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EFFECTS OF SPRINT CYCLING AND STRETCH-SHORTENING CYCLE EXERCISES ON THE NEUROMUSCULAR, IMMUNE AND STRESS INDICATORS IN YOUNG MEN

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Selection of optimal physical load is essential for desired adaptation including health benefits. We hypothesized that neuromuscular, immune and stress indicators will be higher after energy demanding sprint interval exercise (SIE) than to mechanically demanding stretch-shortening cycle exercise (SSE). The main aim of this study was to assess and compare the kinetics of blood brain-derived neurotrophic factor (BDNF), norepinephrine (NE) and cortisol (as stress indicators) and proinflammatory (IL-6) and anti-inflammatory (IL-10) cytokines within 24 hours after metabolically demanding SIE and after muscle damage inducing SSE. Twenty healthy physically active young men randomly assigned to two equal groups to complete 12 bouts of 5 s stationary cycling sprints every 3 min (SIE) or 200 drop-jumps with 30 s interval between each jump (SSE), respectively. Quadriceps muscle maximal voluntary contraction torque and voluntary activation and soreness were measured and blood samples collected before and 2 min, 1 hour, 12 hours and 24 hours after the SIE and SSE. The BDNF, cortisol, IL-6 and NE levels increased more at 2 min after SIE than SSE ($P < 0.05$); however, the IL-10 level did not differ between SIE and SSE. BDNF and cortisol levels were decreased at 24 h after both SIE and especially after SSE. The higher was the initial BDNF level, the greater was its decrease at 24 h after both type of exercise. Before exercise BDNF level correlated closely with the change in central fatigue (decrease in voluntary activation) after both SIE and SSE. We thus conclude that both metabolically demanding SIE and muscle damage inflicting SSE induced long-lasting decrease in circulating BDNF which may not promote brain health. The level of circulating BDNF, but not cortisol, IL-6, IL-10 or NE, was associated with changes in central motor fatigue.

Key words: *brain-derived neurotrophic factor, cortisol, cycling, drop jumps, fatigue, isometric torque, norepinephrine*

INTRODUCTION

It is clear that regular exercise training can affect the production and release of brain-derived neurotrophic factor (BDNF) and that other myokines play a key role in the general well-being, mental and physical health, disease prevention and longevity of humans (1-13). Exercise may induce moderate to large increase in the circulating IL-6 and IL- 10 (2, 14-16) and stress hormone cortisol (17-19). However, hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis may decrease BDNF production *via* increasing cortisol release and activation of the proinflammatory response (e.g., increased IL-6 release) (19). Furthermore, stress may reduce the BDNF level in the brain, which may alter mood and cause depression (20-23).

Selection of optimal exercise training mode and regiments is essential for desired adaptation and health benefits. There is evidence that long-term regular aerobic exercise increases serum BDNF level (3, 24-28). Research also suggested there is a dose-response relationship between exercise intensity and circulating BDNF level (29-31). High-intensity exercise training improves cardiovascular health and increases BDNF level, which may promote brain health (30). CrossFit training changes BDNF level at rest, after Wingate and progressive tests, and improves aerobic capacity and body composition of young physically active men and women (32). By contrast, reviews by Huang *et al*. (24) and Dinoff *et al*. (33) revealed that most studies have reported no effect of strength training on peripheral BDNF level. Therefore it seems the type of physical exercise that subjects brain and skeletal muscles activity-related metabolic stress may cause the BDNF response (34).

It is not clear whether the kinetics of BDNF circulatation is affected by exercise that does not stress the energy-producing systems in muscle cells but causes muscle damage. Previous studies have shown that stretch-shortening cycle exercise (SSE) impair muscle function, simultaneously inducing acute muscle inflammation, and increase in circulating muscle proteins as well as delayed-onset of muscle soreness (35-36), i.e. changes which are widely recognised as indirect markers of exercise-induced muscle damage (37). An example of SSE type of exercise is repeated drop jumps (DJs) with immediate

rebound in explosive manner, each performed every 30 s. We hypothesized that repeated DJ exercise with a high force impact, which ultimately induces damage of the muscle force bearing structures but also because of the brief bursts of muscular activity which are separated by sufficient periods of rest does not allow for significant metabolite built-up and stress on the energy-producing systems (36, 38), should not induce changes in levels of circulating BDNF. In contrast, low mechanically but highly metabolically demanding sprint interval cycling exercise (SIE) was expected to induce substantial response in the levels of circulating BDNF and other myokines. Therefore, the main aim of this study was to assess the kinetics of BDNF, norepinephrine (NE) and cortisol (as stress indicators) and proinflammatory (IL-6) and anti-inflammatory (IL-10) cytokines during the recovery after highly metabolically demanding SIE and muscle damage evoking SSE. The secondary aim was to assess the relationships between changes in the BDNF, NE, cortisol, IL-6 and IL-10, and changes in maximum voluntary contraction (MVC) force and central activation ratio (CAR) after these two different types of exercise.

