Title: Intense resistance exercise increases peripheral brain-derived neurotrophic factor

Authors: Kieran J. Marston, Michael J. Newton, Belinda M. Brown, Stephanie R. Rainey-Smith, Sabine Bird, Ralph N. Martins, Jeremiah J. Peiffer

PII: S1440-2440(17)30347-X
DOI: http://dx.doi.org/doi:10.1016/j.jsams.2017.03.015
Reference: JSAMS 1492

To appear in: *Journal of Science and Medicine in Sport*

Received date: 3-11-2016
Revised date: 20-1-2017
Accepted date: 13-3-2017

Please cite this article as: Marston Kieran J, Newton Michael J, Brown Belinda M, Rainey-Smith Stephanie R, Bird Sabine, Martins Ralph N, Peiffer Jeremiah J.Intense resistance exercise increases peripheral brain-derived neurotrophic factor.*Journal of Science and Medicine in Sport* http://dx.doi.org/10.1016/j.jsams.2017.03.015

Title

Intense resistance exercise increases peripheral brain-derived neurotrophic factor

Authors

Kieran J Marston [a, *], Michael J Newton [a], Belinda M Brown [a, b, c], Stephanie R Rainey-Smith [b, c], Sabine Bird [b, c, d], Ralph N Martins [b, c, d], and Jeremiah J Peiffer [a]

Affiliations

[a] School of Psychology and Exercise Science, Murdoch University, Perth, Western Australia, Australia;

[b] Centre of Excellence for Alzheimer's Disease Research & Care, School of Medical and Health Sciences, Edith Cowan University, Joondalup, Western Australia, Australia;

[c] Sir James McCusker Alzheimer's Disease Research Unit (Hollywood Private Hospital), Perth, Western Australia, Australia;

[d] School of Psychiatry and Clinical Neurosciences, University of Western Australia, Perth, Western Australia, Australia

Corresponding author

*Mr Kieran Marston

School of Psychology and Exercise Science, Murdoch University

90 South Street, Murdoch, Western Australia, 6150

AUSTRALIA.

Phone: +61 (0) 8 9360 7603

Email: K.Marston@murdoch.edu.au

Abstract

Objectives: Brain-derived neurotrophic factor (BDNF) has been shown to increase in an intensity dependent manner in response to aerobic exercise. However, previous research investigating the use of resistance exercise to increase BDNF levels has been less conclusive, likely due to the low intensity nature of traditional resistance exercise programs. This study examined the influence of acute resistance exercise to-fatigue on serum BDNF levels and blood lactate.

Design: Acute crossover study.

Methods: Eleven untrained to intermediately trained males (age: 25.0 ± 1.3 yr) and five untrained females (age: 23.2 ± 1.1 yr) were recruited to undertake two bouts of resistance exercise. Strength (five sets of five repetitions, 180 s recovery) and hypertrophy (three sets of ten repetitions, 60 s recovery) based resistance exercise was implemented to-fatigue to examine the effect on serum BDNF and blood lactate levels immediately post-, and 30 min post-exercise.

Results: An interaction ($p < 0.01$; ES = 0.52) was observed between conditions immediately post-exercise, with hypertrophy resulting in significantly greater BDNF levels when compared with strength exercise. Changes in lactate and BDNF from baseline to post- exercise were positively correlated following hypertrophy exercise ($r = 0.70$; $p < 0.01$), but not correlated following strength exercise ($r = 0.18$; $p = 0.56$).

Conclusions: The use of a to-fatigue hypertrophy based resistance exercise protocol provides the necessary stimulus to increase peripheral serum BDNF. Mechanistically, the presence of lactate does not appear to drive the BDNF response during resistance exercise.

