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Influence of citalopram and environmental temperature on exercise-induced changes in BDNF

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ABSTRACT

Purpose: Serum brain-derived neurotrophic factor (BDNF) is known to increase with exercise. This increase is believed to originate from the brain and it is suggested that monoamines are involved in BDNF regulation. Heat exposure could influence the supposed BDNF output from the brain. Therefore, we hypothesized that administration of a selective serotonin reuptake inhibitor could influence the exercise-induced increase in BDNF, and that peripheral BDNF will be higher when exercise is performed in the heat. *Methods*: Eleven well-trained males performed 4 experimental trials on a cycle ergometer with citalopram or placebo treatment (20 mg in 12 h) in an environmental temperature of 18 °C or 30 °C. Blood samples (BDNF and cortisol) were taken at 4 time points: at rest, after 60 min at 55% W_{max}, after a time trial of 30 min at 75% W_{max} and following 15 min of recovery. Heart rate and core temperature were measured. *Results*: Performance on the time trial was 20% worse in 30 °C compared to 18 °C ($p < 0.01$), without influence of citalopram. Serum BDNF was found to be lower under citalopram treatment, while basal cortisol levels were increased ($p < 0.05$). Exercise triggered an increase in both BDNF and cortisol ($p < 0.001$). BDNF followed the same pattern as core temperature during exercise, with higher levels of both variables in 30 °C. Cortisol was also increased in 30 °C compared to temperate conditions ($p < 0.01$). *Conclusion*: Exercise caused a rise in serum BDNF and cortisol. This increase was enhanced with exercise in the heat. Since permeability of the blood–brain barrier increases with exercise in the heat, the hypothesis was raised that this causes a higher cerebral output of BDNF. Serotonergic stimulation did not increase peripheral BDNF, which was even lower with citalopram administration. Future research should focus on mechanisms behind BDNF increase with exercise.

Brain-derived neurotrophic factor (BDNF), an important neurotrophin, appears to play a role in both neurobiology and metabolism [22], and is known to increase in human serum with acute exercise [6]. Next to exercise, several other factors could play a role in the regulation of BDNF.

In the brain, part of the mechanism in the regulation of BDNF has been attributed to monoamine signaling [4], especially noradrenaline and serotonin (5-HT) [9,11]. An interaction between 5-HT and central BDNF seems to exist in the regulation of neuronal plasticity and survival, and activation of 5-HT receptors can induce transcription of the BDNF gene [16]. Serotonin receptor antagonists modify the exercise-induced BDNF expression in the hippocampus [9]. These data show that monoamines might play a role in the central regulation of BDNF in rodents. Also, long-term treatment with citalopram, a selective serotonin reuptake inhibitor (SSRI), leads to an increase in hippocampal BDNF mRNA [27] and protein [23] levels in rats, that is even enhanced when combining SSRI with voluntary physical activity [27]. This clear effect of 5-HT manipulation is however not found by other studies [7,10]. Even though the results are sometimes ambiguous, these animal studies show the ability of neurotransmitters to interfere in the regulation of BDNF synthesis [9,11].

In humans this influence of monoamines is unclear. Quantification of BDNF in humans is done peripherally, since central measurements are not possible. Studies in patients suffering from depression show that 6 weeks of treatment with a SSRI increases peripheral BDNF in depressed subjects (with lower starting levels of BDNF), but not in control subjects [1]. These manipulations, however, are not combined with exercise regimens, a physiological intervention known to increase monoamine release in the brain [17]. It is not known if changes in the level of monoamines in the

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brain can influence both central and peripheral BDNF protein concentrations during exercise.

Serum BDNF is known to increase under exercise conditions in humans (see Knaepen et al. [13] for review) and the effects of central serotonergic manipulation on the acute exercise-induced increase in peripheral BDNF have not been studied. Our hypothesis is that serum BDNF would be higher under SSRI treatment.

It remains to be determined whether BDNF crosses the blood–brain barrier (BBB) under normal conditions. Literature on the transport of BDNF through the BBB reports contradicting results. Some animal studies suggest that there is a transport system and that BDNF crosses the BBB in both directions [21,24]. This is however not confirmed by other animal studies, indicating that peripheral BDNF is not transported through the BBB [2]. In humans, there is also no clear evidence available for a transport of BDNF through the BBB. Still, some studies suggest that there is a cerebral output of BDNF that even increases 2–3 fold during exercise [14,25]. A study of Watson et al. [32] suggests that BBB permeability is increased with a raise of the core temperature. In this study, subjects were immersed in hot water previous to the exercise. Therefore, if core temperature raises in a sufficient matter with exercise in high environmental temperatures, there could be an increased output of BDNF from the brain.

