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ORIGINAL ARTICLE

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Responses to exercise in the heat related to measures of hypothalamic serotonergic and dopaminergic function

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Abstract We have studied 12 recreationally active men to measure their responses to exercise in the heat and relate these to measures of hypothalamic function explored with a buspirone [5-hydroxytryptamine 1A (5-HT_{1A}) agonist, dopaminergic D_2 antagonist] neuroendocrine challenge, with and without pretreatment with pindolol (5-HT_{1A} antagonist). Pindolol treatment allowed the serotonergic and non-serotonergic components of prolactin release to be distinguished. Subjects exercised at 73 (5)% maximal rate of oxygen uptake ($\dot{V}O_{2max}$) until volitional fatigue at 35°C (relative humidity, 30%). On another two occasions they underwent a buspirone challenge [0.5 mg (kg body mass)$^{-1}$], once with, and once without, pindolol [0.5 mg (kg body mass)$^{-1}$] pretreatment and the circulating plasma concentrations of prolactin were measured for the next 2.5 h. Rectal temperature increased throughout exercise, whilst mean skin temperature remained constant. There was a wide inter-subject variation in prolactin response to the neuroendocrine challenges. The proportion of the prolactin response to buspirone attributable to a non-serotonergic component (most likely dopaminergic) correlated both with exercise duration ($r = 0.657$, $P = 0.028$), rectal temperature at fatigue ($r = 0.623$, $P = 0.041$) and the rate of temperature rise ($r = -0.669$, $P = 0.024$). Our results suggest that high activity of the dopaminergic pathways in the hypothalamus is a predictor of exercise tolerance in the heat.

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Introduction

The ability to undertake strenuous physical work is an important attribute in many occupations as well as in sport and leisure activities. Exercise in hot conditions is a particular problem and there is considerable practical importance in being able to detect individuals who may be intolerant of exercise in the heat, either as a result of an abnormal tolerance of increased body temperature or due to impaired heat loss mechanisms.

During exercise at 60–70% of maximal oxygen uptake ($\dot{V}O_{2max}$) the energy demands are within the aerobic capacity of the body and although there is often an upward drift in oxygen consumption and heart rate (HR) with time, this rarely becomes a limiting factor. In theory, exercise at this intensity should continue until glycogen reserves are exhausted and a relationship between glycogen depletion and fatigue can be demonstrated with well-trained individuals working under cool conditions (Saltin and Karlsson 1972). However, many fit, but not specifically trained, subjects fatigue well before their carbohydrate stores are depleted. The cause of fatigue in the latter cases is not clear but increasing body temperature is likely to be a factor. In contrast to exercise in cool conditions where there is frequently uncertainty as to whether the limitation is one of carbohydrate availability or some other factor, exercise at 60–70% of $\dot{V}O_{2max}$ under conditions of high ambient temperature is not limited by carbohydrate reserves (Galloway and Maughan 1997, 2000) and central factors are of major importance. We have therefore used prolonged exercise in the heat as a model for exploring the mechanisms of central fatigue specifically because it removes the possibility of peripheral failure as a result of glycogen depletion.

As core temperature rises there is an increasing reluctance of subjects to continue working and this is

thought to be a reflex inhibition (Bruck and Olschewski 1987), probably arising in the hypothalamus or brain stem, and may involve serotonergic (5-HT) pathways that project to higher centres. Increasing core temperature either passively, through exposure to high ambient temperature at rest, or actively through exercise, increases central 5-hydroxytryptamine (5-HT) activity (Hori and Harada 1976a, b; Bridge et al. 1999). Hypothalamic 5-HT and dopaminergic activity have both been implicated in the control of thermoregulation and are thought to mediate thermoregulatory responses such as vasodilatation (Cox et al. 1980). Additionally, activity of these pathways results in an increased release of neuroendocrine hormones (Meltzer et al. 1983) and possibly behavioural changes that result in the loss of motivation to continue exercise. Differences in heat tolerance between individuals could be due to intrinsic differences in function of these hypothalamic pathways, through differences in the sensitivity (receptor density) or activity (neurotransmitter release for a given stimulus), giving rise to different thermoregulatory and/or behavioural responses to a given thermal load.

Hypothalamic activity cannot be assessed directly in man, but the release of prolactin, which is stimulated by 5-HT and inhibited by dopaminergic D_2 activity, is often taken as an indirect measure. Data from a range of human and animal studies suggest that the serotonergic neurones of the dorsal raphe nucleus project to hypothalamic sites to stimulate prolactin secretion through activation of 5-HT receptors (Van de Kar et al. 1996). Changes in prolactin levels in the blood therefore provide a useful marker for changes in central 5-HT activity as 5-HT is a prominent excitatory neurotransmitter for prolactin release (Struder and Weicker 2001). Circulating plasma prolactin concentrations rise during fatiguing exercise, largely in response to increases in core and skin temperature (Brisson et al. 1986, 1991; Bridge et al. 1999).

A common technique used to assess hypothalamic 5-HT sensitivity in healthy subjects is to measure the blood prolactin response to a neuroendocrine challenge with buspirone (Meltzer et al. 1983; Anderson and Cowen 1992; Bakheit et al. 1992; Jakeman et al. 1994; Sharpe et al. 1996; Bridge et al. 2001). Jakeman et al. (1994) found a reduced prolactin response to buspirone in highly trained endurance athletes compared with healthy controls. It has been suggested that a higher aerobic fitness provides an advantage during exercise in the heat with an improved ability to tolerate a high core temperature at exhaustion (Selkirk and McLellan 2001). It is interesting therefore to investigate the hypothalamic control of prolactin in relation to exercise tolerance in the heat.