Keywords

Alzheimer's Disease, Strength Training, Neurotrophin, Lactate, Muscular Fatigue

Introduction

Alzheimer's disease (AD), characterised by memory loss and cognitive dysfunction, is a leading cause of death in older adults. Age is the most significant predictor of AD diagnosis; nevertheless, the development of AD neuropathology likely starts decades prior to presentation of clinical symptoms.[1] Following the clinical onset of AD symptoms, progression can be rapid and unpredictable. To date, no effective treatment or cure exists for AD, thus research attention is focusing on the identification of effective preventative strategies to delay or prevent AD. Increasing evidence indicates physical activity, specifically structured exercise, can benefit cognitive health [2] and could potentially be used as a preventative strategy for AD. Mechanistic studies support a relationship between exercise and enhanced brain health in older adults. Specifically, results from exercise interventions have demonstrated upregulation of brain-derived neurotrophic factor (BDNF), a neurotrophin involved in the growth and repair of neural tissue.[3] In human studies, aerobic exercise has been shown to increase circulating levels of BDNF [4,5] and provide a protective influence to cognitive function.[2,4] The influence of aerobic exercise on BDNF appears to be dose dependent with greater levels of peripheral BDNF associated with an increased intensity of aerobic exercise.[4-6] To date, the majority research examining the influence of exercise on BDNF is focused on aerobic based exercise.[4-7] As resistance exercise is routinely prescribed to an ageing population,[8] understanding the influence of this exercise modality on BDNF is essential.

Within the literature, resistance exercise has been shown to improve cognitive function;[9] however, from these studies it is not possible to determine if these effects were mediated by increases in BDNF. Unlike aerobic based exercise interventions, previous studies of resistance exercise and BDNF are equivocal. Some studies report increases in peripheral BDNF follow acute resistance protocols,[10] whereas others report no change:[11,12] These differing results may potentially be due to the intensity of the exercise.[4,13] Indeed, BDNF expression is indirectly associated with lactate,[4] a biomarker of physical fatigue which is elevated in response to higher exercise demands.[14] Furthermore, blood lactate accumulates with each repetition,[15] and has shown reduced clearance from the muscle with shorter periods of recovery.[16] It is possible through the manipulation of acute resistance training variables such as sets, repetitions, load, and recovery that the necessary stimulus

could be provided to increase peripheral BDNF and enhance cognitive function. Manipulation of resistance exercise variables has been shown to elicit differing responses in blood markers; for instance, high load, low repetition, long recovery resistance exercise elevates serum testosterone levels,[13] a hormone linked to cognitive function.[17] Alternatively, moderate load, moderate repetition, short recovery resistance exercise stimulates human growth hormone;[13] which has been previously associated with peripheral BDNF.[18]

The use of exercise to prevent cognitive decline appears promising; however, the lack of data currently available in this field restricts its prescription. The purpose of this study was to examine the peripheral BDNF response to two different, yet intense, sessions of resistance exercise. We recruited individuals less than 30 yr as in this population greater intensity of exercise is possible,[19] thus providing a greater effect for proof of BDNF induction principle and potential translation to older populations in future studies. Furthermore, as preventative strategies of cognitive decline should ideally span many decades: this cohort represents individuals at the beginning of this continuum. A secondary aim of the current study was to compare the lactate response to each exercise condition and determine the association between changes in lactate and BDNF. We hypothesised that the greatest magnitude change in BDNF and lactate would be observed following hypertrophy resistance exercise.

Methods

Sixteen individuals (males, n=11, age 25.0±1.3 yr; females, n=5, age: 23.2±1.1 yr) volunteered to participate in this study. All participants were untrained (n=13) to intermediately trained (n=3) as determined by previous guidelines.[8] Participants were considered low risk for moderate to intense exercise as per the Exercise and Sports Science Australia adult pre-exercise screening tool. Participants completed four exercise sessions (two familiarisation and two experimental sessions) with no less than four and no greater than 10 days between each session. All procedures were approved by the institutional Human Research Ethics Committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Participants were provided with written documentation of the possible risks and benefits related to their participation in this study and signed informed consent was obtained in writing.

Two initial laboratory sessions familiarised participants with the equipment and procedures involved in the study. During the first session, participants were provided verbal and visual instruction regarding the correct lifting technique for seven resistance exercises (bench press, latissimus dorsi pull-down [lat pull-down], leg press, leg extension, seated row, military press and dumbbell arm curl). Assessment of five- and 10- repetition maximum (RM) were conducted in a randomised and counterbalanced order in the following exercise sequence; 1) bench press, 2) seated row, 3) leg press, 4) military press, 5) lat pull-down, 6) leg extension, and 7) arm curl. During 5-RM testing, participants were asked to lift a weight, pre-selected by the researcher, which would result in only five repetitions being able to be completed as per previous guidelines.[20] During each exercise, range of motion was measured using a static measuring tape attached to weight machines and averaged over several repetitions in order to calculate mechanical work completed.[21] Range of motion during the arm curl was measured using a goniometer, and forearm length was measured using a tape measure. During the 10-RM visit, participants completed 10-RM testing using the same exercises and identical methodology to the 5-RM session, with the exception that the maximum weight that could be lifted with correct technique for ten repetitions was determined.