Exercise and heat exposure could not only influence the supposed BDNF output from the brain, but also elicit other peripheral metabolic mechanisms which influence the exercise-induced increase in BDNF. One of these elements is cortisol, which has a negative influence on the expression of BDNF in the brain [28]. The elevated release of glucocorticoids during exercise in the heat [3] could restrain the initial exercise-induced increase of BDNF, as in the hippocampus there is a suppressive effect of glucocorticoids on BDNF expression [28].

The purpose of this study is to examine the effect of exercise on serum BDNF and the influence of SSRI and heat exposure on the exercise-induced changes in BDNF. We hypothesize that both SSRI administration and exercise in the heat are able to induce an enhancement of the exercise-induced increase in serum BDNF.

The study was conducted using a randomized, placebo controlled, double-blinded, cross-over design. All exercises were performed in a climatic chamber, controlling for temperature (18 °C or 30 °C) and relative humidity (maintained between 50% and 60%). Either placebo (PLA) or the SSRI citalopram (CITAL) was administered orally to the subjects before performing the exercise protocol.

Dietary intake was controlled the evening before and the morning of the exercise trial, and subjects were instructed to replicate this prior to all subsequent experimental trials. In the 24 h before each trial, no exercise, alcohol or caffeine consumption was permitted.

Eleven young well-trained male cyclists (age 23.3 ± 5.1 yr, weight 77.4 ± 8.3 kg, height 1.8 ± 0.1 m, maximal power output (W_{max}) 330.7 ± 19.7 W) volunteered to participate in the study, after a complete physical examination. None of the participants took any medication. All subjects received information regarding the experimental protocol and gave written consent, as approved by the Institutional Review Board of the Vrije Universiteit Brussel, Belgium.

At intake, subjects completed an incremental maximal exercise test on a cycle ergometer until exhaustion (80 W + 40 W every 3rd min) in order to determine their W_{max}. This W_{max} was used to calculate the workload throughout the experimental protocol.

All participants completed one familiarization trial (no blood sampling or drug administration) and 4 experimental trials, all separated by 1 week.

The experimental exercise protocol was previously used by our research group [8] and was duplicated for this research. Briefly, subjects remained seated in the climate chamber for 15 min, followed by 60 min cycling at 55% of W_{max}, and a time trial (TT) with an energy expenditure equal to 30 min cycling at 75% of W_{max}. Recovery in the climate chamber lasted for 15 min after the TT.

We repeated both the drug (CITAL) and placebo (PLA) trial in a hot environment (room temperature of 30 °C). Subjects were allowed to drink water ad libitum during exercise.

In both trials at 18 °C, subjects once were administered citalopram (ATC code: N06A B04) and once placebo (lactose) in randomized order and separated by 1 week. Both drug conditions were repeated in 30 °C. Drug administration took place the evening before and the morning of the exercise trial (total dose of 20 mg in 12 h). Both experimentators and subjects were blinded from the drug composition (PLA or CITAL).

Heart rate was registered every 5 min during exercise (Polar Accurex Plus®, Finland). Core temperature was measured at rest, after 60 min cycling, at the end of the TT, and after 15 min of recovery (rectal probe; Gram Corporation® LT-8A, Saitama, Japan).

Blood samples were taken through a venous cannula in a superficial forearm vein at rest, after 60 min at 55% of W_{max}, following the TT, and after recovery. Samples were drawn into 10 mL precooled vacutainer tubes (BD Vacutainer® Plastic SST II Advance Tube) and left to clot for 1 h at room temperature. The resulting serum after centrifugation was stored at −80 °C. BDNF protein concentration was determined using the ChemiKine® BDNF sandwich ELISA kit (CYT306). The kit has a detection range from 7.8 pg/mL to 500 pg/mL. Intra-assay and inter-assay variations are ±3.7% (125 pg/mL) and ±8.5% (125 pg/mL) respectively. Cortisol analysis was performed by a commercial laboratory, blinded from the study. Hematocrit was measured to correct all blood parameters for changes in plasma volume, using the formula of van Beaumont [30].