Buspirone is primarily used as a 5-HT_{1A} receptor agonist but it also has D_2 antagonist activity and thus causes the release of prolactin through these two actions (Eison and Temple 1986). We have recently shown that it is possible to separate these actions by comparing the response to buspirone in the presence and absence of pindolol (Bridge et al. 2001). Pindolol blocks 5-HT_{1A} receptors and thus the prolactin response to buspirone in the presence of pindolol gives a measure of non-5-HT_{1A} activation which is mainly due to D_2 receptor antagonism (Eison and Temple 1986).

There is considerable evidence to support a role for dopamine in the control of body temperature and regulation of heat loss (see Lee et al. 1985 for review) and there has been a recent report of increased dopamine in the preoptic area and anterior hypothalamus in response to raised body temperature (Hasegawa et al. 2000). If the activities of hypothalamic serotonergic or dopaminergic pathways are important in controlling thermoregulation, it might be possible to predict exercise tolerance in the heat from the results of suitable neuroendocrine challenges. The main purpose of the present study was to evaluate this possibility. Consequently, we have compared exercise tolerance at a high ambient temperature with the response to neuroendocrine challenges with buspirone given both with and without pindolol to block 5-HT_{1A} activity.

Methods

General design

Subjects performed an exercise test to volitional fatigue on a cycle ergometer at an ambient temperature of 35°C (relative humidity, 30%) during which blood samples were collected every 10 min and rectal and skin temperatures measured every 5 min. The exercise tests were followed (on separate occasions) by two neuroendocrine challenges with buspirone, one of which was given in the presence of pindolol to block 5-HT_{1A} activity.

Subjects

Twelve recreationally active and healthy subjects participated in the study. The minimum level of activity required for acceptance onto the study was participation in exercise for an hour or more at least three times weekly. Their mean age, body mass and $\dot{V}O_{2max}$ were 22.9 (3.6) years [mean (SD)], 72.8 (5.8) kg and 4.21 (0.55) l min^{-1}, respectively. For the neuroendocrine challenges subjects were screened with a clinical interview to exclude any psychiatric history and to ensure they had been free of any medication for at least 3 weeks prior to the study. The study was approved by the Local Research Ethics Committee and subjects gave their informed consent in writing.

Experimental design

Visit 1

Subjects completed an incremental exercise test to exhaustion on an electrically braked cycle ergometer (Lode Excalibur Sport, Groningen, The Netherlands) to determine maximal aerobic power output (W_{max}) and $\dot{V}O_{2max}$. Workload was increased by 35 W every 3 min until volitional fatigue. Expired gases were analysed and averaged over a 10 s period, using a computerised online system (Oxycon Alpha, Jaeger, Bunnik, The Netherlands). W_{max} was estimated using the following equation from (Kuipers et al. 1985):

$$W_{max} = W_{final} + (t \times W)/T$$

where W_{final} is the power (W) of the last completed stage, t is the exercise time (s) during the final uncompleted stage, T is the duration (s) of each stage and W is the workload (W) increment for each stage.

Visit 2

Subjects arrived at the laboratory at either 0800 hours ($n = 11$), having fasted from midnight, or at 1300 hours ($n = 1$) having fasted for the previous 4 h. A cannula was inserted into an antecubital vein to obtain blood samples. To ensure that subjects began each trial euhydrated they were given a bolus of water [8 ml (kg body mass)$^{-1}$] to consume during the 45 min seated rest period between cannulation and the start of exercise. A resting blood sample was taken and subjects then began to exercise on the cycle ergometer. Exercise continued at a constant work rate of 65% of W_{max} [216 (11) W] and an ambient temperature of 35°C, and 30% relative humidity, until volitional fatigue. Subjects were asked to drink a minimum of 3 ml (kg body mass)$^{-1}$ water every 15 min to maintain hydration during the exercise. HR was continuously recorded (Polar Vantage NV, Polar OY, Finland). Venous blood samples (5 ml) were taken every 10 min during exercise for determination of haematocrit, haemoglobin, lactate and glucose. Whole body ratings of perceived exertion (RPE, Borg 1975) were obtained every 10 min during exercise.

Body temperature measurements

Rectal and skin temperature were recorded every 5 min (Squirrel Meter Logger, Grant Instruments, Cambridge, UK). Mean skin temperature was calculated using the four-site formula of Ramanathan (1964).

Sweat rate

Subjects were weighed nude immediately before the start of exercise and at the point of fatigue after having towelled down. Allowances were made for fluid ingested, respiratory water loss (Snellen 1966), metabolic water (Mitchell et al. 1972) and quantity of blood drawn, to arrive at an overall sweat loss which was divided by time to give an average sweat rate over the entire period of exercise.

Neuroendocrine challenges, visits 3 and 4

Subjects each made two visits to the laboratory and received placebo or pindolol as the pretreatment followed by buspirone as the drug treatment (challenge I and II, respectively). All drugs were administered orally, encased in identical gelatine capsules. Challenge I was preceded by 2 days during which subjects took a placebo and for the 2 days before challenge II they took pindolol (10 mg twice daily). Challenges I and II were randomised and balanced for order and were single-blind to the subjects with respect to pindolol.

Subjects arrived at the laboratory at 0800 hours following an overnight fast although water was allowed ad libitum during the fast and throughout the challenge. After a 15-min rest a 21 guage cannula was inserted into a superficial forearm vein and kept patent with saline (Baxter 0.9%). After a further 45 min rest, a baseline blood sample (3 ml) was taken and the subject ingested either placebo for challenge I, or pindolol [0.5 mg (kg body mass)$^{-1}$, mean dose 37 (3) mg; Sandoz] for challenge II. Serial blood samples were then taken at 15 min intervals for 1 h. Subjects then took buspirone [0.5 mg (kg body mass)$^{-1}$, mean dose 37 (3) mg; Bristol-Myers Squibb] and further blood samples were withdrawn every 15 min for the next 150 min. Subjects rested, but were not allowed to sleep, in a room at an ambient temperature of about 22°C. Venous blood samples were collected in EDTA tubes and plasma was separated by centrifugation and stored at −70°C. All samples were analysed for plasma prolactin concentrations (PRL) within 3 months.