On the subsequent two laboratory sessions, participants completed either strength based or hypertrophy based resistance exercise protocols[13] in a randomised and counterbalanced order in the same sequence as during the RM testing. All sessions commenced with a five min self-paced warm-up on a rowing ergometer at low to moderate intensity followed by low resistance repetitions of all exercises. During the strength based session, participants completed five sets of five repetitions at their 5 RM resistance with 180 s of passive recovery between each set. During the hypertrophy based session, participants completed three sets of 10 repetitions at their 10 RM resistance with 60 s of passive recovery between each set.

Venous blood samples were collected prior to warm-up, immediately after the completion of the exercise, and 30 min post-exercise, for later BDNF quantification. Venous blood samples were obtained from the antecubital vein using a 21-gauge needle into serum separation tubes (SST Vacutainer®, Becton-Dickinson, U.S.A) and left to clot at room temperature before high-speed (1800 · g) centrifugation for 15 min to minimise platelets within the serum. After centrifugation, serum

supernatant was transferred into 1.5 mL aliquots and stored at -80° C for BDNF batch analysis. A further 4.0 mL of venous blood was collected into an ethylenediaminetetraacetic acid tube (EDTA Vacutainer®, Becton-Dickinson, U.S.A) once for platelet count. Prior to warm-up, immediately after the completion of the exercise, and 30 min post-exercise, 0.7 µL of blood was obtained in duplicate from the fingertip and analysed for blood lactate concentration using a handheld lactate analyser (Lactate Plus, Nova Biomedical ®, U.S.A). Serum samples were analysed for total BDNF (precursor and mature isoforms) using a standard enzyme-linked immunosorbent assay technique. Serum BDNF was determined using a commercial kit (HBDP-33K, Milliplex ®, Millipore™, Billerica, USA) as per manufacturer instructions. The manufacturer declares intra- and inter-assay coefficients of variation of less than 10%.

Total mechanical work, volume load and mean tonnage were calculated using the formulae defined in Table 1. We used equation one for all exercises involving vertical displacement (i.e. seated row, lat pull-down, leg extension, military press and bench press). Equation two calculated mechanical work of the incline leg press, which used a cosine to account for an incline of 45 degrees. Equation three calculated work completed for the bicep curl, which required consideration of rotation about the elbow joint, using torque and range of motion of flexion in radians. To provide an overall indication of volume and intensity, total sessional volume was calculated as volume load and mean tonnage using equations four and five.

Differences in lactate and BDNF between and within conditions over time were assessed using linear mixed modelling. Prior to analyses, all variables were assessed for normality using a Shapiro-Wilk test. Furthermore, following the conduct of the LMM, visual inspection of the residual plots did not reveal deviations from normality or homoscedasticity. Significant main effects or interactions were assessed using the Fisher's Least Significant Difference post-hoc test. Effect size estimates (ES; Cohen's d; small=0.2, moderate=0.5, large=0.8) were calculated for the magnitude of difference in lactate between time points, for BDNF between conditions at each time point and for change in BDNF from pre- to immediately post-exercise, and post- to 30 min post-exercise. Differences in total mechanical work (J) between the strength and hypertrophy trials were analysed using a dependent-samples *t*-test. Pearson's bivariate correlations were used to assess the associated

between changes in BDNF and lactate. All statistical analyses were conducted using SPSS (Version 22, IBM®, U.S.A) analysis software with the level of significance set at $p < 0.05$. All data are presented as mean ± 95 % confidence interval (CI), unless otherwise noted.

Results

By design, no differences ($p=0.27$; ES=0.06) in mean mechanical work were observed between the strength (45.2±14.0 kJ) and hypertrophy (46.0±7.5 kJ) protocols. Differences in mean volume load between strength (12642±1679 kg) and hypertrophy protocols (13214±1918 kg) were significant ($p=0.01$) but negligible in magnitude (ES=0.16). Mean tonnage was greater in the strength protocol (70.3±8.7 kg) when compared to the hypertrophy protocol (62.7±9.2 kg; $p<0.01$; ES=0.42). For all participants, platelet count ($232.31±24.20·10^9$/L) was within the normal reported range[22] of 150 to $400·10^9$/L.

