The effects of acute dopamine reuptake inhibition on performance.

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ABSTRACT

Introduction: Acute bupropion (BUP; dopamine/noradrenaline reuptake inhibitor) administration significantly improved time trial performance and increased core temperature in the heat (30°C). **Purpose:** The present study was performed to examine the effect of a dopaminergic reuptake inhibitor on exercise capacity and thermoregulation during prolonged exercise in temperate and warm conditons. **Methods:** Eight healthy well-trained male cyclists participated in this study. Subjects ingested either a placebo (PLAC; lactose; 20mg) or Ritalin (RIT; methylphenidate (MPH); 20mg) one hour before the start of exercise in temperate (18°C) or warm (30°C) conditions and cycled for 60 min at 55% W_{max}, immediately followed by a time trial (TT; pla18 and rit18; pla30 and rit30) to measure exercise performance. **Results:** Ritalin did not influence TT performance at 18°C (P=0.397). TT was completed 16% faster in rit30 (38.1±6.4min) than in pla30 (45.4±7.3min; p=0.049). Power output was higher in rit30, compared to pla30 (p<0.05). In the heat T_{core} was significantly higher at rest (p=0.009), at the start of exercise and throughout rit30 (p<0.05). Throughout rit30 heart rates were significantly higher (p<0.05). Prolactin concentrations decreased after one hour cycling in 18°C (p=0,036) and at rest in 30°C (p=0,007) after RIT administration. **Conclusions:** These results show that RIT has a clear ergogenic effect that was not apparent in 18°C. The combination of a dopamine reuptake inhibitor and exercise in the heat clearly improved performance and appeared to increase metabolic heat production, suggesting an important role for dopamine in the fatigue process.

Key words: central fatigue; ritalin; exercise

Introduction

Paragraph 1 It is well documented that exercise performance is negatively influenced in high environmental temperatures (3, 20). The capacity to exercise in the heat is thought to be primarily limited by thermoregulatory and fluid balance factors (8), and it has further been suggested that the central nervous system (CNS) may become important in the development of fatigue when body temperature is significantly elevated (15). Previous work conducted by Gonzalez-Alonso et al (6) concluded that a high internal body temperature (Tcore) *per se* causes fatigue in trained subjects during prolonged exercise in uncompensable hot environments. Hyperthermia has been demonstrate to exert a profound effect on the CNS, with a reduction in maximal muscle activity (17), altered EEG brain activity (16) and increased perceived exertion (18) reported when body temperature is elevated. These factors could all contribute to the reduction in performance seen when exercise is undertaken in the heat.

Paragraph 2 In a series of studies, Piacentini and colleagues (12, 21, 23, 24) failed to modify performance of a 90 minutes time trial in normal ambient temperatures (18°C), through the manipulation of central neurotransmission. However, the authors detected different hormonal responses depending on the neurotransmitter system triggered by the reuptake inhibitor. The neuroendocrine response to exercise suggested that the drugs did indeed produce a central effect, despite failing to influence performance. These data raise several questions: are the neurotransmitters targeted in these studies involved in fatigue during exercise, was the action of these drugs sufficient to bring about changes in performance or was the protocol employed appropriate to detect changes in performance resulting from these interventions?

Paragraph 3 In a recent study Watson et al (30) examined the effects of Bupropion (BUP; a dual dopamine/noradrenaline reuptake inhibitor) not only in temperate, but also in warm environmental conditions. The major finding was that subjects completed the time trials in the heat 9% faster when BUP was taken, an effect that was not apparent in 18°C. Seven out of nine subjects also attained body core temperatures exceeding 40°C, implying that BUP may dampen or override hyperthermia-induced inhibitory signals arising from the CNS to stop exercising, potentially increasing the risk on developing heat illness. Since the increase in central catecholaminergic neurotransmission may, in part, attenuate the loss of performance when exercise is performed in warm environmental temperatures (30) and DA is involved in both motor behaviour and motivation (14), it would be interesting to elucidate the specific role of DA in this process. Amphetamines are known to increase extracellular DA and have been associated with flushing, sympathetic activation, increased metabolic rate, as well as clinical hyperthermia (4).