Statistical analysis was conducted using Statistica® 6.0 software. A Kolmogorov–Smirnov Goodness of Fit test checked the normality of the data. Data were evaluated by analysis of variance (ANOVA, exercise × drug × temperature) with repeated measures on all factors. Duncan's multi-range post hoc tests were applied to determine specific differences. Statistical significance level was set at $p < 0.05$. All data are presented as mean ± standard error (SEM).

Subjects needed 20% more time to fulfill the TT in 30 °C compared to 18 °C ($p = 0.001$). No significant difference in performance was found between both treatment groups ($p = 0.45$). In the 18 °C condition, subjects completed the predetermined amount of work in 32.0 ± 3.2 min and 32.8 ± 3.1 in the CITAL and PLA trials respectively, whereas in 30 °C they needed 40.0 ± 6.0 and 37.7 ± 4.1 min under CITAL and PLA treatments respectively.

Heart rate increased as result of exercise ($p < 0.001$) and environmental temperature ($p = 0.01$) (exercise × temperature: $p < 0.001$). No drug effect was found.

During exercise, core temperature changed in all subjects ($p < 0.001$) (Fig. 1). Core temperatures were higher in 30 °C compared to 18 °C ($p = 0.005$). Under CITAL treatment core temperature was not significantly different from the PLA trials ($p = 0.15$).

Serum BDNF changed significantly during exercise ($p < 0.001$) (Fig. 2). This increase was already significant after 60 min compared to resting situation ($p < 0.001$), but the TT did not cause an additional increase in BDNF compared to the level after 60 min of exercise ($p = 0.20$). During recovery, a decrease of serum BDNF occurred ($p = 0.001$), to levels not significantly different from resting concentration ($p = 0.10$). The changes in BDNF with exercise were consistent across all treatment groups.

Serum BDNF levels were lower under CITAL treatment compared to the levels of the PLA trial ($p = 0.02$; no interaction with time or temperature), and were higher in 30 °C compared to 18 °C ($p = 0.02$; no interaction with time or treatment).

The rate of change in serum cortisol was significantly different during exercise according to treatment and temperature manip-

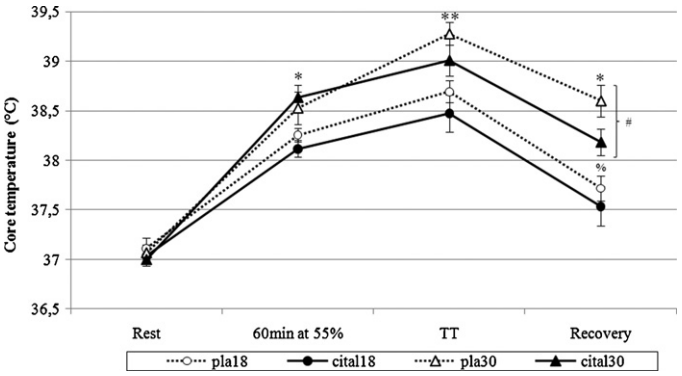

Fig. 1. Core temperature (°C) during the exercise protocol under placebo and citalopram treatment, in 18 °C (pla18–cital18) and 30 °C (pla30-cital30) (mean ± SEM). Exercise caused core temperature to increase ($p < 0.001$). Core temperature was higher in an environmental temperature of 30 °C compared to 18 °C ($p = 0.005$). No effect of drug administration on core temperature was found ($p = 0.15$). *Difference from baseline values in all trials ($p < 0.001$). **Difference from values after 60 min at 55% in all trials ($p < 0.001$). %Decrease after TT in 18 °C, values lower than during exercise, but higher than resting levels. #Main effect of temperature: higher values in 30 °C compared to 18 °C ($p = 0.005$).

ulations (Fig. 3). At rest both in 18 °C and in 30 °C, cortisol levels were higher in the CITAL trial compared to PLA ($p = 0.01$). Serum cortisol changed significantly through the different time points during the experimental protocol ($p < 0.001$; interaction temperature × treatment × time $p = 0.04$). Cortisol concentration increased following the TT ($p < 0.001$) and remained elevated after 15 min of recovery ($p < 0.001$). The hot environment caused cortisol levels to be higher during exercise compared to the temperate condition ($p = 0.03$). At all time points in 30 °C, cortisol levels were higher in the CITAL trial compared to PLA ($p = 0.02$).