Serum BDNF levels measured at baseline, immediately-post, and 30 min post-exercise are shown in Figure 1. An interaction ($p<0.01$; ES=0.52) was observed between conditions immediately post-exercise, with hypertrophy resulting in greater BDNF levels when compared with strength exercise. Within conditions, greater levels of serum BDNF were observed immediately post-exercise compared with baseline ($p=0.01$; ES=0.51) and 30 min post-exercise ($p<0.01$; ES=0.22) in the hypertrophy condition only (Figure 1a). Within the strength protocol, no differences were observed for serum BDNF between any time points. The mean change in BDNF from baseline to post-exercise was significantly greater ($p < 0.01$) in the hypertrophy condition when compared with the strength condition (Figure 1b).

Blood lactate was significantly higher in both conditions immediately post-exercise, when compared to baseline (ES=2.52) and 30 min post-exercise (ES=1.51; Figure 2). An interaction ($p<0.01$; ES=1.2) was observed between conditions immediately post-exercise, with hypertrophy exercise resulting in significantly greater blood lactate concentrations when compared to strength exercise. A positive Pearson's correlation ($r=0.70$; $p<0.01$) was observed between changes in lactate and changes in BDNF concentrations following hypertrophy exercise from baseline to immediately

post-exercise. No correlation (r=0.18; p=0.56) was observed between changes in lactate and changes in BDNF concentrations following strength exercise from baseline to immediately post-exercise.

Discussion

The purpose of this study was to examine the difference in the response of peripheral serum BDNF levels to two single-session matched-work resistance (strength vs. hypertrophy) exercise protocols. The novel findings were; 1) significantly greater serum BDNF levels were observed post-exercise in the hypertrophy condition when compared to the strength condition, and 2) changes in blood lactate were positively correlated with change in BDNF in the hypertrophy condition only.

Within the hypertrophy condition, immediately post-exercise we observed a 13% increase in serum BDNF levels when compared with baseline values. Although our findings are of relatively small magnitude, they are consistent with previous intense resistance exercise research which has reported a 32% increase in serum BDNF in an untrained population.[10] Together these findings support the use of resistance exercise as a stimulus to increase peripheral BDNF; however, they also highlight the sensitivity of peripheral BDNF to variations in resistance training protocols. For instance, although identical inter-set recovery durations (60 s) were utilised in our hypertrophy condition and that of Yarrow et al,[10] we implemented seven exercises as opposed to only two (bench press and squat) which is likely to have influenced the skeletal muscle exposure to peak levels of blood flow prior to our measurements of BDNF. Peak blood flow to muscle is dependent on the mass of active muscle tissue;[23] thus, it is likely that large muscle mass exercise promotes greater release of BDNF as a result of greater blood flow. Furthermore, blood flow velocity through the femoral artery is augmented in an intensity-dependent manner as shown during submaximal leg extension exercise [24] and can increase rapidly by at least 50% immediately upon set completion.[25] Expression of BDNF also appears to be relatively transient, returning to baseline or below baseline within 30 post-exercise.[5,10] Thus, by performing larger muscle mass exercises early in the session it is possible our blood values following the exercise were not representative of peak BDNF expression.

Although some studies within the existing literature [11,12] do not support the use of resistance exercise to acutely increase peripheral BDNF levels; we believe these findings are due to the intensity

of exercise [4,25] and potentially the source of BDNF (i.e. plasma versus serum) used for quantification.[26] Intense exercise is associated with the upregulation of peripheral BDNF [4] as a consequence of increased blood flow and the resultant inter-vessel shear stress.[26] Furthermore, platelet release of BDNF is a major source of serum BDNF and is upregulated during high blood flow related shear stress.[26] The findings from Correia et al[12] are therefore not surprising as the use of plasma samples to measure peripheral levels of BDNF would not have allowed the capture of platelet released BDNF,[26] irrespective of the intensity of their exercise session. The exercise structure (three sets, ten repetitions at 80% or 1RM) utilised by Goekint et al[11] is considered intense and therefore should have resulted in increased levels of peripheral BDNF, however, this study used long inter-set recovery durations which would have reduced the overall intensity of the exercise session and likely the exposure to high limb blood flow.[25] Shorter recovery is accompanied by a maximised 'endurance stimulus' and greater increases in blood lactate,[27] a metabolite previously associated with changes in peripheral BDNF.[4] Intensity of exercise remains the major factor influencing post-exercise increases in serum BDNF; however, it is important to acknowledge other variables (i.e. number of repetitions, session duration, muscle mass utilised) could influence both the peripheral BDNF as well as the ability to obtain accurate measures. Researchers and clinicians should be aware of these additional considerations when attempting to utilise resistance exercise to enhance peripheral levels of BDNF.