Paragraph 4 Ritalin (RIT), an amphetamine – like stimulant, is a well-known DA reuptake inhibitor (5) that is widely administered to treat children with Attention Deficit Hyperactivity Disorder (ADHD). The active substance of RIT is methylphenidate (MPH), which occupies the DAtransporter (DAT; 28) and has a five times higher affinity for the DAT than for the NAtransporter (NAT; 9, 19). To our knowledge, there are no data available on the effects of RIT administration on exercise performance and thermoregulation during prolonged exercise in both normal and high ambient temperatures, even though it is administered to thousands of patients around the world. Therefore, the purpose of the present study is to examine the effect of RIT on exercise capacity and thermoregulation. We hypothesise that acute administration of the DA

reuptake inhibitor RIT will enhance exercise performance and will influence metabolic heat production during exercise in temperate and hot environmental conditions.

Methods

Paragraph 5 Subjects. Eight healthy males (age 26 ± 5y; Ht 1.82 ± 0.06m; mass 77.9 ± 6.4kg; W_{max} 361 ± 18W) participated in this investigation. All subjects were well-trained cyclists or triathletes, but were not accustomed to exercise in a warm environment at the time of the study. Prior to the start of the study all volunteers received written information regarding the nature and purpose of the experimental protocol. Following an opportunity to ask any questions, a written statement of consent was signed. The protocol employed was approved by the Research Council of the Vrije Universiteit Brussel, Belgium.

Paragraph 6 Experimental protocol. The experimental protocol used in this study is identical to the protocol used by Watson et al (30), therefore we will address it briefly. All subjects completed a preliminary maximal exercise test, a familiarisation trial and 4 experimental trials. The preliminary trial consisted of continuous incremental cycle exercise to volitional exhaustion and was used to determine the power output required to elicit 55 % and 75 % of maximal workload (W_{max}). A familiarisation trial was undertaken to ensure the subjects were accustomed to the procedures employed during the investigation and to minimise any potential learning or anxiety effects. This trial was performed in temperate environmental conditions and was identical to the experimental trials in all respects. Experimental trials were undertaken in either

temperate (18°C) or warm (30°C) conditions (trials are referred to as: placebo 18°C 'pla18', placebo 30°C 'pla30', Ritalin 18°C 'rit18' and Ritalin 30°C 'rit30'), with relative humidity maintained between 50 – 60 % in both conditions. All subjects had to complete all experimental trials, which were separated by at least 7 days to minimise the development of heat acclimation and to ensure drug washout. Subjects were instructed to record dietary intake and physical activity during the two days before the first trial, and to replicate this in the two days prior to the subsequent experimental trials. No exercise or alcohol consumption was permitted in the 24 hours before each trial.

Paragraph 7 Subjects entered the laboratory in the morning approximately 90 minutes after consuming a standardised breakfast that included 500 mL of plain water. Nude post-void body mass was measured and an indwelling venous cannula was introduced into a superficial forearm vein to enable repeated blood sampling at rest and during exercise. Subjects inserted a rectal thermister (Gram Corporation LT-8A, Saitama, Japan) 10 cm beyond the anal sphincter for the measurement of core temperature. Surface skin temperature probes (Gram Corporation LT-8A, Saitama, Japan) were attached to four sites (chest, upper arm, thigh and calf) to enable the determination of weighted mean skin temperature (25) and a heart rate telemetry band (Polar Accurex plus, Kempele, Finland) was positioned. Subjects were dressed in only cycling shorts, socks and shoes for all trials.

