effect, Bonferroni post-hoc tests were performed. Interpretations of effect size were evaluated (6) at the following levels: small effect (0.01-0.058), medium effect (0.059-0.137), and large effect (>0.138). For all analyses a criterion alpha level of $p \leq 0.05$ was used to determine statistical significance, and statistical software (SPSS V.21.0, Chicago, IL) was used. All data are reported as mean ± SD.

Results

The effect of these different training paradigms on strength and anthropometric changes have been reported elsewhere (25). For the purposes of this study, no differences were noted at PRE between the groups in the 1RM squat (p=0.694), 1RM bench press (p=0.934) body mass (p=0.715), lean body mass (p=0.611), or percent body fat (p=0.136). Relative energy intake did

not change significantly over the course of the investigation for HI (PRE: 38.2 ± 11.1 $kCal \cdot kg^{-1}$; POST: 31.1 ± 5.3 $kCal \cdot kg^{-1}$) or HV (PRE: 31.7 ± 7.0 $kCal \cdot kg^{-1}$; POST: 29.2 ± 8.1 $kCal \cdot kg^{-1}$).

Changes in plasma BDNF concentrations during PRE and POST are depicted in Fig 1. No training x time x group interaction for plasma BDNF concentration was noted ($F=0.026$, $p=0.994$, $\eta^2=0.002$). However, significant main effects for training ($F=4.434$, $p=0.050$, $\eta^2=0.207$) and time ($F=14.233$, $p<0.001$, $\eta^2=0.456$) were identified. When collapsed across group and training, the acute exercise protocol resulted in significant elevations in BDNF concentrations from BL at IP ($p=0.001$), 30P ($p<0.001$), and 60P ($p<0.001$). Circulating BDNF concentrations, when collapsed across group and time, were significantly elevated ($p=0.050$) from PRE to POST. AUC analysis revealed no significant training x group interaction ($F=0.956$, $p=0.342$, $\eta^2=0.053$) in the BDNF response between HI and HV (see Fig 2). In addition, no main effect for training ($F=2.938$, $p=0.105$, $\eta^2=0.147$) or group ($F=1.499$, $p=0.238$, $\eta^2=0.081$) were noted for the BDNF AUC response.

(Insert Fig 1 and 2 here)

Relative to BL, plasma volume shifts were not significantly different between the two groups at PRE ($p=0.741$) or POST ($p=0.332$). At PRE plasma volume decreased at IP, -8.8 ± 8.6%; increased at 30P 5.2 ± 7.7%; and increased at 60P, 4.7 ± 6.4%. At POST plasma volume decreased at IP, -11.9 ± 5.3%; increased at 30P, 3.2 ± 4.0%; and increased at 60P, 5.8 ± 10.4%. Blood variables were not corrected for plasma volume shifts due to the importance of molar exposure at the tissue receptor level.

Discussion

The primary objectives of this study were to characterize and determine if the BDNF response was different between HI and HV resistance exercise and training. The major findings of this study indicated that BDNF concentrations were significantly elevated following HI and HV resistance exercise in experienced, resistance trained men. In addition, seven weeks of resistance training appears to increase circulating BDNF concentrations in response to the exercise protocol, but did not change resting concentration. This appears to be the first study to compare two commonly used resistance training paradigms on the BDNF response in trained men.

Previous research on the acute BDNF response to resistance exercise has primarily utilized untrained individuals, and the results have been inconclusive (7, 18, 35, 43). Similar to the present study, Yarrow and colleagues (43) reported that resistance training can augment the BDNF response to exercise, but not change resting concentrations. Other studies, using previously untrained or recreationally trained participants of similar age were unable to demonstrate any change in the BDNF response to an acute resistance exercise session (7, 18). These differences may be related to the duration or volume of exercise. Correia and colleagues (7) did not observe any change in BDNF concentrations following five sets of 10 repetitions in the isokinetic knee extension exercise, ($60° \cdot sec^{-1}$). Similarly, Goekint et al. (18) used an exercise protocol of three sets of 10 repetitions (80% 1RM) in six different exercises (a total of 18 sets performed), and reported no change in the BDNF response to the exercise stimulus. However, these exercises were all performed with exercise machines. In contrast, the participants in the present study performed four sets of six exercises (a total of 24 sets) using free weight, multi-joint structural movement exercises that recruited a larger muscle mass than the exercises used in

the previously mentioned studies. Exercises that recruit a greater amount of muscle mass are associated with a greater endocrine and biochemical response compared to single-joint or confined movement exercises that recruit a smaller muscle mass (23). The difference in musculature recruited may provide a plausible rationale for the difference in the present study and those of Corriea et al. (7) and Goekint et al. (18). It is also possible that a threshold stimulus of volume performed, muscle mass activated, and/or duration of activity is necessary to stimulate a resistance exercise-induced BDNF response.