Hypertrophy and strength based resistance protocols were selected for this study as both provide benefits to populations throughout a lifespan. Nevertheless, differences in the practical aims of these protocols (i.e. increasing muscle mass versus strength) required necessary manipulation of inter-set recovery which likely influenced the BDNF response. Lower recovery time during the hypertrophy protocol (60 s) would have resulted in longer periods of continuous exposure of skeletal muscle to high blood flow and a resultant increase in the release of BDNF from the endothelium and platelets.[6,26] Indeed, blood flow velocity peaks in the femoral artery immediately following quadriceps exercise [25,28], and can take up to 90 s to return to baseline velocities.[28] Based on this finding, 60 s of recovery was likely not adequate for muscle blood flow to return to a resting state during the hypertrophy protocol, thus extending periods of high blood flow and related shear stress. Recovery during the strength protocol (180 s), however, would have allowed muscle blood flow to return to a

rested state, limiting exposure to shear stress within the arteries. In addition, the increased recovery time during the strength protocol would have allowed greater periods of BDNF removal through uptake in the periphery [10] and possibly the brain.[29]

The presence of elevated blood lactate is a hallmark sign of intense exercise [14] and has previously been shown to be associated with serum BDNF during aerobic exercise.[4] Indeed, Ferris et al[4] observed a significant positive relationship (r=0.57) between serum BDNF and lactate measured immediately after a graded exercise test. In the current study, changes in BDNF and lactate levels from baseline to immediately post-exercise were highly correlated in the hypertrophy protocol; yet, no association was observed in the strength protocol. This likely indicates that the hypertrophy protocol alone elicited an 'endurance stimulus',[27] resulting in greater changes in blood lactate and BDNF. However, it is equally possible that the total duration of the exercise session (~40 min hypertrophy, ~120 min strength) influenced this relationship as amount or rate of metabolic uptake of either lactate or BDNF may occur throughout the acute exercise sessions.[10,29] Based on the inconsistent associations between protocols for blood lactate and BDNF expression, we suggest that lactate is merely a by-product of fatigue and may not be essential in the peripheral expression of BDNF.

To our knowledge, we are the first to demonstrate a difference in BDNF expression between two structurally different, yet work- and volume-matched, resistance exercise protocols. However, we acknowledge limitations in the present study that should be addressed in future studies. The use of a small sample size (n=16) and the recruitment of healthy participants may influence the generalisation of our findings. Additionally, our sample population were volunteers, and while not highly trained, this method of recruitment may have led to a sampling-bias, which could reduce the ability to generalise our findings to ageing or unhealthy populations. The measurement of total BDNF using commercially available ELISA kits, although used extensively in the literature, may have been associated with minor technical issues such as inter-plate variability. Nevertheless, we validated our results by repeating samples across plates and found >90% corroboration. This study provides important information on the acute influence of resistance exercise on BDNF expression; however, future studies should aim to establish the time-frame for these changes through inclusion of measurement time-points beyond 30 min. Future studies should also consider measurement of both

precursor and mature forms of BDNF, particularly as these two isoforms have been demonstrated different effects on neurons.[30] Finally, although animal studies demonstrate the ability of BDNF to cross the blood-brain barrier,[29] this is yet to be established in humans. We can only confirm our hypothesis that training-induced increases in peripheral BDNF reflect increases in brain BDNF, following evidence that BDNF crosses the blood-brain barrier in humans.

Conclusion

Our findings indicate that the use of a to-fatigue hypertrophy-style exercise protocol provides the necessary stimulus to increase peripheral serum BDNF if coupled with short inter-set recovery durations. Mechanistically, as lactate increased significantly following both protocols, yet was only associated with a change in BDNF following hypertrophy exercise, we suggest that lactate is not driving BDNF expression. Based on our findings, the use of to-fatigue hypertrophy based resistance exercise should be considered in exercise programs to enhance the possibility of a cognitive benefit due to increased BDNF expression.

Practical Implications

- Acute resistance exercise increases serum BDNF concentrations when performed at 100% of 10RM with 60 seconds of recovery in between sets.
- While the use of the current hypertrophy protocol should be tolerable to both younger and older adults, practitioners should still undertake appropriate screening and program individualisation.
- The expression of serum BDNF is likely reliant on intensity of exercise.
- Hypertrophy resistance exercise is likely to provide cognitive benefit due to increased BDNF expression.