Paragraph 8 Subjects then entered a climatic chamber maintained at the appropriate environmental conditions and rested in a seated position for 15 minutes. During this period temperatures and heart rate were recorded at 5 minute intervals and a resting venous blood sample was drawn immediately before the start of exercise. The exercise

protocol consisted of 60 minutes constant load exercise at a workload corresponding to 55 % W_{max}, followed by a time trial (TT) to measure exercise performance. There was a 1 to 2 minute delay between the end of the constant load exercise and the beginning of the TT, to program the ergometer (Lode Excalibur Sport, Groningen, Holland). The TT required the subjects to complete a predetermined amount of work equal to 30 minutes at 75 % W_{max} as quickly as possible (10). Subjects began the TT at a workload corresponding to 75 % W_{max}, but were free to increase or decrease their power output as desired from the outset. During the TT a computer program displayed a bar indicating the percentage of total work completed to give the subject an indication of their progress. Throughout the protocol no feedback was provided regarding time lapsed, power output, pedal cadence or heart rate. During exercise subjects had *ad libitum* access to plain water.

Paragraph 9 Core and skin temperatures and heart rate were recorded at 5 minute intervals during exercise. Ratings of perceived exertion (RPE; 2) and thermal stress (assessed using a 21-point scale ranging from unbearable cold to unbearable heat) were assessed every 15 minutes during the initial 60 minutes and at 10 minute intervals during the TT. Venous blood samples were drawn after 60 minutes of constant load exercise and at the end of the TT. Following the completion of the TT, subjects returned to a seated position where recovery was monitored for 15 minutes and a further blood sample was obtained. The probes and cannula were then removed and nude body mass was then re-measured to allow the estimation of sweat losses.

Paragraph 10 Drugs. Subjects ingested 20mg RIT or a placebo (PLAC: lactose) one hour before the start of exercise. This rather low dose (the maximum dose for an adult is

1,3mg/kg spread over an entire day) was chosen due to the unknown reactions to the combination of extreme heat stress and exercise. The treatment was randomised and administered in double-blind crossover manner. RIT and PLAC capsules were prepared by an independent pharmacy to appear indistinguishable with regard to dimensions, weight and colour.

Paragraph 11 Blood collection and analysis. Venous blood samples were drawn directly into pre-cooled vacutainer tubes (BD Vacutainer, Plymouth, UK). 10 mL samples were collected into a plain tubes and left to clot for 1 hour at room temperature before centrifugation. The resulting serum was stored at $-20^{\circ}C$ for the determination of prolactin (PRL; Roche Diagnostics, Mannheim, Germany), cortisol (Diasorin, Stillwater, USA) and growth hormone (GH; Pharmacia & Upjohn Diagnostics, Uppsala, Sweden). Samples for plasma adrenocorticotropic hormone (ACTH) and beta-endorphin (Nichols Institute Diagnostics, CA, USA) were collected into 4.5 mL tubes containing K_3EDTA. An additional 7.5mL was added to lithium heparin. A 0.5 mL aliquot of whole blood was extracted and used for the determination of haemoglobin and haematocrit, with these used to estimate percent changes in plasma volume relative to the pre-exercise sample. Sodium metabisulphate (5 mg) was then added to the remaining whole blood prior to centrifugation.

Paragraph 12 Statistical Analysis. Data are presented as means ± standard deviation (SD), unless otherwise stated. To evaluate differences in TT performance, 2-factor (temp x drug) repeated measures ANOVA were employed. Data collected over time were analyzed using 3-factor (temp x drug x time) ANOVA with repeated measures. Pairwise differences were identified using Tukey's post-hoc test as appropriate.

Statistical significance was accepted at P < 0.05. To improve the clarity of figures, differences present between environmental conditions are described in the text.

Results

Paragraph 13 All subjects completed all the experimental trials. Exercise performance was significantly influenced by environmental temperature (p<0.001; Fig. 1), with subjects taking longer to complete the predetermined amount of work in the heat. Acute RIT supplementation increased exercise performance in warm (p=0.049) but not temperate (p=0.397) conditions. Subjects finished 16% faster, when RIT was ingested compared to the PLAC (pla30: 45'24" ± 7'18", rit30: 38'06" ± 6'24"; Fig. 1).