MATERIALS AND METHODS

Participants

Twenty healthy and physically active men participated in this study after signing an informed consent form. They were randomly assigned to two exercise groups of 10 participants in each group: one group was assigned to perform SSE and the other SIE (*Table 1*). None of the participants was under any type of antidepressant treatment. All participants had not been involved in any jumping or leg strength training programs during the past years. The experimental protocol was approved by the Kaunas Regional Biomedical Research Ethics Committee and conformed to the Declaration of Helsinki.

Experimental protocol

The experiment protocol is described in *Fig. 1*. The first visit to the laboratory involved familiarization with the experimental procedures and equipment and each participant's tolerance to electrical stimulation ware assessed. In this session, the participants learned to achieve and maintain a maximum-effort contraction of quadriceps femoris for 3 – 4 s with the TT-100 Hz superimposed on the voluntary contraction. The participants were instructed to refrain from performing physical exercises and ingesting caffeine or alcohol for at least 24 hours, and to sleep at least 8 hours the night before the experiment. The experiment was performed between 8.00 – 11.00 in the morning and participants were also asked to refrain from consuming food before baseline measurements. All measurements were performed, and the data and blood samples were collected before and 2 min, 1 h, 12 h and 24 h after the SSE and SIE exercises. In addition, blood samples were collected and MVC and CAR were measured after 100 DJs in SSE group. Isometric torque was measured and electrical stimulation was performed after 8 min warm-up of stationary cycling with the power (W) equal to the participant's approximate body weight (kg).

Performance of sprint interval exercise

The SIE exercise comprised 12 × 5 s of all-out cycling bouts with 3 min rest between each. The resistance was set at 7.5% of body weight on a Monark 828E cycle ergometer (Monark Exercise AB, Sweden). The power output was measured in W.

Performance of stretch-shortening cycle exercise

The participants performed 200 intermittent DJs with a 30 s interval between each jump from a height of 0.5 m comprising a countermovement to a 90° knee angle followed by an immediate maximum rebound. During the DJs, the participant's hands were placed on the waist. DJs were performed using a contact mat (Powertimer Testing System, Newtest, Finland). The height of the jumps was calculated by applying the following formula: H = 1.226 × Tf^2 (m), where Tf = flight time (s) (39). The contact

Table 1. Physical characteristics of the subjects.

	SSE (n = 10)	SIE (n = 10)
Age, years	29.8 ± 9.3	22.6 ± 5.2
Body height, m	1.81 ± 0.1	1.81 ± 4.4
Body mass, kg	81.7 ± 5.2	76.5 ± 9.1

Values are shown as mean ± S.D. SSE, stretch shortening cycle exercise group; SIE, sprint interval cycling exercise group.

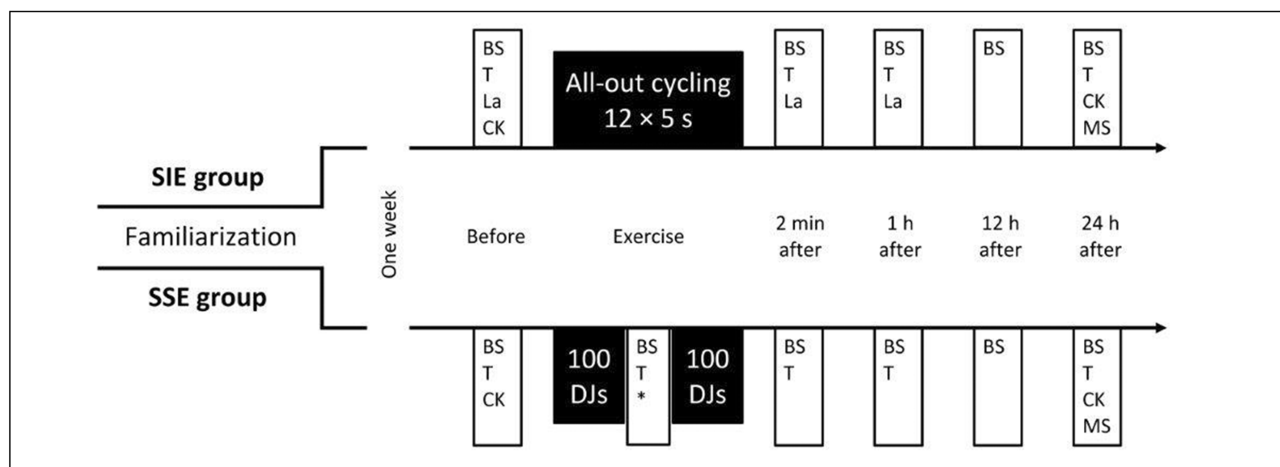

Fig. 1. Graphical overview of the experimental protocol. SSE, stretch-shortening cycle exercise; SIE, sprint interval cycling exercise; BS, blood samples (human brain-derived neurotrophic factor, cortisol, interleukin 6, interleukin 10, norepinephrine); La, lactate; CK, creatine kinase; T, testing (maximum voluntary contraction torque, central activation ratio); MS, muscle soreness; * - testing for 7 minutes.