The relationship of BDNF and resistance training has generally been examined in elderly or clinically relevant populations (14-16, 24, 36, 39). Previous research from our laboratory (16) and others (14, 24, 36, 39) have shown that resistance training does not significantly change resting BDNF concentrations. Recently Forti and colleagues (15) reported a significant increase in resting BDNF concentrations in elderly men (> 65 y) who participated in a 3-day per week, 12-week mixed, low intensity (60 repetitions at 20% of 1RM, and 10-20 repetitions at 40% of 1RM with no rest) resistance training program. However, in that same study no changes were noted in resting BDNF concentrations in elderly men performing low intensity (1 set of 80-100 repetitions at 20% of 1RM) or higher intensity (2 sets of 10-15 repetitions at 80% of 1RM with 1-min rest between sets) training programs. In addition, no changes were noted in elderly women who participated in all three training programs. Walsh and colleagues (42) reported that 8 weeks of resistance training in older adults (60 – 77 years) was unable to change either resting or the exercise response of BDNF. The ability of resistance training to elevate resting BDNF concentrations may be a function of both age and training status. Younger, and more experienced resistance trained adults appear to not be as sensitive as an older, untrained population to stimulate changes in resting BDNF. However, we observed a significant effect of training on

297 circulating BDNF, supported by the strong effect sizes observed in the temporal (η^2=0.207) and
298 AUC (η^2=0.147) responses. These results are in accordance with Yarrow and colleagues (37),
299 who demonstrated 5 weeks of resistance training was able to alter the BDNF response in
300 untrained men.

301 Increases in circulating BDNF in response to metabolic challenges are suggested to have
302 a role in regulating peripheral energy metabolism within the brain and in peripheral neurons (26).
303 Elevations in circulating concentrations of BDNF resulting from an elevation in metabolic stress
304 does provide support for a duration/volume threshold stimulus (13, 17, 34). Previous research
305 has shown cortisol concentrations to be inversely related to BDNF (2, 21). We have previously
306 reported the cortisol response of the current study (25). The cortisol response at POST was
307 attenuated in HV but not in HI. Although the attenuated cortisol response of HV may explain the
308 increase in circulating plasma BDNF at POST, the similar cortisol response between PRE and
309 POST for HI does not provide support. Therefore, it does not appear that cortisol influenced
310 changes in the BDNF response observed in this study. Additional research is necessary to
311 provide further insight to the mechanism governing BDNF changes to training.

312 The role of circulating BDNF is ambiguous. Much of our present understanding focuses
313 on BDNF's role as a neurotrophin in the brain (40), however, its role in modulating peripheral
314 neurogenesis is less understood. Current evidence indicates plasma BDNF is a proxy marker of
315 BDNF production in the brain (34), however BDNF can also be synthesized peripherally (40).
316 The importance of the resistance training induced increase in BDNF has been suggested to be
317 related to improvements in cognitive function, memory and mood (1, 8, 10). Further research is
318 still needed to delineate the potential physiological role that BDNF has in the neuromuscular
319 system, especially in apparently healthy, trained individuals.

Conclusions

This investigation appears to be the first study to explore the BDNF response to different resistance training paradigms in experienced, resistance trained men. The results of this study demonstrate that the BDNF response is significantly elevated following both the high intensity and high volume training protocols, with no differences between the protocols. In addition, 7-weeks of training did appear to increase the BDNF response to exercise. Future research appears warranted in examining the potential role that elevated BDNF concentrations may have on neuromuscular adaptations.

Conflicts of Interest

No funding was received for the purposes of this study. The authors declare no conflicts of interest.