INSERT FIG. 1 HERE

Paragraph 14 As the TT required the completion of a predetermined amount of work, the time taken to complete the protocol was directly related to the power output maintained throughout this period. After PLAC treatment the power output was significantly higher in the temperate trials in comparison with the trials in warm environmental conditions (p=0.010), this was only obvious after 30min in the time trial after RIT administration (p=0.016). In the 30°C trials, in contrast with the trials in 18°C (Fig. 2A), a difference in power output was apparent between the PLAC and RIT trial from the start of exercise till near completion of the target amount of work (p<0.045; mean power output in rit30: 226 ± 37W, in pla30: 196 ± 35W; Fig. 2B).

INSERT FIG. 2 HERE

Paragraph 15 Core temperature increased significantly after 5 and 10 minutes of rest following RIT administration in the heat (p=0.013; Fig. 3), while in temperate conditions no such effect was present (p=0.360). Exercise produced a gradual increase in core temperature in all trials (p<0.001; Fig. 3). Ambient temperature and RIT both influenced Tcore during exercise. Tcore rose significantly higher in rit30 then in the pla30 after 5, 15 and 20 minutes of fixed intensity exercise (p<0.039) and at all times (p<0.043) except the 15 minutes marker (p=0.052) during the TT and the recovery. Tcore rose till 40.0 ± 0.6°C at the end of exercise in rit30. During the trials in temperate conditions significant increases in Tcore were observed only after 5 and 20min in rit18TT (p=0.022 and 0.025 respectively) in comparison to pla18TT, reaching a maximum average temperature of 39.5 ± 0.6°C at the end of exercise. No differences in weighted mean skin temperature were obvious between PLAC and RIT. Skin temperature increased during exercise in all conditions (p<0.001), reaching a plateau after 15min in pla30 and rit30 and after 20min in pla18 and rit18.

INSERT FIG. 3 HERE

Paragraph 16 Ambient temperature increased mean heart rates in the corresponding trials (pla18: 145 ± 8 b/min and pla30: 152 ± 10 b/min; rit18: 151 ± 9 b/min and rit30: 160 ± 9 b/min; Fig. 4). Heart rates after 40min fixed intensity exercise were significantly higher in the rit30 compared to the pla30 (pla30 170 ± 7 b/min and rit30 178 ± 12 b/min). During the TT, drug treatment induced significant increases in heart rate in normal temperature after 15 (p=0.025) and 25 minutes (p=0.033) and at the end

of the TT (p=0.009). In addition, the drug treatment significantly increased heart rate at every time point during exercise in the heat (p<0.046; Fig. 4). During recovery in 18°C heart rate was only significantly elevated after 5min in the RIT trial (p=0.024), while this was the case at every time point in the heat (p<0.046).

INSERT FIG. 4 HERE

Paragraph 17 Ratings of perceived exertion (RPE) were similar between PLAC and RIT treatment in temperate conditions (Fig. 5A). During the initial 60min of fixed intensity exercise in the heat RPE rose significantly higher in the PLAC treatment (pla30: 16.6 ± 1.3; rit30: 14.5 ± 1.7; p=0.034; Fig. 5B). In the TT this difference disappeared. The subjects' ratings of thermal stress (TS) were elevated by the higher ambient temperature (p<0.001), but not influenced by the drug treatment. Both RPE and TS scores increased during exercise (p<0.001). The loss of body mass after exercises, corrected for fluid intake, was significantly higher in the warm compared to the temperate trials (pla18: 2.44 ± 0.50l and pla30: 3.33 ± 0.62l; rit18: 2.37 ± 0.27l and rit30: 3.21 ± 0.58l; p=0.004), but no effect of RIT on sweat losses was found.