time was measured during the DJs. Each participant received verbal feedback about his performance after each jump and was encouraged to execute all jumps as high as possible. The best jumps of the first three and of the last three jumps during SSE exercise and then best of the three jumps at 24 h after SSE were used in the analyses.

Rating of perceptions

The perception of effort was measured at the beginning and the end of every bout of SIE and SSE using the 15-point 'Rating of Perceived Exertion' (from 6 to 20 points) scale (40). Standardized instructions for memory anchoring of the scale were given to each participant before the test.

Isometric torque and central activation ratio (CAR)

The isometric torque of the knee extensor muscles was measured using an isokinetic dynamometer (System 3; Biodex Medical Systems, Shirley, NY). The participant sat upright in the dynamometer chair with the knee joint positioned at a 120° angle (180° is full knee extension). MVC was reached and maintained for ~2 s before relaxation and was measured twice; each separated by a 2 min rest interval and larger value was used in the analyses. The equipment and procedure for electrical stimulation were essentially the same as previously described (36, 38). Intra-class correlation coefficient of voluntary contraction force for repeated measures varied from 0.90 to 0.98 depending on measurement time, while coefficient of variation was < 5%. Direct muscle stimulation was applied using two carbonized rubber electrodes covered with a thin layer of electrode gel (ECG-EEG Gel; Medigel, Modi'in, Israel). One of the electrodes (6 × 11 cm) was placed transversely across the width of the proximal portion of the quadriceps femoris. Another electrode (6 × 20 cm) covered the distal portion of the muscle above the patella. A standard electrical stimulator (MG 440; Medicor, Budapest, Hungary) was used. The electrical stimulation was delivered in square-wave pulses of 0.5 ms duration. The CAR was obtained during the 5 s MVC. At ~3 s of the MVC, a 250 ms test train of stimuli at 100 Hz (TT-100 Hz) was superimposed on the voluntary contraction. The CAR was calculated as the ratio of the maximum voluntary torque to the peak torque generated with an additional TT-100 Hz superimposed on the MVC (41). The 5 s MVC with the superimposed stimuli was performed twice; the larger CAR value was used in the analyses. Intra-class correlation coefficient of CAR for repeated measures varied from 0.88 to 0.97 at different measurement time, with coefficient of variation below 3%.

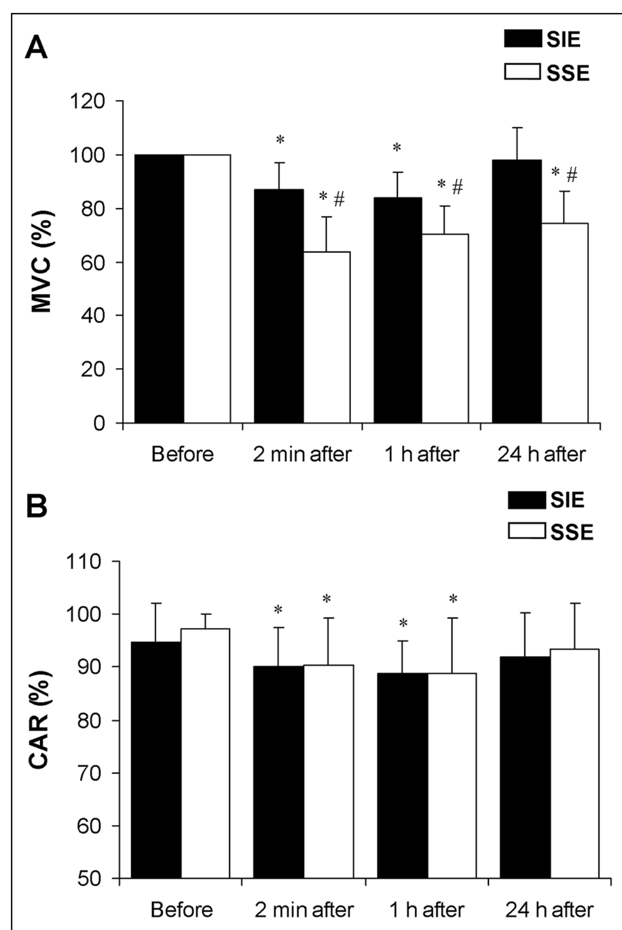

Fig. 2. Time course of changes in the maximal voluntary contraction (MVC, A) torque and central activation ratio (CAR, B) after sprint interval cycling exercise (SIE) and stretch-shortening cycle exercise (SSE).
MVC values in response to exercise were expressed in percentage of 'before' (100%). * $P < 0.05$ compared with before level; # $P < 0.05$ compared with SIE. Values are shown as mean ± S.D.