Blood analysis

Haematocrit was measured by centrifugation in triplicate. Blood glucose and lactate concentrations were measured using enzyme-linked assays (Sigma, Poole, UK); haemoglobin concentration was measured using the cyanomethaemoglobin method (Sigma). PRL was measured by a radioimmunoassay (Skybio, UK). Average inter- and intra-assay coefficients of variation of the assay were 5.9% and 2.7% respectively. All plasma samples from a single subject were assayed in the same batch.

Statistical analysis

Total hormone release in response to buspirone was measured from the area under the curve of hormone concentration with time (AUC) calculated using the trapezoid method from the time of buspirone administration and was corrected for the average resting concentration, from the preceding 60 min. When there was no increase, or a reduction, in prolactin concentration after buspirone administration, the area under the curve was taken as zero. Data were tested for approximation to a normal distribution. Exercise data were analysed up to 40 min to include the maximum number of subjects ($n = 9$) and were tested using repeated measures ANOVAs (SPSS 10). P values were corrected for sphericity using the Huynh-Feldt method, and significant differences between time points were identified using Tukey's post hoc test. Where data were found to be not normally distributed (PRL concentration), non-parametric Friedman's tests and Wilcoxon signed rank tests were used. Correlations were calculated using the Pearson's correlation. Data are reported as means (SEM) unless otherwise stated.

Results

Exercise trials

Exercise time and perception of exertion

Mean $\dot{V}O_2$ was 3.06 (0.13) l min^{-1} during exercise which was 73 (5)% $\dot{V}O_{2max}$. Exercise times ranged from 20 min to 98 min [51.3 (6.6) min, Table 1]. RPE increased during the exercise and was significantly higher than the initial value after 30 min (Fig. 1) and values at fatigue were 20.

Body temperature and sweat rate

Rectal temperature rose steadily throughout the exercise (Fig. 2) and was 38.8 (0.1)°C at the time of volitional fatigue. Mean skin temperature rose significantly in the first 10 min of exercise ($P < 0.05$, Fig. 2) and thereafter remained constant with a value at fatigue of 34.9 (0.3)°C. All subjects ingested water at the minimum required rate during exercise [3.0 ml (kg body mass)$^{-1}$ (15 min)$^{-1}$] the mean rate was slightly higher than this at 4.3 (0.4) ml (kg body mass)$^{-1}$ (15 min)$^{-1}$. There was an average weight loss of 0.4 (0.1) kg during exercise. Sweat rate ranged from 1.02 l h^{-1} to 2.32 l h^{-1} with a mean value of 1.67 (0.12) l h^{-1} (Table 1).

Table 1 Individual subject data for maximal oxygen uptake ($\dot{V}O_{2max}$), exercise times, prolactin response to buspirone, the non-5-HT component of the buspirone response and exercise lactate concentrations

Subject no.	$\dot{V}O_{2max}$ (l min^{-1})	Exercise time (min)	Rectal temperature at fatigue (°C)	Sweat rate (l h^{-1})	Area under curve for buspirone challenge (mIU min^{-1} l^{-1})	Non-5-HT component %	Plasma lactate at 10 min (mmol l^{-1})	Plasma lactate at fatigue (mmol l^{-1})
1	4.01	92.5	39.1	2.08	25,943	100	2.74	5.90
2	4.35	98.7	39.1	2.32	41,273	100	3.11	8.23
3	4.92	48.5	39.8	1.63	0	0[a]	8.34	11.64
4	4.32	53.9	39.1	1.94	25,579	78	3.18	5.72
5	3.41	60.8	38.6	1.17	20,145	52	3.04	4.54
6	3.77	35.8	38.4	1.11	67,481	46	5.64	3.67
7	5.30	43.5	38.9	2.08	31,183	44	4.30	6.66
8	3.46	43.0	38.2	1.48	42,379	15	3.44	3.61
9	4.27	40.4	38.0	1.69	7,838	0	1.93	2.65
10	3.91	43.4	39.1	1.02	2,970	0	6.28	8.23
11	4.56	20.7	38.3	1.79	65,138	0	4.35	3.95
12	4.21	34.3	38.7	1.75	23,438	100	3.38	4.26
Mean	4.21	51.3	38.8	1.67	29,447	49	4.14	5.40
SD	0.55	23.0	0.5	0.41	21,775	41	1.80	2.50

[a]Subject 3 had no prolactin response above baseline to challenges with buspirone alone or to pindolol + buspirone and therefore a non-5-HT component was not calculated, as a result he is excluded from all correlations

Blood and metabolic parameters

There were no changes in haematocrit [44.3 (1)% pre vs 45.0 (0.9)% post] or haemoglobin [14.6 0.7 g dl^{-1} pre vs 15.2 (0.7) g dl^{-1} post] concentration during exercise. At fatigue the mean calculated decrease in plasma volume was 3.9 (1.0)%. Blood lactate concentration increased during the first 10 min of exercise (Fig. 3) but remained at this level to the time of volitional fatigue. Plasma lactate concentration at fatigue was 5.40 (0.72) mmol l^{-1}. Plasma glucose concentration did not deviate during exercise, and at fatigue it was 5.86 (0.43) mmol l^{-1} (Fig. 3). No change was seen in the respiratory exchange ratio [0.97 (0.02)] during the course of exercise indicating a consistent source of fuel throughout the exercise.