Acknowledgements

The authors would like to extend thanks to the participants who volunteered their time and effort and to NL, AR and NG for their time and assistance. This project was conducted using donated funds from the McCusker Charitable Foundation and student allocated funds. The authors of this article declare no conflicts of interest in the development and completion of this study.

References

1. Villemagne VL, Burnham S, Bourgeat P et al. Amyloid beta deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's disease: a prospective cohort study. *Lancet Neurol* 2013; 12(4):357-367.
2. Lautenschlager NT, Cox KL, Flicker L et al. Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: a randomized trial. *JAMA* 2008; 300(9):1027-1037.
3. Mattson MP, Maudsley S, Martin B. BDNF and 5-HT: a dynamic duo in age-related neuronal plasticity and neurodegenerative disorders. *Trends Neurosci* 2004; 27(10):589-594.
4. Ferris LT, Williams JS, Shen CL. The effect of acute exercise on serum brain-derived neurotrophic factor levels and cognitive function. *Med Sci Sports Exerc* 2007; 39(4):728-734.
5. Nofuji Y, Suwa M, Sasaki H et al. Different circulating brain-derived neurotrophic factor responses to acute exercise between physically active and sedentary subjects. *J Sports Sci Med* 2012; 11(1):83-88.
6. Rasmussen P, Brassard P, Adser H et al. Evidence for a release of brain-derived neurotrophic factor from the brain during exercise. *Exp Physiol* 2009; 94(10):1062-1069.
7. Winter B, Breitenstein C, Mooren FC et al. High impact running improves learning. *Neurobiol Learn Mem* 2007; 87(4):597-609.
8. American College of Sports Medicine Position Stand. Progression models in resistance training for healthy adults. *Med Sci Sports Exerc* 2009; 41(3):687-708.
9. Liu-Ambrose T, Nagamatsu LS, Graf P et al. Resistance training and executive functions: a 12-month randomized controlled trial. *Arch Intern Med* 2010; 170(2):170-178.
10. Yarrow JF, White LJ, McCoy SC et al. Training augments resistance exercise induced elevation of circulating brain derived neurotrophic factor (BDNF). *Neurosci Lett* 2010; 479(2):161-165.
11. Goekint M, De Pauw K, Roelands B et al. Strength training does not influence serum brain-derived neurotrophic factor. *Eur J Appl Physiol* 2010; 110(2):285-293.

12. Correia PR, Pansani A, Machado F et al. Acute strength exercise and the involvement of small or large muscle mass on plasma brain-derived neurotrophic factor levels. *Clinics* 2010; 65(11):1123-1126.

13. Kraemer WJ, Marchitelli L, Gordon SE et al. Hormonal and growth factor responses to heavy resistance exercise protocols. *J Appl Physiol* 1990; 69(4):1442-1450.

14. Smith EW, Skelton MS, Kremer DE et al. Lactate distribution in the blood during steady-state exercise. *Med Sci Sports Exerc* 1998; 30(9):1424-1429.

15. Denton J, Cronin JB. Kinematic, kinetic, and blood lactate profiles of continuous and intraset rest loading schemes. *J Strength Cond Res* 2006; 20(3):528-534.

16. Ratel S, Bedu M, Hennegrave A et al. Effects of age and recovery duration on peak power output during repeated cycling sprints. *Int J Sports Med* 2002; 23(6):397-402.

17. Janowsky JS. Thinking with your gonads: testosterone and cognition. *Trends Cogn Sci* 2006; 10(2):77-82.

18. Khan AS, Sane DC, Wannenburg T et al. Growth hormone, insulin-like growth factor-1 and the aging cardiovascular system. *Cardiovasc Res* 2002; 54(1):25-35.

19. Woo JS, Derleth C, Stratton JR et al. The influence of age, gender, and training on exercise efficiency. *J Am Coll Cardiol* 2006; 47(5):1049-1057.

20. Baechle TR, Earle RW. *Essentials of Strength Training and Conditioning,* 3rd ed., United States, Human Kinetics, 2008.

21. Blazevich AJ, Jenkins DG. Effect of the movement speed of resistance training exercises on sprint and strength performance in concurrently training elite junior sprinters. *J Sports Sci* 2002; 20(12):981-990.

22. Giles C. The platelet count and mean platelet volume. *Br J Haematol* 1981; 48(1):31-37.

23. Joyner MJ, Casey DP. Regulation of increased blood flow (Hyperemia) to muscles during exercise: A hierarchy of competing physiological needs. *Physiol Rev* 2015; 95(2):549-601.