Blood variables

Blood samples for separation of serum were collected into vacuum tubes by venepuncture with a gel separator (5 mL). Then samples were allowed to clot and the serum was separated by centrifugation (1200 *g* for 15 min) at room temperature. Blood samples for measurement of NE in plasma were collected into vacuum tubes with anticoagulant. The serum and plasma samples were aliquoted and stored at –70°C until analysis. The concentrations of human BDNF, cortisol, IL-6 and IL-10 were measured in serum. The concentrations of NE, BDNF, IL-6 and IL-10 were measured using a Gemini immunoassay ELISA analyser (Stratec Biomedical GMBH, Birkenfeld, Germany). Cortisol concentration was measured using an AIA-2000 automated enzyme (RE52061, IBL International GMBH, Hamburg, Germany) immunoassay analyser (Tosoh Corp., Tokyo, Japan). About 5 mL of blood was drawn from the median cubital vein and were centrifuged immediately and analysed for CK activity using a Spotchem EZ SP-4430 biochemical analyser (Menarini Diagnostics, Winnersh, Wokingham, UK) with soft reagent strips (Arkray Factory, Inc., Shiga, Japan). A blood sample (0.3 μL) was taken from a fingertip, and the La concentration was measured using a portable analyser (Lactate Pro™ LT-1730, Arkray Inc., Kyoto, Japan).

Soreness

The severity of soreness of the quadriceps was rated subjectively by the participants after 2 – 3 squats using a 0 – 10 point scale before and 24 hours after SIE and SSE (42, 43).

Statistical analysis

Descriptive data are presented as mean ± standard deviation (S.D.). Statistical analysis involved general linear model analysis of variance (ANOVA) for repeated measures with SIE and SEE as a between-group factor, and time as within-group factor on dependent variables (MVC, CAR, BDNF, NE, cortisol, IL-6 and IL-10). One-way ANOVA for repeated measures as a time factor was used to determine the effects of the SIE on the cycling power (W) and La concentration; and the effects of the SEE on the blood

CK, DJs height, DJs contact time and knee angle. If significant effects were found, Sidak's *post hoc* adjustment was used for multiple comparisons across a set of conditions within each repeated-measures ANOVA. Statistical significance was defined as P < 0.05. For all ordinal data the non-parametric Wilcoxon signed-rank test was used to compare the changes in subjective ratings of perceptions (muscle soreness and RPE). Pearson correlation coefficients were used to identify relationships between variables. Statistical analyses were performed using IBM SPSS Statistics software (v. 22; IBM Corporation, Armonk, NY).

RESULTS

The average power during first and series of 12 modified Wingate tests (SIE) was 780.5 ± 90.8 W and 798.8 ± 109.3 W, respectively (P > 0.05 between series). The height of DJs decreased by 3.5% ± 2.8% (P > 0.05) and 8.7% ± 4.8% (P < 0.05) after 100 and 200 DJs, respectively, and did not recover within 24 h after the SSE session. The contact time during DJs increased by 14.5 ± 10.5% after 200 DJs and did not recover within 24 h after exercise (P < 0.05). The average knee angle was 83.1 ± 5.6° during the squats and did not change significantly during the 200 DJs. The average jump height for all 200 DJs was 35.6 ± 5.2 cm. The average contact time was 0.507 ± 0.030 s on the platform (at the beginning 0.471 ± 0.044 s).

Changes in perceived load effort

Perceived load effort was 11.9 ± 2.8 points and 13.0 ± 2.4 points at the start of SIE and SSE, respectively (P > 0.05) and 16.3 ± 2.4 points and 14.9 ± 2.4 points at the end of exercise (P < 0.05).

Changes in lactate concentration during sprint interval exercise

Lactate concentration was 1.6 ± 0.6 mmol/L before exercise and 14.1 ± 4.6 mmol/L (P < 0.01) and 2.6 ± 1.3 mmol/L at 2 min after and 1 hour after SIE, respectively.

Changes in voluntary muscle performance

MVC and CAR decreased significantly after both SIE and SSE (*Fig. 2*). MVC decreased more after SSE than after SIE (P < 0.001); however, the magnitude of the decrease in CAR did not differ significantly between SIE and SSE. MVC had not recovered at 24 h after SSE. There was no significant difference in CAR between level before and after 100 DJs (94.8 ± 7.8%).