Cardiovascular and respiratory parameters

Heart rate increased during exercise from 153 (4) beats min^{-1} at 5 min to 168 (5) beats min^{-1} after 40 min of exercise (i.e. from approximately 77% to 85% of maximum HR measured during the $\dot{V}O_{2max}$ test). Ventilation increased during exercise from 76.8 (5.4) l min^{-1} at 15 min to 82.0 (6.8) l min^{-1} after 30 min, ($P < 0.05$).

Neuroendocrine challenges

The oral administration of buspirone resulted in a robust prolactin response in all but subject 3 (Fig. 4, Table 1). In the combined challenges, pindolol was given 60 min

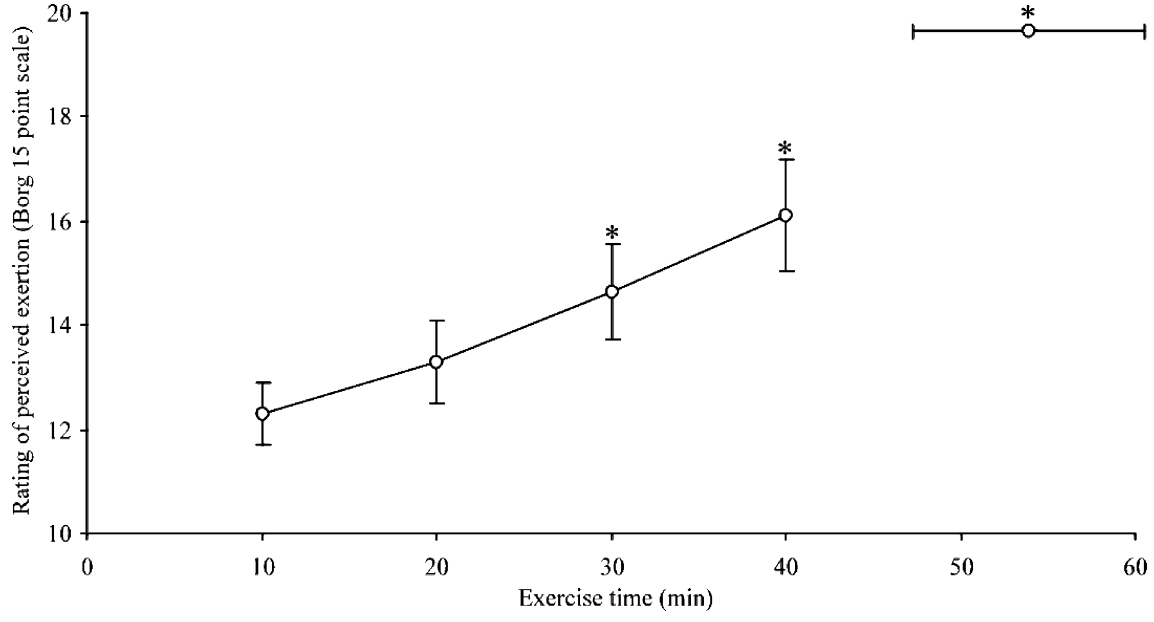


Fig. 1 Rating of perceived exertion (Borg scale) during the course of the exercise. *Significant difference from the 10 min time point, $P < 0.05$; data are means (SEM)

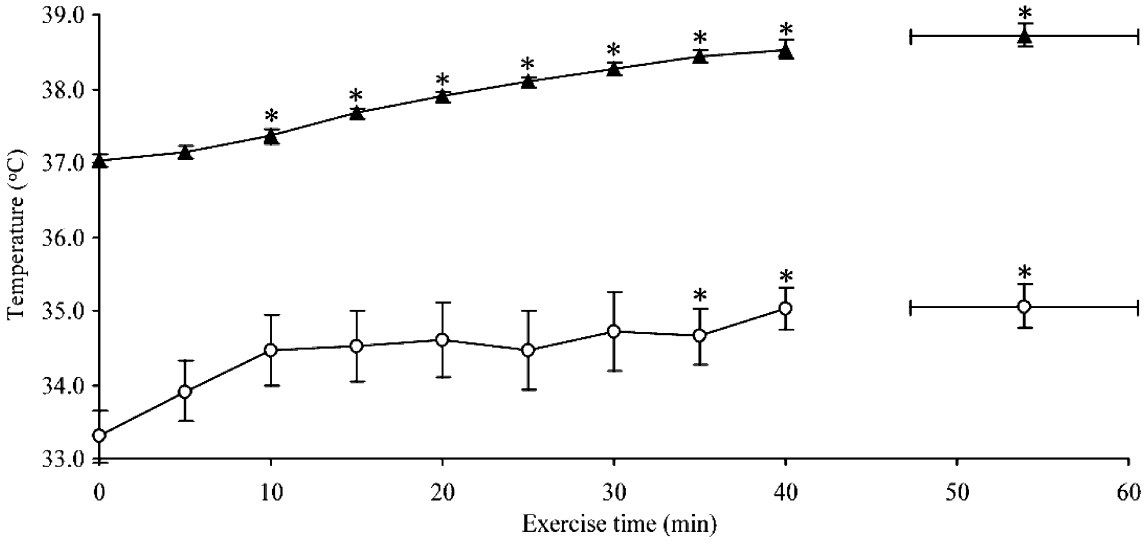


Fig. 2 Rectal (*triangles*) and mean skin temperatures (*circles*) during exercise. *Significant difference from time point 0, $P < 0.05$; data are means (SEM)

before the buspirone and during this time the resting prolactin fell, on average, by 34%. Compared with buspirone alone, the prolactin response to buspirone in the presence of pindolol was reduced in all but two subjects, the peak response being reduced by about one-third and the time of the peak response delayed by approximately 30 min [81 (10) min buspirone compared with 113 (9) min pindolol + buspirone, $P = 0.039$ Fig. 4].