24. Rådegran G. Ultrasound doppler estimates of femoral artery blood flow during dynamic knee extensor exercise in humans. *J Appl Physiol* 1997; 83(4):1383-1388.

25. Takahashi T, Saitoh T, Okada A et al. Differences in femoral artery blood velocity among active, inactive and passive recovery modes following knee extension and flexion exercise. *Therapeutic Research* 2006; 27(7):1393-1403.

26. Fujimura H, Altar CA, Chen R et al. Brain-derived neurotrophic factor is stored in human platelets and released by agonist stimulation. *Thromb Haemost* 2002; 87(4):728-734.

27. Ross MD, Wekesa AL, Phelan JP et al. Resistance exercise increases endothelial progenitor cells and angiogenic factors. *Med Sci Sports Exerc* 2014; 46(1):16-23.

28. Wesche J. The time course and magnitude of blood flow changes in the human quadriceps muscles following isometric contraction. *J Physiol* 1986; 377(1):445-462.

29. Pan W, Banks WA, Fasold MB et al. Transport of brain-derived neurotrophic factor across the blood-brain barrier. *Neuropharmacology* 1998; 37(12):1553-1561.

30. Teng HK, Teng KK, Lee R et al. ProBDNF induces neuronal apoptosis via activation of a receptor complex of p75NTR and sortilin. *J Neurosci* 2005; 25(22):5455-5463.

Figure captions

Figure 1. Mean (±95% CI) levels of (a) BDNF immediately before (Pre), after (Post) and 30 min (30 Post) post hypertrophy (■) and strength based (□) exercise, and (b) change in BDNF from baseline to after (Post) and 30 min (30 Post) post hypertrophy (■) and strength based (□) exercise. * Significantly greater BDNF in hypertrophy compared with strength ($p < 0.01$). ** Post greater than Pre ($p = 0.01$) and 30 min ($p < 0.01$) post in hypertrophy only. *** Greater change ($p < 0.01$) in BDNF following hypertrophy compared with strength exercise at Post time-point.

Figure 2. Mean (±95% CI) blood lactate concentration measured immediately before (Pre), after (Post) and 30 min (30 Post) post hypertrophy (■) and strength based (□) exercise protocols. *Significantly greater lactate post-exercise following hypertrophy when compared with strength exercise ($p < 0.01$). **Post measures greater ($p < 0.01$) than pre and 30 min post values.