Changes in creatine kinase activity and muscle soreness

The participants reported feeling muscle pain and rated the pain as 6.5 ± 2.2 and 0.1 ± 0.7 points at 24 h after the SSE and SIE, respectively. Creatine kinase activity in the blood increased from 164.7 ± 100.0 IU/L before to 1670.6 ± 888.2 IU/L at 24 h after SSE (P < 0.001) and from 123.5 ± 64.7 IU/L before to 282.4 ± 123.5 IU/L 24 h after SIE (P < 0.05). At 24 h after exercise, creatine kinase activity differed significantly between SSE and SIE (P < 0.001).

Changes in norepinephrine, brain-derived neurotrophic factor, cortisol, IL-6 and IL-10 concentrations

NE increased significantly (P < 0.001) from 5.1 ± 4.3 ng/mL before to 26.3 ± 10.1 ng/mL after SIE but did not change significantly after SSE (6.1 ± 4.3 to 8.9 ± 5.4 ng/mL).

The before level of BDNF, cortisol, IL-6 and IL-10 concentrations are listed in *Table 2*. BDNF increased significantly after SIE, but the level was significantly lower at 12 h and 24 h after both types of exercise compared with before (P < 0.05; *Fig 3*). Relatively to before level, BDNF was significantly lower in SSE group than in SIE group at 24 h after exercise (P < 0.05).

Serum cortisol level increased significantly after SIE (P < 0.001) and decreased significantly after SSE (P < 0.05; *Fig 3*). Reduction in cortisol level was observed already after 100 DJs (78.7 ± 40.6% of baseline; P < 0.05). Interestingly, the cortisol level remained elevated for up to 1 hour after SIE (P < 0.05), when BDNF had been already recovered to before values. Cortisol level was significantly lower at 24 h after SIE and SSE

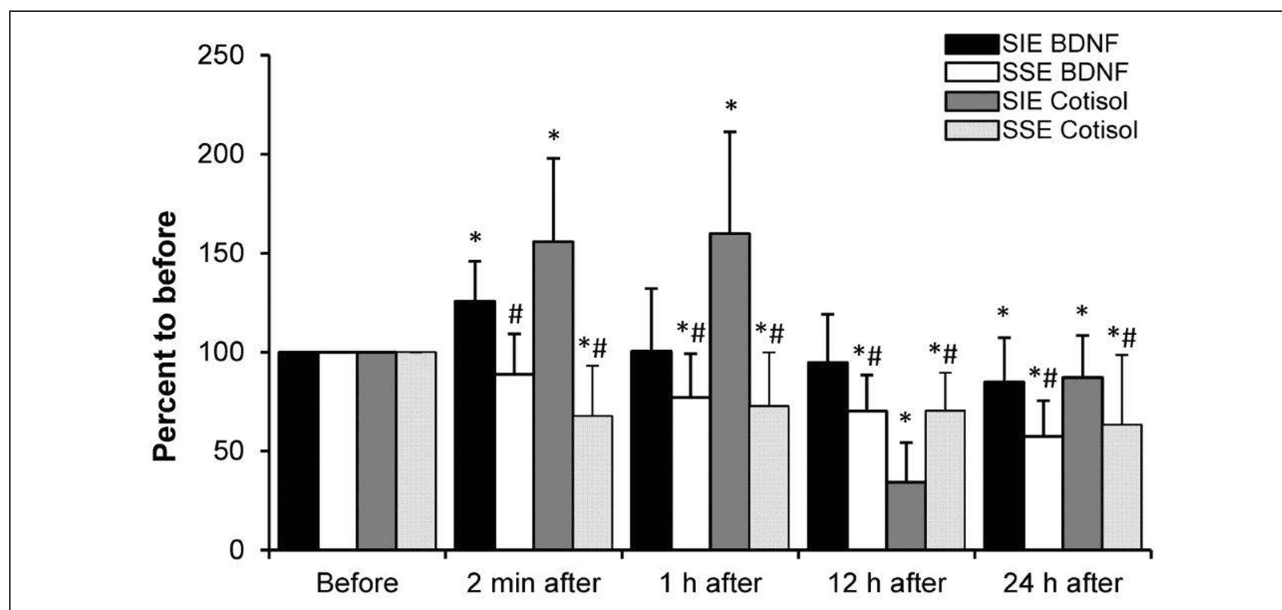

Fig. 3. Changes from the before mean level (100%) in the brain-derived neurotrophic factor (BDNF) and cortisol after sprint interval cycling exercise (SIE) and stretch-shortening cycle exercise (SSE).
*P < 0.05 compared with before level; #P < 0.05 compared with SIE. Values are shown as mean ± S.D.

compared with before level (P < 0.05) and decreased more after SSE than after SIE (P < 0.05). The largest decrease in cortisol level occurred at 12 h after SIE (P < 0.05, compared with all other times).