Subtracting the AUC of the pindolol + buspirone response from the AUC of the response to buspirone alone for each subject allowed the proportions of their serotonergic and nonserotonergic components to be calculated. The nonserotonergic component of the buspirone response ranged from 0 to 100% with a mean value of 49 (12)% (Table 1).

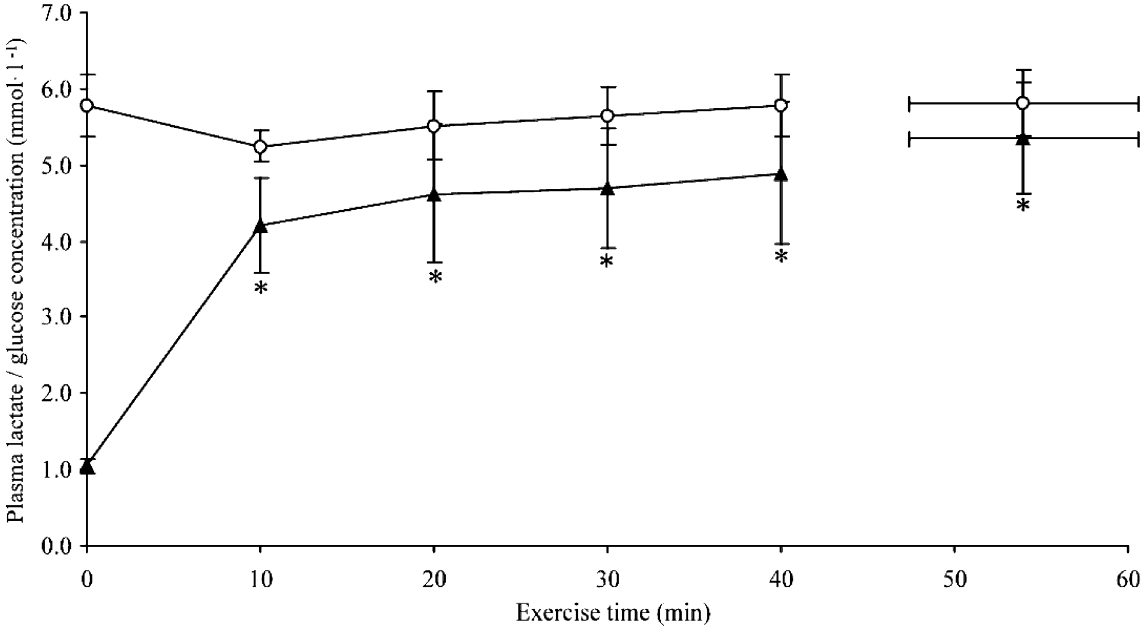
Correlations

Correlations were sought between values derived from the neuroendocrine challenges and indices of performance during exercise. Statistical data are presented in Table 2.

Discussion

The results presented here suggest that some of the inter-individual differences in hypothalamic serotonergic and dopaminergic function may explain, in part, the indi-

Fig. 3 Plasma lactate (*triangles*) and glucose (*circles*) concentrations during exercise. Lactate concentrations rose significantly in the first 10 min but remained constant thereafter while glucose showed no significant fluctuations. *Higher than time point 0 for lactate, $P < 0.05$. Data are means (SEM)



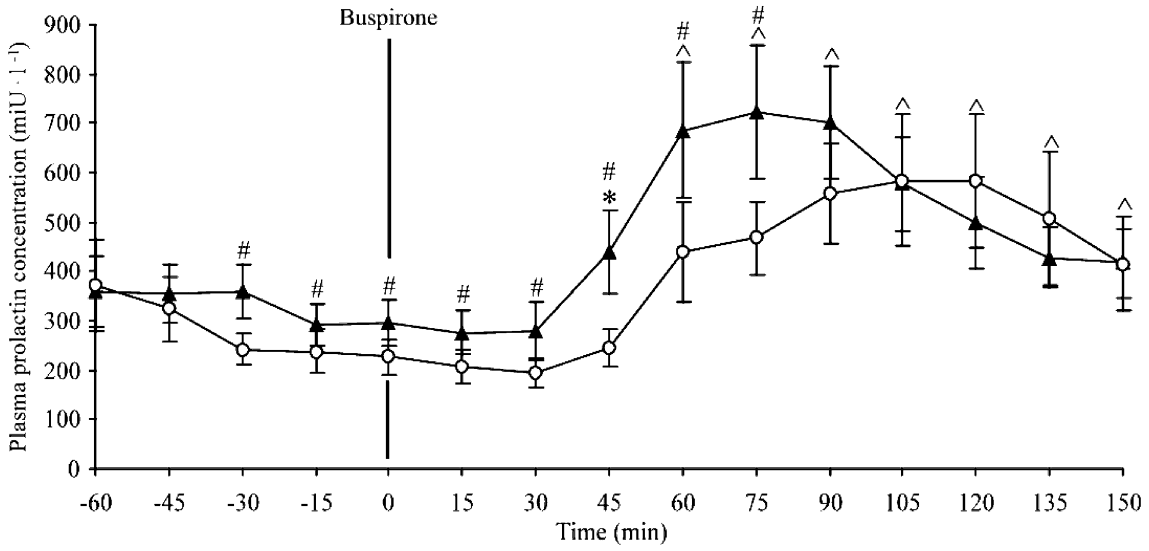


Fig. 4 Prolactin response to challenges with buspirone (*circles*) and pindolol + buspirone (*triangles*). Pindolol was administered at the −60 min time point and buspirone at time point 0. *Significant difference from time point 0 in buspirone trial, $P < 0.05$. ^Significant difference from time point 0 in both trials, $P < 0.05$. #Significant difference between trials at that time point, $P < 0.05$. Data are means (SEM)

vidual variation in exercise tolerance in the heat. In general, those subjects who exercised for the longest duration had a prolactin response to buspirone which was largely attributed to its action as a dopamine antagonist.