Figure 1

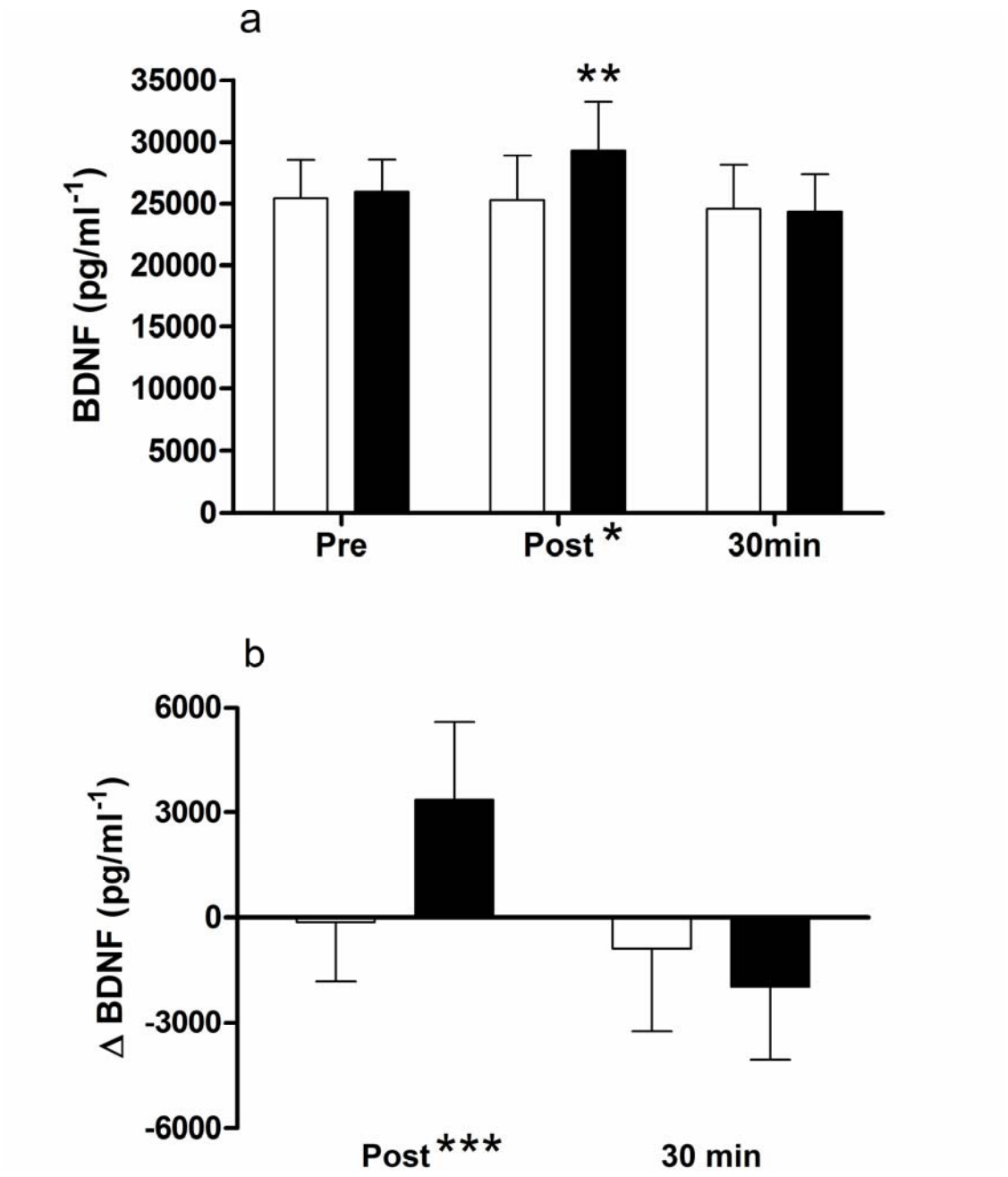

Figure 2

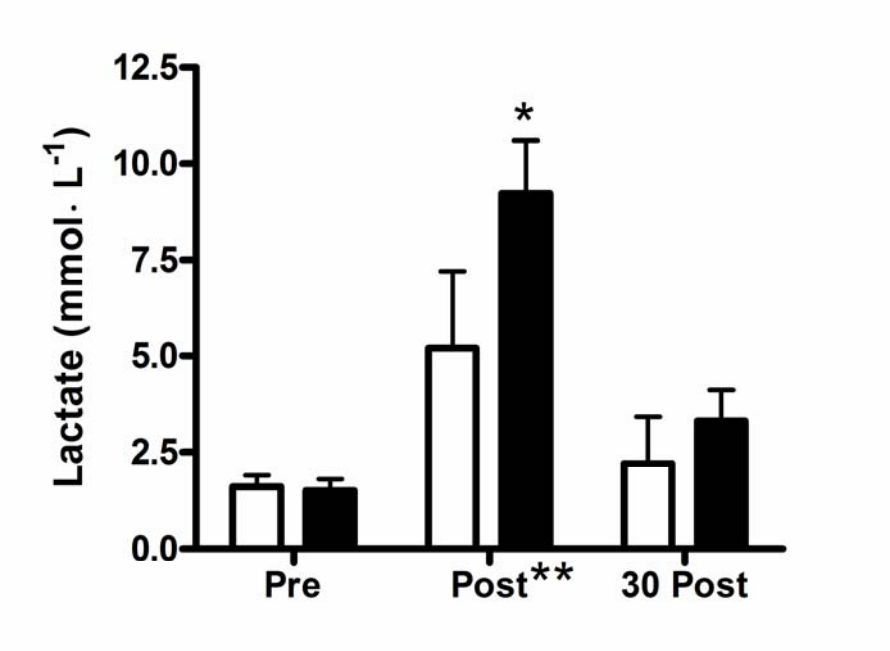

Table 1. Equations used to calculate total mechanical work, Volume Load and Mean Tonnage.

Equation No.	External Measure	Equation
1	Mechanical Work	$W = f \cdot d$
2	Mechanical Work (Leg Press)	$W = (f \cdot \text{cosine} \cdot 45) \cdot d$
3	Mechanical Work (Arm Curl)	$W = t \cdot \theta$
4	Volume Load	$VL = m \cdot \text{repetitions}$
5	Mean Tonnage	$MT = VL / \text{repetitions}$

Note. ***W*** = mechanical work, **f** = force, **d** = displacement, **t** = torque, **θ** = theta (angle in radians), **VL** = volume load, **m** = mass, **MT** = mean tonnage.