Low Volume High Intensity Interval Exercise affects Serum BDNF and proBDNF levels in Sedentary Healthy Men.

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Abstract

Exercise and dietary modifications help improve energy balance and glucose control. High intensity interval exercise (HIIE) induces an increase in serum brain-derived neurotrophic factor (BDNF) with a corresponding decrease in its precursor (proBDNF). Pro-BDNF, possesses biological activities opposite those of BDNF. However, only few reports on the effect of HIIE on proBDNF compared to extensive studies on the BDNF. Normal, healthy, male adults performed six sessions of HIIE in a span of 2 weeks. Venous blood was collected, from which fasting blood sugar, glycated haemoglobin, serum insulin, BDNF and proBDNF were measured using ELISA. Marked decrease in markers of glycemic control were recorded following the intervention. A reduction in proBDNF and increase in BDNF was also observed post exercise. We found a strong negative relationship between BDNF and FBS post exercise. HIIE reduces BDNF and proBDNF healthy men.

Keywords: BDNF, proBDNF, high intensity interval exercise, Glycemia.

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Introduction

Brain derived neurotrophic factor (BDNF) exists in both precursor BDNF (proBDNF) and mature BDNF (mBDNF) forms in the serum. The proBDNF is cleaved by tissue-type plasminogen activator (t-PA), p11 and matrix metalloproteinase-9 (MMP-9) to form mature BDNF.\textsuperscript{1,2} The precursor and mature BDNF bind to p75 neurotrophin receptors (p75NTR) and tyrosine kinase B receptors (TrkB) thus they have opposing biological actions.\textsuperscript{3,4} While proBDNF is proapoptotic,\textsuperscript{5} involved in neurite outgrowth or collapse anti-plasticity\textsuperscript{4} and facilitation of long-term depression (LTD),\textsuperscript{6} mBDNF on the other hand, is involved in long-term potentiation (LTP), which plays an important role in synaptic plasticity.\textsuperscript{7,8}

Exercise has always been thought to have positive effects on physical health, mental health and longevity.\textsuperscript{9} Activity induced-BDNF signalling has been shown to be dependent on duration of exercise and intensity.\textsuperscript{10} Aerobic resistance, endurance and high intensity interval training (HIIE) all affect BDNF concentration levels in different ways. While some studies observed changes after 30-minutes,\textsuperscript{10,11} others found that long-term, regular exercise has positive effects as well. There is paucity of data on the effect of HIIE on proBDNF compared to the numerous reports on its effect on BDNF levels. This study aims to determine the effect of HIIE on both serum proBDNF and mBDNF levels in normal male individuals.

Methodology

Study design

The study was longitudinal in design covering two weeks of HIIE program at Murtala Muhammad Specialist Hospital, Kano. Apparently healthy male participants were screened and sampled using simple random sampling technique. Subjects were matched for age and educational status. Each subject signed an informed consent form and the physical activity readiness questionnaire of American College of Sports Medicine was filled prior to participation. Sample size was calculated by G-power software, using an effect size (d) of 0.8, a level of significance of 0.05 and a power of 0.95. A total sample size (n) of 35 was obtained. Expected dropout rate of 10% was added to the calculated sample size (n=39). Subjects with drug or alcohol abuse/dependence were excluded from this study. They exercised on a stationary erect cycle ergometer (E-fit) 3 times per week for 30 minutes each time including warm up and cool down phases. The karven formula was used to determine the Heart Rate max (HRmax) of each subject and those that were unable to pedal for 30 min at 60% of their HRmax were excluded. The protocol for this study was approved by the Human ethics committee, Kano State Ministry of Health (MOH/Ofi/797/T.1/912).

Anthropometry

Weight and height were measured using calibrated weighing scale and stadiometer. Body mass index (BMI) was calculated using weight/height squared (kgm\textsuperscript{-2}). Subjects with BMI values >30 kgm\textsuperscript{-2} were excluded from the study.