The existence of central fatigue during submaximal exercise is difficult to prove since, to date, it can only be surmised from the absence of signs of peripheral muscle failure. Recently, however, Nybo and Nielsen (2001a) have shown that subjects made hyperthermic by exercise in the heat were unable to fully activate their quadriceps and that this effect was accompanied by changes in their electroencephalogram. These observations add weight to the suggestion that raised core temperature itself is the signal inhibiting exercise rather than some consequence of the elevated temperature, such as altered blood flow to the working muscles (Nielsen et al. 1997; Nybo et al. 2001; Nybo and Nielsen 2001a, b, c).

The results presented here add further weight to these arguments. Blood lactate levels rose initially during the exercise but then remained constant, indicating that the working muscles had achieved equilibrium, with energy supply from oxidative metabolism matching the energy demands. Subjects remained euglycaemic, and respiratory exchange ratio values remained stable, indicating that there was no change in the proportion of fat and carbohydrate oxidisation. Heart rate and ventilation tended to increase throughout exercise but at no stage did they approach values that would be considered to be limiting for exercise.

RPE increased throughout exercise in parallel with the increase in rectal temperature. The end point of exercise for our subjects occurred at somewhat lower values of core temperature than found by Nielsen et al. (1997) and Gonzalez-Alonso et al. (1999). This may, in part, reflect a difference between rectal and oesophageal sites of measurement or differences in the type of subjects used. In their studies, Nielsen et al. (1997) and Gonzalez-Alonso et al. (1999) used subjects who were endurance-trained cyclists, whilst our subjects, although generally fit and familiar with cycling exercise, were a more heterogeneous group. Additionally, our results do not show such a tight relationship between fatigue and final core temperature, as suggested by Nielsen et al.

Table 2 Pearson correlation coefficients (r), significance values (P) and number of samples (n)

Variable		Area under curve for buspirone challenge	Non-5-HT component	5-HT component	% Non-5-HT
Time to fatigue	r	−0.155	0.661	−0.576	0.657
	P	0.630	0.019*	0.050	0.028*
	n	11	11	11	11
Sweat rate	r	0.087	0.534	−0.189	0.534
	P	0.789	0.074	0.557	0.090
	n	11	11	11	11
Rate of rectal temperature rise	r	−0.158	−0.616	0.234	−0.669
	P	0.625	0.033*	0.464	0.024*
	n	11	11	11	11

*Significant linear correlation at the indicated P value

(1997) and Gonzalez-Alonso et al. (1999), since some of our subjects reached volitional fatigue at nearly 40°C while others did so only at about 38°C (Table 1). It is possible that the cause of voluntary exhaustion in this study is more due to a combination of core and skin temperatures, rather than the attainment of a specific high core temperature. This is consistent with the suggestion of Cheung and McLellan (1998) that in moderately fit subjects, the cause of voluntary exhaustion during exercise in the heat is a combination of skin and core temperatures.

The neural pathways involved with central fatigue are poorly understood but there has been interest in the involvement of serotonergic activity since the work of Newsholme and colleagues (e.g. Newsholme et al. 1987). Serotonergic pathways in the hypothalamus are involved in the control of prolactin secretion, an increase of which is associated with the development of fatigue (Marvin et al. 1997). Central fatigue is most evident when working in the heat (Nybo and Nielsen 2001a) and the hypothalamus is also the site of much of the body's thermoregulatory control (Boulant 1981), suggesting that variations in activity or sensitivity of pathways in this region may account for some of the variations in endurance capability.

The interpretation of the results of the neuroendocrine challenges presented here rests first on the selectivity and potency of the 5-HT_{1A} antagonist action of pindolol and secondly on the lack of any complicating actions. Pindolol has been shown to have a high affinity for 5-HT_{1A} receptors (Hoyer 1988) and does not appear to possess any activity at dopamine receptors (Hjorth and Carlsson 1986). Additionally positron emission tomography scanning has shown that a 20 mg dose of pindolol, without a priming dose, resulted in 46% postsynaptic 5-HT_{1A} receptor occupancy (Rabiner et al. 2000). Whilst this is by no means a total blockade of postsynaptic receptors, the results also show that the occupancy is dose-dependent (Rabiner et al. 2000). It is therefore likely that with the priming dose given on the 2 days before the buspirone challenge and the relatively high dose given an hour before the buspirone [37 (3) mg, 0.5 mg (kg body mass)$^{-1}$] in this study, that a higher 5-HT_{1A} receptor occupancy had been achieved. Indeed Rabiner et al. (2000) suggest that a 30 mg dose would be enough to fully block the functional responses to buspirone.

A complicating issue to the neuroendocrine challenges is pindolol's β-adrenoceptor antagonist action for which it is probably best known (Aellig 1976). The β-adrenoceptor antagonist propanolol has been reported to increase the prolactin response to pharmacological challenges (Laakmann et al. 1986). It is possible that pindolol may have a similar action but since pindolol has been found to consistently reduce prolactin levels, any stimulatory action will have led to an underestimation of the size of the 5-HT_{1A} component rather than falsely attributing this component to serotonergic activity. Pindolol, however, does have some intrinsic sympathomimetic activity (Aellig 1976) and it is conceivable that pindolol could act in part, and/or in some individuals, as a β-adrenoceptor agonist which could lead to a reduction in prolactin release via this mechanism. Whilst these mechanisms have to be considered, it is unlikely that they played a major role in influencing prolactin release in this study.