IL-6 level increased (P < 0.05) at 2 min after SSE and 1 h after SIE, and remained significantly higher (P < 0.05) at 12 h after SIE and SSE (*Fig. 4*). IL-10 level was unchanged after both exercise protocols.

Relationships

The before BDNF level correlated inversely with the change in BDNF level after SIE (r = –0.89) but not after SSE (r = 0.04). The before BDNF level correlated inversely with the percentage change in BDNF level after SSE and SIE (respectively, r = –0.69 and r = –0.74 at 24 h). The before BDNF level correlated with the changes in the CAR after 200 DJs (r = 0.65) and 24 h after SSE (r = 0.79). However, the before BDNF level correlated inversely with the CAR 2 min and 24 h after SIE (r = –0.76 and r = –0.95, respectively).

There was significant relationship between the change in BDNF level and change in the CAR 2 min and 24 h after SIE (r = 0.95 and r = 0.87, respectively). However, there were no significant relationships between the change in BDNF level and the CAR for the same times after SSE (r = 0.14 and r = 0.02 respectively).

There was a significant positive relationship between the change in subjective effort and BDNF 24 h after SIE (r = 0.79). However, these variables did not correlate significantly during or after SSE (r = 0.1 – 0.2).

The decrease in BDNF level 24 h after SSE correlated inversely with the change in the CAR at that time (r = –0.85). The change in cortisol level 24 h after SSE also correlated inversely with the change in the CAR at that time (r = –0.77). These variables were not significantly correlated for SIE. Interestingly, the changes in BDNF correlated significantly with the changes in cortisol levels 24 h after both SSE and SIE (r = 0.74 and r = 0.94, respectively).

The decrease in BDNF level 24 h after SSE correlated negatively (r = –0.71) with the decrease in IL-6 level at that time. The changes in cortisol did not correlate significantly with the changes in IL-6 levels 24 h after both SSE and SIE (r = 0.11).

DISCUSSION

The present study compared the effect of two different types of exercise on the neuromuscular, immune and stress indicators in young healthy men. The main findings were as follows: 1) the responses of circulating BDNF, cortisol, IL-6 and NE were greater after exercise that taxes the energy-producing systems (SIE) than after exercise which places a large mechanical stress and elicits muscles damage (SSE). Despite these differences, IL-10 level did not change after either exercise; 2) circulating levels of BDNF and cortisol decreased significantly at 24 h after both SIE and especially after SSE. The higher the initial BDNF level, the greater was a decrease in BDNF level at 24 h after both types of exercise; 3) larger decrease in BDNF level after SSE was associated with less central fatigue (CAR) at 24 h after SSE; 4) initial BDNF level correlated closely with the change in central