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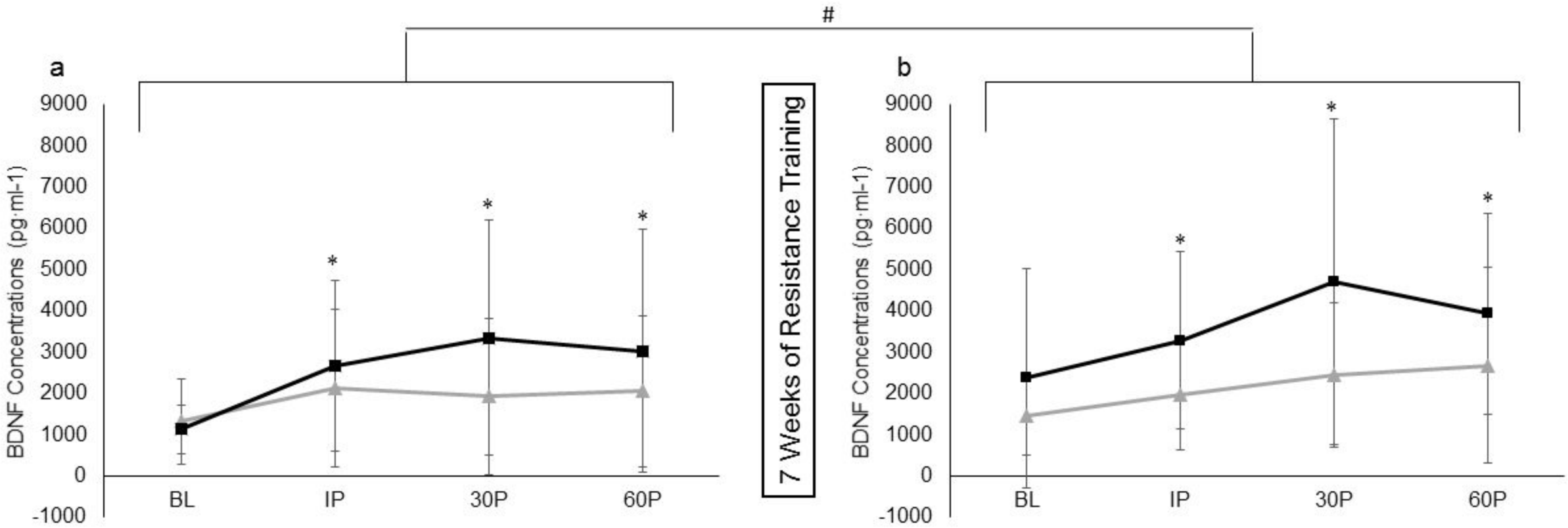
Figure Legends