The work presented here is the first to make a direct comparison between exercise performance in the heat and hypothalamic sensitivity assessed by a neuroendocrine challenge. It is also the first to dissect the buspirone challenge into its component parts so that we have been able to directly compare endurance with the different components of the response to buspirone. From the data presented in Table 1 it is evident that the total prolactin response to a buspirone challenge bears no relationship to performance in the heat. Comparison of two subjects illustrates the point. Subjects 2 and 8 had similar total prolactin responses (42,000 and 41,000 mIU min^{-1} l^{-1}) but the endurance time for subject 2 was over twice that for subject 8.

Separating the buspirone response in the present study into serotonergic and nonserotonergic components (Fig. 4) shows that, on average, the two release mechanisms were in very similar proportions (approximately 50%) to those reported previously (Bridge et al. 2001). The data in Table 1 are notable in that they show a very wide variation in the proportions of 5-HT and non-5-HT components ranging from 100% of one, to 100% of the other. This is a feature that has been commented upon previously (Bridge et al. 2001) and it prompts the question of whether the wide variation in neuroendocrine response is related to the wide variation in endurance performance seen in the heat (Table 1).

We therefore sought evidence of relationships between the separate components of the buspirone response and endurance exercise performance. Table 2 presents the statistical data and while it is evident that there was no relationship between the total buspirone response and exercise performance, there was a high positive correlation between the non-5-HT component of the response and time to fatigue. A similar high correlation was found between time to fatigue and the proportion of the total prolactin response to buspirone attributable to the non-5-HT component. In these circumstances it is not clear whether it is a large non-5-HT component or a small 5-HT component that is the most appropriate predictor of performance.

Tolerance of high core temperature may be one factor determining endurance performance, the rate of temperature rise is clearly another key factor and it notable that while the best performers had the highest core temperatures at fatigue, the rate at which their temperatures rose was lower than for other subjects. There were strong negative correlations between the absolute size and the proportion of the buspirone response attributed to dopaminergic (non-5-HT) activity and the rate of rise of rectal temperature (non-5-HT component, Table 2).

For a given rate of heat production the rise of temperature will depend on the ability to dissipate heat, mainly by the evaporation of sweat in a hot environment. Differences in the rate of temperature rise during exercise might, therefore, be expected to be reflected in sweat rates that, in turn, might correlate with some aspect of the neuroendocrine challenges. There was a trend suggesting that sweat rate was related to the non-5-HT component of the buspirone challenge in a similar manner that was the converse of the rate of rise of temperature, but this did not reach statistical significance (Table 2).

In summary, our results show that a substantial portion of the variation in endurance capacity of normal subjects exercising in hot conditions may be explained by their differing responses to neuroendocrine challenges with buspirone, coupled with pindolol used to block the 5-HT_{1A} component. It appears that a high dopaminergic (non-5-HT) component is associated with better exercise performance and this may be related to the absolute magnitude of the response or to the high ratio of dopaminergic to serotonergic activities. Subjects with high sensitivity of these postulated dopaminergic pathways might benefit in two ways: the first is an improvement in central tolerance of a high core temperature, while the second is a slower rate of rise of core temperature. These findings could be further investigated by the use of a specific probe of dopaminergic receptor function rather than interpreting results from the two neuroendocrine challenges used in this study. Assessment of thermoregulatory capacity as rest alongside that during exercise would also allow further elucidation upon the results.

The neuroendocrine challenges we have described quantify the activity of hypothalamic pathways that appear to be involved in both thermoregulation and the perception of exertion and thereby the desire, or ability, to continue exercise. Such tests may throw light on the fundamental mechanisms of central fatigue while they could also prove to be a way of identifying individuals who are well adapted to exercise in the heat. Conversely those who are not well-adapted may be at risk of developing heat illness since high heat tolerance but poor thermoregulation would be a dangerous combination.

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References

Aellig WH (1976) beta-Adrenoceptor blocking activity and duration of action of pindolol and propranolol in healthy volunteers. Br J Clin Pharmacol 3:251–257

Anderson IM, Cowen PJ (1992) Effect of pindolol on endocrine and temperature responses to buspirone in healthy volunteers. Psychopharmacology (Berl) 106:428–432

Bakheit AMO, Behan PO, Dinan TG, Gray CE, O'Keane V (1992) Possible upregulation of hypothalamic 5-hydroxytryptamine receptors in patients with postviral fatigue syndrome. BMJ 304:1010–1012

Borg G (1975) Simple ratings of perceived exertion. In: Borg G (ed) Physical work and effort. Pergamon, New York, pp 39–46

Boulant JA (1981) Hypothalamic mechanisms in thermoregulation. Fed Proc 40:2843–2850

Bridge MW, Allen T, Sharma A, Jones DA (1999) Effect of ambient temperature on exercise-induced prolactinaemia. J Physiol (Lond) 521:103P

Bridge MW, Marvin G, Thompson CE, Sharma A, Jones DA, Kendall MJ (2001) Quantifying the 5-HT1A agonist action of buspirone in man. Psychopharmacology (Berl) 158:224–229

Brisson GR, Audet A, Ledoux M, Matton P, Pellerin-Massicotte J, Peronnet F (1986) Exercise-induced blood prolactin variations in trained adult males: a thermic stress more than an osmotic stress. Horm Res 23:200–206

Brisson GR, Peronnet F, Perrault H, Boisvert P, Massicotte D, Gareau R (1991) Prolactinotrophic effect of endogenous and exogenous heat loads in human male adults. J Appl Physiol 70:1351–1355

Bruck K, Olschewski H (1987) Body temperature related factors diminishing the drive to exercise. Can J Physiol Pharmacol 65:1274–1280

Cheung SS, McLellan TM (1998) Heat acclimation, aerobic fitness, and hydration effects on tolerance during uncompensable heat stress. J Appl Physiol 84:1731–1739

