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Decreased Neuroendocrine Responses to Meta-Chlorophenylpiperazine (m-CPP) but Normal Responses to Ipsapirone in Marathon Runners

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Several clinical studies suggest antidepressive and anxiolytic effects of regular aerobic exercise. To study the effects of exercise on central serotonergic receptor sensitivity, we performed neuroendocrine challenges using oral doses of meta-chlorophenylpiperazine (m-CPP, 0.4 mg/kg), ipsapirone (0.3 mg/kg) and placebo in 12 marathon runners and 12 healthy controls not practicing regular exercise. After administration of the nonselective serotonergic agonist m-CPP, which exerts a number of well-reproducible effects mainly by means of its action on 5-HT_{2C} receptors, marathon runners showed a significantly reduced cortisol response in comparison to the control group. There was also a statistical trend toward a blunted prolactin response after m-CPP in the athlete group. In contrast, the increase of cortisol and the hypothermia observed after administration of the 5-HT_{1A} agonist ipsapirone were of the same magnitude in both groups. The behavioral response to m-CPP or ipsapirone and the mean maximal increases of plasma adrenaline and noradrenaline did not differ between the marathon and the control group. In conclusion, exercise-induced downregulation of 5-HT_{2C} receptors could play an important role in mediating the anxiolytic and antidepressive effects of exercise.

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KEY WORDS: *Exercise; Marathon running; Serotonin; Meta-chlorophenylpiperazine (m-CPP); Ipsapirone*

Several studies of healthy volunteers have shown a positive effect of endurance training on anxiety, depressive symptoms, self-esteem, concentration, sexual satisfaction, and stress tolerance (de Coverley Veale 1987; Farmer et al. 1988; Hughes 1984; Lennox et al. 1990; MacMahon 1990; Sothman et al. 1992). There is also some evidence that exercise is effective against mild-to-moderate depression and against anxiety disorders (Doyne et al. 1987; Greist et al. 1979; Martinsen et al. 1985; McCann and Holmes 1984; Pappas et al. 1990; Sexton et al. 1989). Research in sports medicine has focused on physiological and immunological consequences of exercise, and little is known about changes in central neurotransmitter function associated with acute or regular endurance training.

Several lines of evidence suggest that motor activity affects central serotonin metabolism. In the cerebrospinal fluid of depressed patients, the concentration of the serotonin metabolite 5-HIAA was significantly higher after 4 hours of motor activity than in the same patients after bed rest (Post et al. 1973). Aerobic exercise causes a rise of free fatty acids (Davis et al. 1992; Fischer et al.

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1991), which displace free tryptophan (TRP) from its plasma–protein-binding sites (Blomstrand et al. 1988; Chaouloff et al. 1986). This leads to an increase of free TRP in relation to other large neutral amino acids (LNAA) (Chaouloff et al. 1989). Because the TRP influx into the brain correlates with the TRP/LNAA plasma ratio (Fernstrom and Wurtman 1971; Wurtman and Fernstrom 1976), exercise leads to a higher precursor availability in the brain, which, in turn, stimulates 5-HT synthesis (Broocks et al. 1989; Chaouloff 1997). Data from animal studies show that hyperactivity is also associated with an increased turnover of serotonin in the mediobasal hypothalamus (Broocks et al. 1991). On the basis of these findings, we have hypothesized that repeated stimulation of central serotonin turnover by exercise could lead to an adaptive downregulation of 5-HT_{2C} receptors. Clinical studies in patients with obsessive–compulsive disorder (OCD) have shown that chronic administration of clomipramine was associated with a significantly diminished behavioral and hyperthermic response to m-CPP, although the same dose of m-CPP had led to significantly higher plasma concentrations of m-CPP (Zohar et al. 1988). Accordingly, reduced behavioral sensitivity to m-CPP was also observed after chronic administration of fluoxetine to OCD patients (Hollander et al. 1992). Following 3 weeks of paroxetine treatment, both the prolactin and hyperthermic responses to m-CPP were significantly attenuated in seven healthy volunteers (Quested et al. 1997).