This study confirms that exercise increases peripheral BDNF concentrations. Our reported BDNF levels at baseline are situated within the range of published peripheral BDNF concentrations in healthy subjects (4.7–30.9 ng/mL [13]), but are relatively low. In our study, all subjects were well-trained and previous studies have indicated that resting BDNF concentrations in athletes are lower than in untrained subjects [5,20], which could explain our lower starting values for BDNF.

The increase in BDNF with exercise follows the same pattern as the changing core temperature and is enhanced in a hot environment. Surprisingly, CITAL treatment decreases serum BDNF concentrations without altering the BDNF kinetics during exercise. We hypothesized that both variables would be able to induce an enhancement of the exercise-induced increase in BDNF. This hypothesis was confirmed by the results of exercise in a hot environment. However, with administration of a SSRI, the hypothesis needs to be rejected.

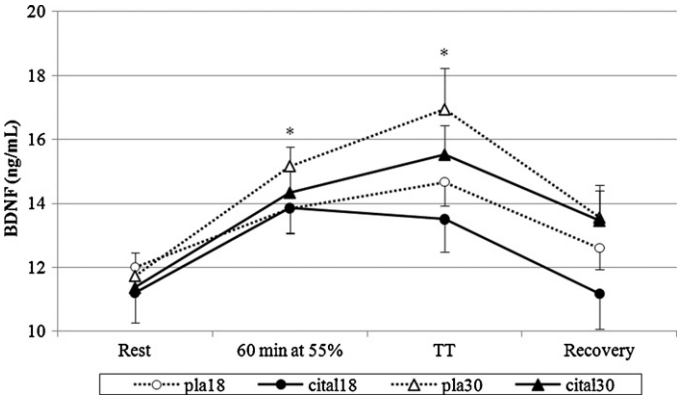

Fig. 2. Serum BDNF levels (ng/mL) during exercise under placebo and citalopram treatment, in 18 °C (pla18–cital18) and 30 °C (pla30–cital30) (mean ± SEM). Exercise caused an increase in serum BDNF after 60 min at 55% of W_{max} and after the TT. BDNF concentration was higher in 30 °C compared to 18 °C ($p = 0.02$). Citalopram elicited lower serum BDNF levels compared to placebo ($p = 0.02$). Exercise effect: significant difference from baseline values (*$p < 0.001$).

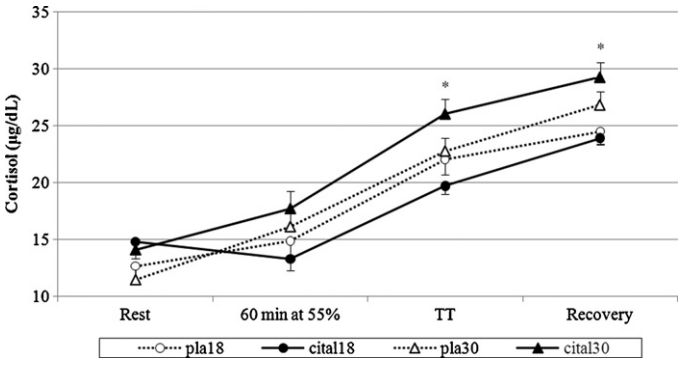

Fig. 3. Cortisol levels (µg/dL) during the exercise protocol in 18 °C and 30 °C after placebo or citalopram administration (mean ± SEM). Serum cortisol increased after the TT at 75% of W_{max} and remained high during recovery. Higher cortisol levels were found in 30 °C compared to 18 °C ($p = 0.03$). Serum cortisol was increased under citalopram treatment in 30 °C compared to placebo ($p = 0.02$). Exercise effect: significant difference from baseline values (*$p < 0.001$).

The involvement of monoamines in the induction of central BDNF raises the question whether these mechanisms are related to the exercise-induced increase in serum BDNF, since exercise itself increases monoaminergic neurotransmission in the brain [17]. Previously, acute administration of a selective noradrenaline reuptake inhibitor did not have an effect on changes in peripheral BDNF during exercise [8]. In the present study, overall serum BDNF levels are significantly lower under acute CITAL treatment compared to PLA, suggesting a decrease in BDNF release from the brain and/or the periphery. With administration of antidepressants, there appears to be a biphasic change in hippocampal BDNF gene expression [12]. A single injection of fluoxetine decreases BDNF mRNA expression in the hippocampus, while chronic treatment causes an increase. If this decrease in BDNF mRNA expression is also valid for peripheral levels, this could be translated into a lower BDNF protein production and explain our results with acute citalopram administration.