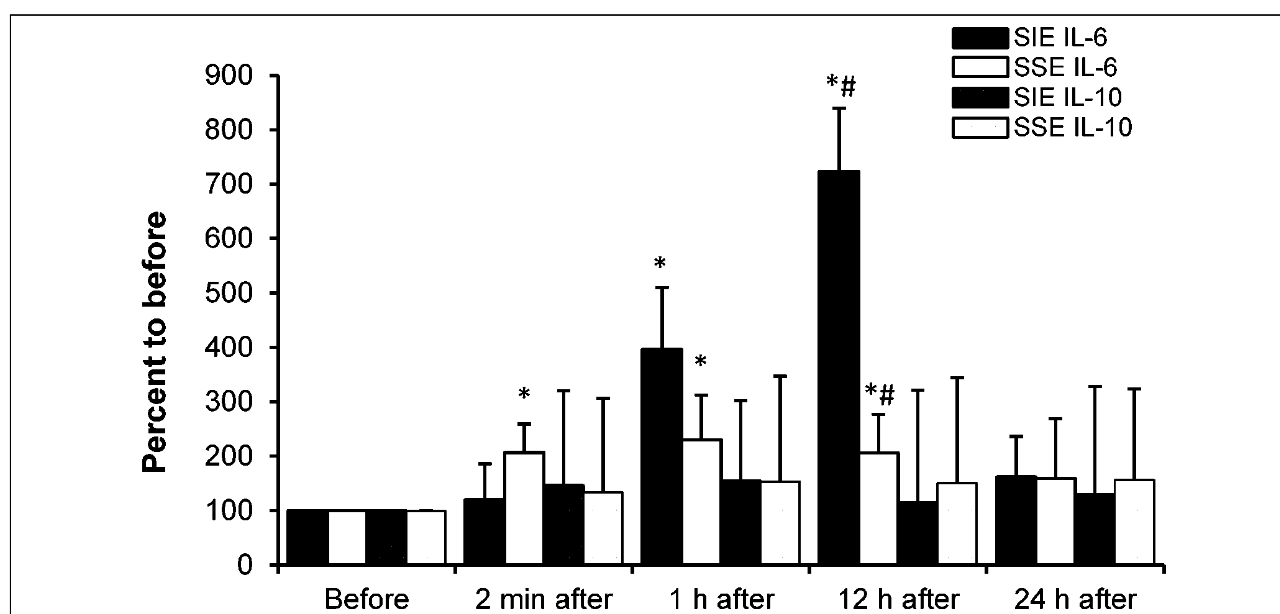

Fig. 4. Changes from the before mean level (100%) in interleukin-6 (IL-6) and interleukin-10 (IL-10) after sprint interval cycling exercise (SIE) and stretch-shortening cycle exercise (SSE). *P < 0.05 compared with before level; #P < 0.05 compared with SIE. Values are shown as mean ± S.D.

Table 2. Blood markers before exercise.

	Cortisol, nmol/L	IL-6, pg/mL	IL-10, pg/mL	BDNF, ng/mL
SSE	425.9 ± 158.2	2.3 ± 1.5	3.1 ± 1.3	24.6 ± 6.5
SIE	439.2 ± 147.5	1.7 ± 1.9	9.4 ± 6.7*	24.7 ± 6.9

*P < 0.05 compared with before level. Values are shown as mean ± S.D. SSE, stretch shortening cycle exercise group; SIE, sprint interval cycling exercise group; IL-6, interleukin 6; IL-10, interleukin 10; BDNF, human brain-derived neurotrophic factor.

fatigue after both SIE and SSE. The higher the initial BDNF level, the smaller was a change in the CAR at 24 h after SSE, but greater the change in the CAR after SIE; 5) the greater was an increase in BDNF level after SIE, the smaller change in CAR at 24 h after SIE; 6) The increase in subjective effort during SIE was significantly related to a prolonged decrease (at 24 h after exercise) in BDNF.

Effects of stretch-shortening cycle exercise and sprint interval exercise on neuromuscular fatigue

The findings of our research are consistent with those of other authors who have shown that after eccentric or SSE exercise muscle force and neuromuscular performance remain decreased for up to several days (35, 36). Other characteristic markers of muscle damage such as the increased muscle soreness and plasma CK activity also manifested in our study which imply the main cause of the decrease in voluntary muscle performance after DJs was associated with damage to the force-bearing structures (35, 36, 38) and excitation-contraction coupling (37, 38). Differently, MVC decreased by ~13% and did not recover to the initial level (*Fig. 2A*) within 24 h after SIE even though the CK activity and muscle pain were significantly lower at 24 h after SIE compared with the same time after SSE. The main cause of fatigue in SIE is undoubtedly related to the disturbance of energy-producing systems and metabolite accumulation. These changes affect myosin cross-bridge adhesion to actin filaments, which decreases muscle force (44, 45) and the activation of muscle fibres by reduced Ca^{2+} content in the sarcoplasmic reticulum (46). In both SIE and SSE, there was a significant decrease of ~5 – 6% in CAR, which also contributed to decline in neuromuscular performance.

Effects of stretch-shortening cycle exercise and sprint interval exercise on hormones and cytokines

We found that activity of hypothalamic-pituitary-adrenal axis (i.e., cortisol level) and the autonomic nervous system activity (norepinephrine level) was higher after SIE as compared with after SSE, but the activity of anti-inflammatory components of the immune system (IL-10) did not differ in response to SIE and SSE. The increase in circulating IL-6 after both types of exercise is consistent with the findings of other researchers (14, 47). However, in our study IL-10 level did not change, while others have reported an increase (14, 47). This discrepancy might have arisen because if the differences in intensity and especially the duration of applied exercise, while exercise mode has little effect (48). The results are in accord with our hypothesis that the BDNF concentration increases significantly after SIE but did not change after SSE possible because stress on the energy-producing systems in the brain and muscles is the main factor for increase BDNF production and release. For SSE protocol we used as many as 200 DJs, while the long rest between the jumps (30 s) should have allowed the muscles and nervous system to restore high energy phosphates. We have not found reports of similar experiments to measure BDNF kinetics after high mechanical loading (SSE) that induces muscle damage. However, other researchers have concluded that BDNF concentration does not increase after strength training exercise (24, 33).