During the last decade, m-CPP has been used frequently to probe human serotonergic function (Kahn and Wetzler 1991; Murphy et al. 1996; Murphy et al. 1991). Generally, it has been found to elicit neuroendocrine responses (e.g., elevations in plasma cortisol, ACTH, and prolactin), physiological effects (e.g., increases in blood pressure and temperature), and behavioral effects, which showed a characteristic pattern depending upon the neuropsychiatric disorder studied (Brewerton et al. 1992; Kahn and Wetzler 1991; Murphy et al. 1996; Murphy et al. 1991). Based on studies of second messenger system effects, antagonist profiles, and cross-tolerance investigations with 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C} agonists, the effects of m-CPP on prolactin, CRH/ACTH/cortisol, body temperature, as well as anorectic, anxiogenic, and other behavioral responses have most commonly been attributed to actions mediated by 5-HT_{2C} receptors, where m-CPP acts as a partial agonist (Aulakh et al. 1992; Calogero et al. 1993; Kennett et al. 1989; Mazzola-Pomietto et al. 1995).

Ipsapirone has shown anxiolytic effects in animal anxiety models (De Vry et al. 1991). It has been investigated in single-dose challenge paradigms to assess the physiological functions mediated by 5-HT_{1A} receptors in humans, and to evaluate whether the functional responsivity of the 5-HT_{1A} receptor complex might be altered in patients with neuropsychiatric disorders and following treatment of these disorders. The 5-HT_{1A} binding sites are predominantly located on serotonergic neurons in the raphe nuclei (presynaptic autoreceptors) and in limbic structures (postsynaptic receptors). Agonistic properties at presynaptic somatodendritic sites have been observed, resulting in decreased serotonergic neurotransmission (Peroutka 1985). At postsynaptic sites, ipsapirone acts as a partial agonist. Ipsapirone, given in doses of 0.1, 0.2, and 0.3 mg/kg to male volunteers, produced dose-dependent, statistically significant increases in plasma cortisol and ACTH at the two higher ipsapirone doses (Kahn et al. 1994; Lesch et al. 1989). Ipsapirone also induced dose-dependent reductions in body temperature without any effects on blood pressure, heart rate, or respiratory rate (Lesch et al. 1990; Lesch et al. 1989). Animal research has shown that acute or chronic motor activity does not affect 5-HT_{1A} receptor associated behavior in rats (Chaouloff 1994).

In the present study, we performed neuroendocrine challenges using m-CPP, ipsapirone, and placebo in marathon runners and healthy untrained controls to compare 5-HT_{2C} and 5-HT_{1A}-specific psychobehavioral and neuroendocrine response patterns. The fitness level of all subjects was verified by bicycle spiroergometry.

METHOD

Study Design

To compare the psychobehavioral and neuroendocrine effects of orally administered m-CPP (0.4 mg/kg), ipsapirone (0.3 mg/kg), and placebo, marathon runners and healthy volunteers participated in three challenge sessions, conducted in a randomized double-blind fashion on separate days.

Subjects

Twelve marathon runners and 12 healthy controls of comparable age and sex distribution were recruited by newspaper advertisements. The marathon runners were required to cover a weekly running distance of at least 60 km per week and to have practiced regular training habits for at least 2 years prior to the study. The inclusion criterion for the control subjects was abstinence from regular aerobic exercise for at least 2 years prior to the study. All subjects received financial compensation for their participation. The Structured Clinical Interview for *DSM-III-R* (SKID) revealed no evidence of a psychiatric disorder for any subject. None of the volunteers had a history of significant medical disorders, and all volunteers had a normal physical examination, electrocardiogram, and routine laboratory tests prior to inclusion in the study. All volunteers had to be drug-free for at least 3 weeks prior to and during testing. This was verified by urinary drug screening prior

to the first challenge. After the entire procedure had been explained, all participants gave written, informed consent. The trial was approved by the Ethics Committee of the Medical Faculty of the University of Göttingen. The marathon and the control group did not significantly differ from each other with respect to age (33.9 ± 6.7 vs. 33.45 ± 5.4 years), sex distribution (male/female: 9/3 vs. 6/6), weight (69.5 ± 10.8 vs. 70.7 ± 10.3 kg), and height (176.0 ± 6.9 vs. 174.2 ± 7.3 cm).