High intensity interval exercise HIIE

Following familiarisation session with exercise equipment, subjects commenced training which involved six supervised HIIE sessions over 2 weeks (with a minimum of 24 hrs interval between the sessions). Each session consisted of 10 cycling intervals for 60 seconds which were interrupted with 60 seconds of recovery period. Training was performed on a cycle ergometer (KPT Exercise bike, B20400-C, Pakistan) set in constant watt mode at a pedal cadence of 80–100 revolutions/min. Individual workloads were selected to elicit a heart rate of 90% HRmax during the intervals. During recovery, participants rested or pedalled slowly against a resistance of 50 W. Each training session consisted of a 3-min warm-up and 2-min cool-down at 50 W. Therefore, the training protocol involved a total of 25 min of high-intensity exercise within a total time commitment of 75 min/wk.

Blood analyses

Baseline venous blood samples were collected and analysed for blood glucose, HbA1c, BDNF and proBDNF concentration prior to HIIE. Point of care was used to determine HbA1C, while Accucheck glucometer was used to determine the fasting blood sugar. The blood samples were kept at room temperature for 1 h before being centrifuged (4 000g, 10 min) to obtain serum. The resulting serum was stored in a −20 °C freezer until analyses of serum BDNF, pro-BDNF and Insulin using enzyme linked immunoassay following manufacturer’s instruction (Melsin medical, China).

Statistical analysis

Data were analysed using IBM SPSS version 22 (IBM SPSS, Chicago, IL, USA). The data were subjected to Shapiro-Wilk’s normality tests, after which paired t-test was used to determine the effect of exercise in this study. Pearson’s correlation was used for test of relationship.

Results

Table 1 shows the baseline characteristics of the 39 apparently healthy male participants who participated and completed the study. About 50% of the subjects had normal BMI, 46% were overweight and about 5% were obese. The systolic and diastolic blood pressures both fall within the normal physiologic range. Fasting blood glucose (FBG) was observed to be above the normal physiologic range among the subjects (FBG = 5.4 mmol/L). HbA1c levels were observed to fall within the normal range, that is less than 6.5%. The median serum BDNF levels obtained was 0.24 uIU/ml, while median proBDNF and Insulin levels were 2.19 uIU/ml and 3.14 uIU/ml respectively.
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Table 1: Baseline characteristics of Participants.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Median (Min. – Max.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Yrs)</td>
<td>35 (35-64)</td>
</tr>
<tr>
<td>BMI (Kg/M^2)</td>
<td>23.13 (14.00 – 30.42)</td>
</tr>
<tr>
<td>SYST BP (mmHg)</td>
<td>120 (100 – 130)</td>
</tr>
<tr>
<td>DIAST BP (mmHg)</td>
<td>70 (40 – 98)</td>
</tr>
<tr>
<td>FBS (mmol/L)</td>
<td>5.35 (4.5 – 6.4)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.0 (3.24 – 6.2)</td>
</tr>
<tr>
<td>BDNF</td>
<td>1.43 (0.75 – 1.78)</td>
</tr>
<tr>
<td>Pro-BDNF</td>
<td>2.19 (1.41 – 3.23)</td>
</tr>
<tr>
<td>Insulin</td>
<td>3.14 (1.03 – 4.67)</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>77 (62 – 98)</td>
</tr>
</tbody>
</table>

Table 2: Effect of HIIE on biochemical proBDNF, BDNF and some parameters.

<table>
<thead>
<tr>
<th></th>
<th>Pre-Exercise (Mean ± SD)</th>
<th>Post-Exercise (Mean ± SD)</th>
<th>t-statistic</th>
<th>p-value</th>
<th>BDNF</th>
<th>ProBDNF</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBS (mmol/L)</td>
<td>5.47 ± 0.52</td>
<td>4.47 ± 0.47</td>
<td>8.075</td>
<td>0.001*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA1C (%)</td>
<td>5.29 ± 0.47</td>
<td>5.18 ± 0.73</td>
<td>0.467</td>
<td>0.649</td>
<td></td>
<td></td>
</tr>
<tr>
<td>INSULIN</td>
<td>4.37 ± 1.66</td>
<td>2.37 ± 0.54</td>
<td>3.211</td>
<td>0.012*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>1.06 ± 0.36</td>
<td>0.47 ± 0.17</td>
<td>4.609</td>
<td>0.001*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BDNF</td>
<td>1.04 ± 0.29</td>
<td>1.37 ± 0.19</td>
<td>2.959</td>
<td>0.014*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ProBDNF</td>
<td>2.36 ± 0.57</td>
<td>1.75 ± 0.50</td>
<td>2.723</td>
<td>0.019*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FBG was found to be significantly higher before the HIIE intervention. Table 2 shows the changes in serum concentrations of BDNF, proBDNF, Insulin and Insulin resistance before and after the intervention. There was no significant decrease in HbA1c (p = 0.649). A significant improvement in glycemic control as well as increased serum BDNF with an accompanying decrease in proBDNF were observed.