INSERT FIG. 5 HERE

Paragraph 18 All measured hormone concentrations rose significantly during exercise in all trials (p<0.025). Circulating serum PRL levels were influenced by drug administration and ambient temperature. In temperate conditions there was a trend for the PRL concentration to be decreased at rest in rit18 (p=0.066). After 60min of fixed intensity exercise the PRL concentration was significantly lower in rit18 in comparison

to pla18 (p=0.036; pla18: 8.0 ± 2.8ng/ml; rit18 6.6 ± 2.2ng/ml; Fig. 6A). In the heat the

resting PRL concentration was significantly lower after RIT administration (p=0.007), a

trend towards a lower PRL concentration was visible after 60min fixed intensity

exercise (p=0.065). In temperate conditions plasma ACTH levels were significantly

elevated at rest after RIT administration (p=0.036; pla18: 21.6 ± 7.4ng/l; rit18: 26.1 ±

5.7ng/l; Fig. 6B). No differences in ACTH concentrations between drug treatments

were apparent in the heat. Growth hormone concentrations were significantly lower

after 60min fixed intensity exercise in the heat when RIT was taken (p=0.034; pla30:

18.8 ± 11.3ng/l; rit30: 13.3 ± 8.3ng/l; Fig. 6C), while no differences appeared in

temperate conditions. No differences in cortisol (Fig. 6D) and beta-endorphin levels

were detected between trials (Fig. 6E).

INSERT FIG. 6A,B,C, D, E HERE

Discussion

Paragraph 19 The current study investigated the effects of acute oral administration of

RIT (a DA reuptake inhibitor) on exercise performance, thermoregulation and hormonal

responses to prolonged exercise in both temperate and warm environments. The

improved exercise performance in the heat and increased core temperature and heart

rate in both normal and warm conditions are in line with the results previously found by

Watson et al (30) after BUP administration, which also enabled the maintenance of a

higher power output during a TT in warm conditons. It appears that this response is

accompanied by an increased core temperature and heart rate, but with the same

perception of effort and thermal stress. Similarly these and other studies that used

nutritional and pharmacological manipulations of catecholaminergic neurotransmission confirmed the lack of performance improvements in 18°C (13, 21, 24, 27, 30), suggesting that dopaminergic neurotransmission may only have a significant role in fatigue when exercise is undertaken in warm environmental temperatures.

Paragraph 20 The combination of MPH, that has a potent dopaminergic activity, and high ambient temperatures, increased core temperature at rest in the heat. The mechanism behind this increase is not completely clear, possibly an increase of the metabolic rate causes the increase in core temperature (4). Malberg & Seiden (11) reported that the effect of MDMA on body temperature was influenced by ambient temperatures; rats given MDMA in 20°C developed hypothermia, whereas those given MDMA in 26-30°C developed hyperthermia. Additionally, most studies investigating the effects of amphetamines point out its thermogenic effect (4, 7).

Paragraph 21 In the present study 4 out of 8 subjects reached a core temperature above 40°C in the rit30, with one subject even exceeding 41°C after exercise, while there was only one subject that had 40.0°C at the end of the TT in pla30. There is a clear increase in metabolic heat production during the TT in rit30, with a greater rate of rise in core temperature seen during this trial. This may have resulted from an increased drive to perform and consequently higher power outputs at every time point except the 15 minutes marker in comparison to pla30. This result appears remarkable as we administered a rather low dose (20mg) of MPH, given the maximal therapeutic dose is set at 60mg/day. It is important to note that even at this low dose there is a potentially increased risk of developing heat illness, when performing hard exercise in warm conditions. Interestingly, the perceptional response to an increased core temperature and

heart rate seems to be dampened by RIT, as RPE was significantly higher in pla30 after 60 minutes of fixed intensity exercise and no changes in thermal stress were found. These findings might in part result from increased drive to continue exercise following RIT administration, given the role of dopamine in feelings of arousal and motivation, as was previously stated by Volkow and colleagues (29). As in the BUP trial in the heat (30), it appears that RIT administration, even at low doses, might result in an inhibition of signals arising from the CNS to cease exercise because of hyperthermia, and enable subjects to maintain a high power output even at that time.