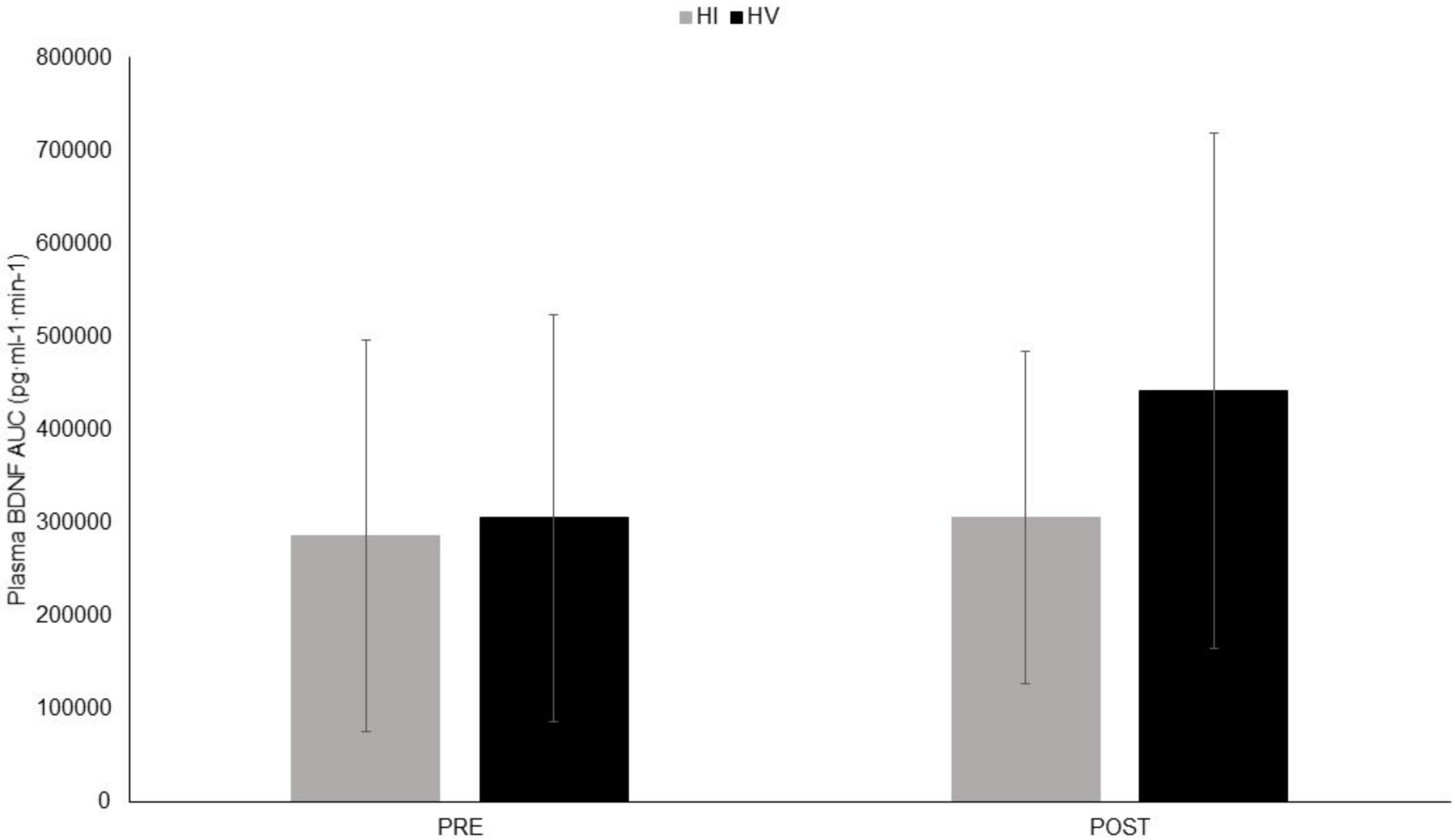
Figure 1. Temporal circulating brain derived neurotrophic factor (BDNF) concentrations at rest (BL), immediately after (IP), 30 minutes after (30P), and 60 minutes after (60P) either a high-intensity, low volume (HI; light line with triangles) or low-intensity, high volume (HV; dark line with squares) resistance exercise protocol before (PRE; A) and after (POST; B) 7 weeks of resistance training. Data are presented at mean ± SD. * = Significant difference compared to BL when groups are collapsed across group and training session. # = Significant difference at POST as compared to PRE when collapsed across time and group.

Figure 2. Area under the curve (AUC) of plasma BDNF before (PRE) and after (POST) 7 weeks of either a high-intensity, low volume (HI) or low-intensity, high volume (HV) resistance training program.

Table 1 Resistance training program

Program variable	Preparatory phase both groups	High Volume (HV)	High Intensity (HI)
Exercise prescription			
Training duration	2 weeks	8-weeks	8-weeks
Training intensity	80-85% 1RM	70% 1RM	90% 1RM
Training volume	4 sets x 6-8 repetitions	4 sets x 10-12 repetitions	4 sets x 3-5 repetitions
Rest time	1-2 minutes	1 minute	3 minutes
Exercises			
Day 1	Day 2	Day 3	Day 4
Back squats	Bench press	Back squats	Bench press
Deadlifts	Incline bench press	Deadlifts	Incline bench press
Leg press	Dumbbell flys	Barbell lunge	Incline dumbbell flys
Lat pull downs	Seated shoulder press	Seated row	Seated shoulder press
Barbell bent-over rows	Lateral dumbbell raise	Dumbbell pullover	Lateral dumbbell raise
Barbell biceps curls	Triceps extension	Dumbbell biceps curl	Triceps extension


#
a
b
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
BDNF Concentrations (pg·ml-1)
BL
IP
30P
60P
*
7 Weeks of Resistance Training


HI
HV
800000
700000
600000
500000
400000
300000
200000
100000
0
Plasma BDNF AUC (pg·ml-1·min-1)
PRE
POST