Another possible explanation is the increase of cortisol with CITAL treatment and the suppressive effect of glucocorticoids on BDNF [28]. Previously, it has been shown that, in rodents, a single injection of corticosterone decreases hippocampal BDNF mRNA (after 3 h) and protein (after 4–6 h) expression [28]. In the hippocampus, the decreased level of BDNF, together with elevated levels of adrenal-glucocorticoids can contribute to atrophy and cell loss [19]. In our study basal serum cortisol levels are higher in both the CITAL trials, as can be expected from previous research [18]. This might subsequently have contributed to the lower peripheral BDNF levels during these trials.

During exercise, these higher cortisol levels caused by the physical effort, did however not lead to lower BDNF concentrations in the periphery. Exercise in 30 °C induced higher levels of serum BDNF compared to the 18 °C trial, despite higher cortisol concentrations. Rojas Vega et al. [26] suggest that, most likely, the acute changes in serum cortisol caused by a single exercise bout are too brief to have a negative influence on BDNF and neuroplasticity. If these strenuous exercise bouts are frequently repeated, this could however lead to a negative influence on neuroplasticity [26].

Thus, it appears that the change in central neurotransmission does influence peripheral BDNF at rest, but the exercise-induced

increase in serum BDNF in humans is not dependent on brain serotonergic neurotransmission. In the future, 'in vivo' animal studies could be helpful to understand the exact mechanism of exercise-induced BDNF increase and the role of neurotransmitters.

We have put forward the hypothesis that, the increase in serum BDNF with exercise would be enhanced with exercise in the heat, and peripheral BDNF concentrations would follow a parallel pattern as the core temperature during exercise. This hypothesis was confirmed by the results of our study, clearly showing higher peripheral BDNF concentrations in the 30 °C trials.

It has been suggested that there exists an output of BDNF from the human brain [14,25]. One possible hypothesis for our results is, that the enhancement in core temperature with acute exercise allows a higher passage of BDNF from the brain into the periphery, resulting in increasing serum BDNF concentrations. Watson et al. [32] previously demonstrated that the permeability of the blood–brain barrier can increase with exercise in the heat, coming with a raise core temperature [32]. However, the design of this latter study is quite different from ours, since they applied water immersion previous to the exercise. Therefore, their results cannot simply be generalized to all exercise studies and we should be careful to compare these findings with our study. Future research should combine the measurement of BDNF with the analysis of S100β concentration – a central nervous system-specific protein, used as a peripheral marker of blood–brain barrier permeability – and investigate if both parameters are correlated. Based on the results of our study, we cannot prove whether these changes occur due to changes in blood–brain permeability or due to alternative peripheral mechanisms, and this core temperature hypothesis is still highly speculative and certainly needs further investigation. High intensity exercise is also related to changes in other parameters that could play a role, as there are changes in glucose uptake, energy metabolism and blood lactate concentration [29]. It has been shown that hypoglycemia and intermittent fasting both increase BDNF levels [31]. This involvement of BDNF in energy metabolism and blood glucose control could play a role with strenuous exercise. Also blood lactate has the potential to stimulate BDNF blood concentrations, and might also be an important contributing element with acute exercise [29].

The target of BDNF in the periphery with exercise in healthy subjects remains to be determined. Matthews et al. [15] suggest that, since BDNF enhances lipid oxidation in the muscles, BDNF could be taken up by muscles.

One of the limitations of our study is the small sample size ($n = 11$), which increases the risk of committing a type II error. For example, core temperature seems to be slightly lower under CITAL treatment, but this is not statistically different. A greater sample size could make the results of this study stronger, but, since the experimental protocol requires a high intensity exercise, it is quite demanding of the subjects, and this makes it difficult to increase sample size. We should also take into account that any explanation in the field of peripheral BDNF and exercise in human studies is still rather speculative, and other studies are definitely needed to elaborate this topic, and to substantiate the hypotheses put forward in this discussion.

Exercise causes an increase in serum BDNF and cortisol, in agreement with previous research [6,26]. We find lower serum BDNF levels with CITAL administration, probably due to a higher cortisol concentration. Moreover, the exercise-induced increase in peripheral BDNF seems to be related to a corresponding increase in core temperature throughout the different time points during the experiment. Future studies should focus on the origin of the exercise-induced increase in serum BDNF and the relevance of peripheral BDNF to central levels.

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