Paragraph 22 Hormonal responses to exercise after manipulation of catecholaminergic neurotransmission have been studied before. BUP has been reported to influence ACTH, cortisol, beta-endorphin values at rest and during prolonged exercise (21); these changes were, in part, attributed to the noradrenergic properties of the drug. Watson et al (30) reported increased plasma ACTH and cortisol concentrations at rest and ACTH levels during exercise after BUP administration, while no influence on GH and PRL. Changes in circulating PRL concentrations have previously been employed in defining serotonergic activity, but its reliability has been questioned (12). Ben-Jonathan (1) established that hypothalamic DA release inhibits PRL secretion from the anterior pituitary. Slattum et al (26) also found (+)-amphetamine suppressed PRL secretion in human subjects and a rat study by Piacentini et al (22) resulted in decreased PRL concentrations after BUP administration, indicating an important role for the DA system. The present study agrees with these findings, since PRL concentrations showed significant decreases after 60min in rit18 compared to pla18 and at rest between rit30 and pla30. At rest in 18°C (p=0.066) and after sixty minutes in the heat (p=0.065)

significance was marginally missed, indicating a strong effect of MPH on PRL concentrations, even at a low dose of the drug.

Paragraph 23 Although DA is reported to have an inhibitory effect on most pituitary hormones except for GH (21), the present study showed a significantly lower GH concentration after 60min of exercise in rit30.

In 18°C there is some evidence for a catecholaminergic effect of RIT, since plasma ACTH concentrations are higher at rest in rit18. The higher ACTH concentration remained during exercise but due to large intra-subject variations no significance could be proven.

Paragraph 24 In conclusion, acute RIT administration resulted in a significant improvement in the time to complete a predetermined amount of work in a warm environment. This ergogenic effect was not apparent at 18°C. Core temperature in rit30 increased to a mean of 40,0 ± 0.6°C with 4 out of 8 subjects reaching core temperatures above 40°C and 1 subject attaining 41°C after exercise. However, no differences between PLAC and RIT were apparent in perceived thermal stress, and after sixty minutes of exercise in the heat the perceived exertion was significantly higher in the PLAC situation. These results suggest that RIT exerts equal or even more pronounced effects on exercise performance, metabolic heat production and hormonal responses than previously demonstrated with BUP.

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Figure legends

Fig. 1: Time trial time in the four experimental trials (mean ± SD).
* denotes a significant difference between the PLAC and the corresponding time point on the RIT trial (p<0.05).

Fig. 2: Time trial power output in temperate (A) and warm (B) conditions (mean ± SD).
* denotes a significant difference between the PLAC trial and the corresponding time point on the RIT trial (p<0.05).

Fig. 3: Core temperature in temperate (A) and warm (B) conditions (mean ± SD).
* denotes a significant difference between the PLAC trial and the corresponding time point on the RIT trial (p<0.05).
§ denotes a significant difference between the PLAC trial and the corresponding time point on the RIT trial (p<0.05).

Fig. 4: Heart rates in temperate (A) and warm (B) conditions (mean ± SD).
* denotes a significant difference between the PLAC trial and the corresponding time point on the RIT trial (p<0.05).
§ denotes a significant difference between the PLAC trial and the corresponding time point on the RIT trial (p<0.05).

Fig. 5: RPE scores in temperate (A) and warm (B) conditions (mean ± SD).
* denotes a significant difference between the PLAC trial and the corresponding time point on the RIT trial (p<0.05).

Fig. 6: PRL (A), ACTH (B), GH (C), cortisol (D) and B-end (E) concentrations at rest, after 60 minutes, at the end of the time trials and after 15 minutes recuperation (means ± SD).
* denotes a significant difference between the PLAC trial and the corresponding time point on the RIT trial in 18°C (p<0.05).
§ denotes a significant difference between the PLAC trial and the corresponding time point on the RIT trial in 30°C (p<0.05).