Challenge Procedures

There was an interval of at least 48 hours between two challenges. On the day of each challenge session, subjects arrived at the sleep laboratory of the Department of Psychiatry (University of Göttingen) at approximately 12:30 for a standardized meal. During the challenge sessions, subjects abstained from eating or sleeping and remained supine with the head elevated. The timing of recumbancy was equal for all subjects. At 13:00, an intravenous catheter was placed in an antecubital vein for repeated blood sampling. At 14:30, 2 to 4 capsules of either m-CPP (0.4 mg/kg), ipsapirone (0.3 mg/kg), or placebo were administered orally.

Behavioral effects were assessed using the Acute Panic Inventory (Dillon et al. 1987) and a modified version of the NIMH Self-Rating Scale (Murphy et al. 1989) that comprises 24 questions and defines six subscales of behavioral change: anxiety, activation-euphoria, altered self-reality, depressive affect, dysphoria, and functional deficit. Behavioral ratings were completed at 14:00, 14:30, 15:00, 15:30, 16:00, 16:30, 17:30, and 18:30. A summary measure of behavioral change (designated "total score on the NIMH scale"), defined by the combined scores for the anxiety, activation-euphoria, dysphoria, altered self-reality, depression, and functional deficit subscales, was included in the analysis to assess the over-all effect of each drug challenge on behavior.

Baseline blood samples were drawn at 14:00 and at 14:30 (immediately prior to medication intake), and serial blood draws were subsequently made at 15:00, 15:30, 16:00, 16:30, 17:30, and 18:30. Samples were immediately placed on ice, centrifuged within 15 min of collection, and the plasma was stored at −70°C until assay. Plasma samples were assayed for prolactin, cortisol, noradrenaline (NE), adrenaline, and plasma concentrations of m-CPP and ipsapirone. Throughout each challenge session, oral temperature as well as blood pressure and heart rate were measured at 30-min intervals.

Plasma concentrations of m-CPP were measured by high-performance liquid chromatography (HPLC) using a method described by Murphy and co-workers (Murphy et al. 1989). Ipsapirone was measured by HPLC and UV detection. Prolactin and cortisol were determined by enzyme-linked immunoassay (ELISA) (Immundiagnostica Enzyme Test™ Cortisol, No 1288946, and Prolactin, No 1448609. Boehringer-Mannheim); the interassay variability was 6.5 to 7.5% for prolactin and 6.2 to 7.9% for cortisol. NE and adrenaline were measured by HPLC as previously described (Pirke et al. 1985); the average interassay variability was 6.2% for NE and 8.4% for adrenaline. Urine samples were screened for benzodiazepines by EMIT.

Bicycle Spiroergometry

An incremental bicycle spiroergometry was performed by all subjects on a Bosch ERG 551 bicycle ergometer. Their workload was increased every 3 min until subjective exhaustion. The starting load ranged between 50 and 100 watts, depending upon body weight, sex, and age; that is, subjects with lower body weight (which usually means lower leg muscle strength) and higher age were started with 50 watts only. The increment was 25 or 50 watts according to the criteria mentioned. Capillary blood samples were taken from the right earlobe in the resting state and during the last 10 s of each stage. Exspiratory air was collected using a standardized Douglas-bag sampling method during the last min of each working stage. Lactate measurements were done enzyme-photometrically. Peak power output (P_{max}), physical work capacity at a heart rate of 150/min (PWC 150), and maximal oxygen consumption (V_{O2max}), heart rate (HR), vital capacity (VC), and maximal heart rate (HR_{max}) were determined using standard procedures. For each stage, subjects were asked to rate the degree of their perceived exertion (RPE) by means of the Borg Scale (Borg and Noble 1974). A physician was present during the entire procedure. There was a minimum of at least 48 hours between spiroergometry and a neuroendocrine challenge.