Interesting finding is that BDNF level decreased 24 h after exercise and this decline was significantly greater after SSE than after SIE (*Fig. 3*). The correlation analysis showed that the higher the initial BDNF level, the greater the decrease at 24 h after both SIE and SSE. We speculate that the long lasting decline in BDNF level is an indicator of inadequate motor system adaptation. Rest period of 24 h was not sufficient for BDNF to recover after exercise induced stress. If the increase in BDNF level after exercise enhances brain health, our finding that BDNF level was supressed for such a long time after both SIE and SSE suggests that both exercise may not promote brain health. We have not come across any reports of a decrease in BDNF level 12 – 24 h after exercise. On the contrary, Ieraci *et al*. (49) reported that BDNF returned to the initial level within 24 h after exercise. Rojas Vega *et al*. (50) and Saucedo Marquez *et al*. (30) found that BDNF level recovered to the initial level within 15 – 20 minutes after exercise. However, long-term regular aerobic training was reported to increase the serum BDNF level at rest and the BDNF level remained elevated for 2 days after acute aerobic exercise (25). In another study, serum BDNF level increased at the point of exhaustion during incremental cycle ergometry, but recovered in 10 – 15 min after exercise, whereas cortisol concentration was higher than at rest (50). It was recently suggested that BDNF is released when nociceptors are activated and acts as a central modulator of pain (51). However, we found no significant correlation between changes in BDNF level and muscle soreness after SSE.

It is interesting that the reduction in BDNF level was closely associated with the reduction in cortisol level for both exercises. While many studies have found a negative correlation between cortisol and BDNF level (17-19), Saucedo Marquez *et al*. (30) did not find an inverse correlation between cortisol and BDNF levels in humans.

We found inverse correlation between the changes in IL-6 and BDNF levels 24 h after SSE. It could be speculated that decline in BDNF level is related with the proinflammatory process, which is supported by the findings of other researchers (2, 15, 16, 52). Notable, moderate-intensity interval training increases serum brain-derived neurotrophic factor level and decreases inflammation in Parkinson's disease patients (11). Our results have shown that severe muscle damaging exercise decrease BDNF similarly to stressful conditions (49), implying that because of this side-effect it may not be the exercise mode of choice for depression prone individuals.

Relationship between BNDF and central motor fatigue

It was surprising that the initial BDNF level could predict prolonged central motor fatigue after both SSE and SIE. Other researchers have reported that BDNF level at rest is lower in exercise-trained compared with untrained people (24, 53). We speculate that the higher training level of our subjects was related to the smaller decrease in voluntary activation capacity after SIE. It is difficult to explain why the higher baseline BDNF level would cause a smaller prolonged change in the CAR after SSE because one might expect a different direction of change - the lower the initial BDNF level, the smaller the prolonged decline in the CAR.

Given that the change in circulating BDNF level after an exercise load is larger in trained people than in untrained people (54), we suggest that the greater the change in BDNF level after SIE, the smaller the long-term decline in the CAR. It seems that a lower initial BDNF level and a larger its increase after SIE exercise should be related to better performance in trained people.

As reduced circulating BDNF is associated with depression in patients (20-23), it could be anticipated that the decrease in BDNF level at 24 h after both SIE and SSE reflects central motor fatigue. However, the correlations of our study suggest the opposite; that is, the large decrease in BDNF level observed at 24 h after SSE was associated with a lower level of central fatigue. The decrease in involuntary muscle strength after SSE is generally greater than the decrease of voluntary muscle strength (36, 38), and thus the relationship between changes in BDNF level and involuntary muscle strength should be studied further.

We speculate that a larger decrease in BDNF level the day after exercise was caused by a greater perceived effort and stress during SIE. The psychological predictions of BDNF kinetics after SIE

exercise do not seem surprising when considering the conclusions of other researchers that the brain perceives exercise intensity first (55). In addition, the brain sensitivity to exercise induced oxidative stress might depend on age, as has been shown in response to endurance training in rats (56). The brain is the central organ for perceiving stressors *via* multiple interacting mediators included the HPA axis, autonomic nervous system, their nonlinear interactions with the metabolic system and the pro- and anti-inflammatory components of the immune defence system (55).

Limitations

Plasma BDNF concentration reflects brain BDNF levels more accurately than does serum BDNF (57). However, as serum BDNF level has been shown to be decreased in depression (57) and psychosocial stress (58), in the current study BDNF measurements were made in serum and not plasma. There was about 6 year's difference in the subjects' age between SIE and SSE groups but we believe it did not have an important effect for most of the variables assessed in present study. Finally, more information about general mental health of the study participants may have provided better understanding of the changes of circulating BDNF.

We conclude that several stress indicators in the blood (BDNF, NE, cortisol) enlarges immediately after metabolically demanding exercise but not after exercise inducing muscle damage. However, BDNF have substantially declined 24 h after both types of exercise suggesting that both energetically stressful and strenuous muscle damaging exercise induce long lasting stress which may not promote brain health. The level of BDNF but not of IL-6, cortisol, IL-10 and norepinephrine, was related to changes in central motor fatigue.

Conflict of interests: None declared.

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