Table 3 shows a strong negative correlation between BDNF and FBS. A positive relationship was observed between proBDNF, FBS, Insulin and Insulin resistance.

Table 3: Correlation between BDNF, proBDNF and some metabolic parameters

<table>
<thead>
<tr>
<th></th>
<th>BDNF</th>
<th>ProBDNF</th>
</tr>
</thead>
<tbody>
<tr>
<td>r</td>
<td>p-value</td>
<td>r</td>
</tr>
<tr>
<td>FBS</td>
<td>-</td>
<td>0.610** 0.003</td>
</tr>
<tr>
<td>INSULIN</td>
<td>0.677** 0.001</td>
<td>0.304 0.131</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>0.678** 0.001</td>
<td>0.529** 0.008</td>
</tr>
</tbody>
</table>

Discussion

In this study, we investigated the effect of low volume HIIE on BDNF and proBDNF. We found that after six exercise sessions in a span of 2 weeks (with at least 24 hrs interval between each session), there was a significant decrease in FBS, insulin and HOMA-IR. This shows that exercise lowers FBS and insulin resistance. The results of this study conformed with the study by Winding and colleagues which reported that HIIE reduced HbA1c, fasting glucose and HOMA-IR. Decreased HbA1c was also observed in healthy older males. A meta-analysis also reported that HIIE significantly reduced the BMI, HbA1c, fasting insulin and improved cardiorespiratory fitness. Fasting insulin and insulin resistance after HIIE in healthy, nondiabetic individuals showed up to 33% improvement. Contrarily, in individuals with T2DM, up to 60% improvement in insulin sensitivity was reported. Low volume HIIE showed highly significant effects on glycemic control in T2DM patients. HIIE was found to significantly lower insulin resistance and also causes a number of skeletal muscle adaptations that enhance skeletal muscle fat oxidation and improved glucose tolerance.

The brain-derived neurotrophic factor (BDNF) has been shown to participate in physiological processes such as glucose homeostasis and lipid metabolism. Our study determined the effect of six bouts of HIIE sessions on serum BDNF and proBDNF. Similar results were reported in a study of the effect of a single bout of HIIE session which reported an increase in serum BDNF. Similarly, a single session of HIIE significantly elevated
peripheral plasma BDNF levels immediately after the exercise. This was however found to revert to baseline concentrations 60-mins after the intervention. In the study involving healthy participants, serum BDNF was found to be increased after HIIE intervention. Animal studies indicate increased mRNA levels of BDNF and GDNF, as well as BDNF protein after the animals were subjected to HIIE, which they attributed to increased H2O2 levels. This was confirmed by in vitro and in vivo studies which showed a link between H2O2 and BDNF expression. Contrary to our findings, Vosadi and colleagues (2015), reported that although no significant change in BDNF levels following HIIE and endurance training (ET), HIIE produced a higher increase in hippocampal BDNF compared to ET. However, all these studies did not report on the effect of the intervention on proBDNF, which we found to be significantly decreased following the intervention. This agrees with the study by Luo and colleagues in 2019 in which Hippocampal BDNF levels were found to be upregulated, while proBDNF levels were downregulated after four weeks if HIIE. It has been shown that tissue plasminogen (tPA), cleaves plasminogen to plasmin and in turn converts the precursor proBDNF to mBDNF. tPA has been reported to be increased with exercise, the increase even more significant with HIIE when compared to MICT. We could therefore say that the intervention may have increased tPA which then increased cleavage of proBDNF to BDNF. Hence, providing a possible explanation for the increase in BDNF levels with the corresponding decrease in proBDNF.

Conclusion
Low volume- High intensity interval exercise is effective in enhancing glycemic control, increasing BDNF and decreasing proBDNF levels.

Author Contributions Statement
FRM conceived the research idea, developed the theory, carried out the experiment, performed statistical analysis, interpreted the findings of this work and drafted the manuscript. EMM and SAI supervised the conduct of this study in its entirety, assisted in data interpretation and manuscript writing.

Conflict of Interest Statement
The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References