Data Analysis

The maximal increase of all parameters (maximal decrease for temperature) were used as the primary response criteria. It was calculated individually using the greatest positive difference between the baseline value and each of the following six time points. The maximal increase of psychobehavioral and hormonal parameters following the administration of m-CPP, ipsapirone or placebo was calculated and compared with the Wilcoxon–Mann–Whitney U-test between marathon athletes and controls. For temperature changes after administration of ipsapirone, maximal decreases of temperature were used. In addition, data were also examined using a three-factor repeated measures analysis of variance model (ANOVA). The first repeated factor, drug challenge, was defined by two pharmacological challenges given to subjects on different days: m-CPP/placebo or ipsapirone/placebo. The second repeated factor, time, was defined by baseline followed by six

postbaseline time points. These time points were selected on the basis of findings from earlier studies in which m-CPP was administered orally (Murphy et al. 1989). The third factor, group, was defined by the marathon and the control group. A conventional univariate repeated measures approach was taken to investigate the main effects of drug challenge, time, group and the following interactions: drug challenge × time, drug challenge × group, and drug challenge × time × group.

Post hoc analyses were only performed in the case of significant main effects of drug challenge, group, and the interactions mentioned above. If the main effect of drug challenge or the interaction of drug challenge and time were significant, further analysis was done comparing changes from baseline after drug intake with those after placebo for each time point separately. If the main effect of group or the interaction of group and drug challenge was significant, further analysis was done comparing changes from baseline after drug intake in marathon runners with those in controls for each time point separately. A p-value of less than 0.05 was interpreted as significant for the main effects and all further analysis. Regarding the main effects and the interaction, p-values were adjusted using the Greenhouse–Geisser correction (Greenhouse and Geisser 1959) provided that the responding epsilon was less than 1.

The baseline values for all psychobehavioral and neuroendocrine data on the 3 challenge days were used to calculate a mean baseline value for every subject. In a second step, these means were used to compare baseline variables in the athlete and the control group by exact Wilcoxon analysis; p-values were adjusted by the Bonferroni–Holm method. Comparisons for the spiroergometric data were performed by the exact version of the Wilcoxon–Mann–Whitney U-test. Categorial data were compared with Fisher's Exact Test. Two-tailed tests were used throughout. All statistical analyses were done using SAS 6.11 software (SAS 1989).

RESULTS

Spiroergometry

Table 1 shows the results from spiroergometric testing in the athlete and the control group. As expected, there were highly significant differences in all measures of aerobic fitness when marathon runners were compared to untrained controls. There were no statistical differences between the two groups as regards vital capacity, maximal heart rate, respiratory exchange ratio (at baseline and at maximum power output), and self-rated perceived exertion.

Table 1. Measures of Spiroergometric Performance in Marathon Runners and Untrained Healthy Controls

	Marathon Runners (n = 12)	Control Subjects (n = 12)	p-value
V_{O2max} (ml per min × kg body weight)	55.6 ± 8.2	36.2 ± 6.7	<.001
P_{max}/kg (watts per kg body weight)	4.71 ± 0.69	2.79 ± 0.56	<.001
PWC_{150}/kg (watts at heart rate 150/min./kg)	2.95 ± 0.55	1.65 ± 0.53	<.001
$P_{Lac4/kg}$ (watts at 4 mmol lactate/kg)	3.27 ± 0.52	2.01 ± 0.47	<.001
VC (liters)	5.22 ± 0.21	4.7 ± 0.67	ns
HR_{max} (heart rate per minute)	186.2 ± 13.1	185.8 ± 9.8	ns
$RER_{baseline}$ (respiratory exchange ratio)	0.81 ± 0.07	0.87 ± 0.01	ns
RER_{max} (max. respiratory exchange ratio)	1.08 ± 0.04	1.08 ± 0.06	ns
Lac_{max} (mmol/l)	12.4 ± 2.1	9.59 ± 2.6	<.012
RPE_{max} (perceived exertion)	19.0 ± 1.9	18.9 ± 1.7	ns

Data (mean ± SD) were compared by exact Wilcoxon analysis (two-tailed test).