Cox B, Kerwin RW, Lee TF, Pycock CJ (1980) A dopamine-5-hydroxytryptamine link in the hypothalamic pathways which mediate heat loss in the rat. J Physiol (Lond) 303:9–21

Eison AS, Temple DL (1986) Buspirone: Review of its pharmacology and current perspectives on its mechanisms of action. Am J Med 80:1–9

Galloway SD, Maughan RJ (1997) Effects of ambient temperature on the capacity to perform prolonged cycle exercise in man. Med Sci Sports Exerc 29:1240–1249

Galloway SD, Maughan RJ (2000) The effects of substrate and fluid provision on thermoregulatory and metabolic responses to prolonged exercise in a hot environment. J Sports Sci 18:339–351

Gonzalez-Alonso J, Teller C, Andersen SL, Jensen FB, Hyldig T, Nielsen B (1999) Influence of body temperature on the development of fatigue during prolonged exercise in the heat. J Appl Physiol 86:1032–1039

Hasegawa H, Yazawa T, Yasumatsu M, Otokawa M, Aihara Y (2000) Alteration in dopamine metabolism in the thermoregulatory center of exercising rats. Neurosci Lett 289:161–164

Hjorth S, Carlsson A (1986) Is pindolol a mixed agonist–antagonist at central serotonin (5-HT) receptors? Eur J Pharmacol 129:131–138

Hori T, Harada Y (1976a) Midbrain neuronal responses to local and spinal cord temperatures. Am J Physiol 231:1573–1578

Hori T, Harada Y (1976b) Responses of Midbrain raphe neurons to local temperature. Pflugers Arch 364:205–207

Hoyer D (1988) Functional correlates of serotonin 5-HT1 recognition sites. J Recept Res 8:59–81

Jakeman PM, Hawthorne JE, Maxwell SRJ, Kendall MJ, Holder G (1994) Evidence for downregulation of hypothalamic 5-hydroxytryptamine receptor function in endurance-trained athletes. Exp Physiol 79:461–464

Kuipers H, Verstappen FT, Keizer HA, Geurten P, van Kranenburg G (1985) Variability of aerobic performance in the laboratory and its physiologic correlates. Int J Sports Med 6:197–201

Laakmann G, Schoen HW, Zygan K, Weiss A, Wittmann M, Meissner R (1986) Effects of receptor blockers (methysergide, propranolol, phentolamine, yohimbine and prazosin) on desimipramine-induced pituitary hormone stimulation in humans. II. Prolactin. Psychoneuroendocrinology 11:463–474

Lee TF, Mora F, Myers RD (1985) Dopamine and thermoregulation: an evaluation with special reference to dopaminergic pathways. Neurosci Biobehav Rev 9:589–598

Marvin G, Sharma A, Aston W, Field C, Kendall MJ, Jones DA (1997) The effects of buspirone on perceived exertion and time to fatigue in man. Exp Physiol 82:1057–1060

Meltzer HY, Flemming R, Robertson A (1983) The effect of buspirone on prolactin and growth hormone secretion in man. Arch Gen Psychiatry 40:1099–1102

Mitchell JW, Nadel ER, Stolwijk JA (1972) Respiratory weight losses during exercise. J Appl Physiol 32:474–476

Newsholme EA, Acworth IN, Blomstrand E (1987) Amino acids, brain neurotransmitters and a functional link between muscle and brain that is important in sustained exercise. Adv Myochem 1:127–133

Nielsen B, Strange S, Christensen NJ, Warberg J, Saltin B (1997) Acute and adaptive responses in humans to exercise in a warm, humid environment. Pflugers Arch 434:49–56

Nybo L, Nielsen B (2001a) Hyperthermia and central fatigue during prolonged exercise in humans. J Appl Physiol 91:1055–1060

Nybo L, Nielsen B (2001b) Middle cerebral artery blood velocity is reduced with hyperthermia during prolonged exercise in humans. J Physiol (Lond) 534:279–286

Nybo L, Nielsen B (2001c) Perceived exertion is associated with an altered brain activity during exercise with progressive hyperthermia. J Appl Physiol 91:2017–2023

Nybo L, Jensen T, Nielsen B, Gonzalez-Alonso J (2001) Effects of marked hyperthermia with and without dehydration on $\dot{V}O_2$ kinetics during intense exercise. J Appl Physiol 90:1057–1064

Rabiner EA, Gunn RN, Castro ME, Sargent PA, Cowen PJ, Koepp MJ, Meyer JH, Bench CJ, Harrison PJ, Pazos A, Sharp T, Grasby PM (2000) beta-Blocker binding to human 5-HT(1A) receptors in vivo and in vitro: implications for antidepressant therapy. Neuropsychopharmacology 23:285–293

Ramanathan NL (1964) A new weighting system for mean surface temperature of the human body. J Appl Physiol 19:531–533

Saltin B, Karlsson J (1972) Muscle glycogen ultilisation during work of different intensities. In: Al PE (ed) Muscle metabolism during exercise. Plenum, New York, pp 289–299

Selkirk GA, McLellan TM (2001) Influence of aerobic fitness and body fatness on tolerance to uncompensable heat stress. J Appl Physiol 91:2055–2063

Sharpe M, Clements A, Hawton K, Young AH, Sargent P, Cowen PJ (1996) Increased prolactin response to buspirone in chronic fatigue syndrome. J Affect Disord 41:71–76

Snellen JW (1966) Mean body temperature and the control of thermal sweating. Acta Physiol Pharmacol Neerl 14:99–174

Struder HK, Weicker H (2001) Physiology and pathophysiology of the serotonergic system and its implications on mental and physical performance. Part I. Int J Sports Med 22:467–481

Van de Kar LD, Rittenhouse PA, Li Q, Levy AD (1996) Serotonergic regulation of renin and prolactin secretion. Behav Brain Res 73:203–208