Table 2. Baseline Psychobehavioral and Neuroendocrine Variables in Marathon Runners (n = 12) and Healthy Controls (n = 12)

	Marathon Runners (mean, SD)	Control Subjects (mean, SD)	p value
Acute panic inventory (Score)	0.25 (20)	0.14 (0.2)	ns
NIMH scale (Score)			
Activation	0.28 (0.40)	0.03 (0.1)	.088
Altered self-reality	0.08 (0.21)	0.05 (0.2)	ns
Anxiety	0.11 (0.03)	0.15 (0.4)	ns
Depression	0.03 (0.09)	0.01 (0.1)	ns
Dysphoria	0.06 (0.12)	0.08 (0.2)	ns
Functional deficit	0.19 (0.30)	0.05 (0.2)	ns
Hormones			
Cortisol (μg/dl)	7.67 (2.11)	8.71 (4.7)	ns
Prolactin (μU/ml)	116.3 (46.8)	206.8 (83.5)	.01
NA (ng/l)	216.25 (70.49)	218.9 (84.0)	ns
Adrenaline (ng/l)	32.73 (23.5)	27.5 (14.7)	.071
Temperature (°C)	36.52 (0.27)	36.73 (0.27)	.054

Data are given as mean (SD) and were compared by exact Wilcoxon analysis (two-tailed test).

Comparison of Psychobehavioral and Neuroendocrine Variables at Baseline

Table 2 shows mean baseline values for behavioral, temperature, and hormonal data calculated from the baseline parameters of the three challenge tests. In comparison with controls, the plasma level of prolactin was significantly decreased in marathon runners. There was also a statistical trend toward decreased temperature and an increased activation score at baseline in the marathon group. All other behavioral and neuroendocrine data did not differ between marathon runners and controls at baseline.

Psychobehavioral Response to m-CPP and Ipsapirone

Figure 1 illustrates the maximum increase in self-rated measures of anxiety (API) and the sum score of the NIMH Rating Scale following the administration of ipsapirone, m-CPP, and placebo. In summary, the behavioral response to ipsapirone and m-CPP was not significantly different between marathon runners and controls. After administration of m-CPP, the ANOVA did not reveal any significant main effects for the behavioral ratings as measured by the sum score of the NIMH Rating Scale or the API in marathon athletes or controls. In contrast, after administration of ipsapirone, there were significant effects for drug challenge (F = 13.31; df = 1,21; p = .0015), time (F = 11.62; df = 6,126; p = .0005), and the interaction of drug challenge with time (F = 9.66; df = 6,126; p = .0015). The ANOVA did not reveal any significant main effects for group or for the interactions (drug challenge × group, and drug challenge × time × group).

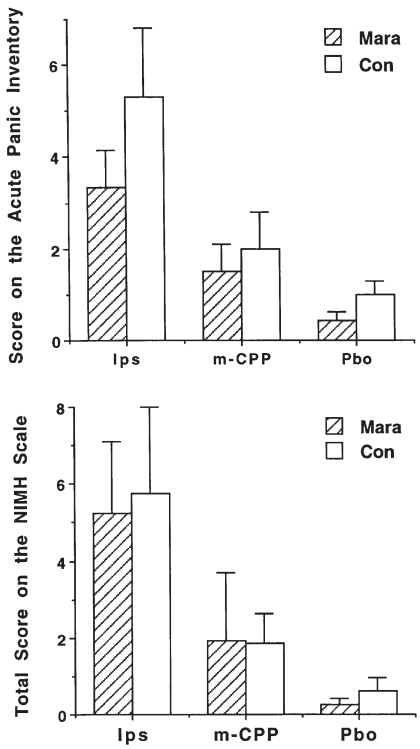

Figure 1. Maximum increase in self-rated measures of anxiety (Acute Panic Inventory) and the sum score of the NIMH Rating Scale in marathon runners (Mara, n = 12) and healthy controls (Con, n = 12) following the administration of ipsapirone, m-CPP, and placebo. Comparisons between marathon runners and controls were done by with the Wilcoxon–Mann-Whitney test. No significant differences were found between the groups.

Neuroendocrine and Body Temperature Changes

The mean maximal changes in hormone concentrations were compared between marathon runners and controls by the exact Wilcoxon–Mann–Whitney U-test. As Figure 2 illustrates, the m-CPP-induced maximal cortisol response was significantly lower in the athlete group as compared to the controls ($p = .006$). There was also a statistical trend toward a blunted prolactin response in the marathon group ($p = .089$). All other hormonal responses following m-CPP, ipsapirone, or placebo were not significantly different between the marathon and the control group.

In Figure 3, the mean changes in plasma concentrations of cortisol between baseline and selected post-baseline time points are compared graphically for drug challenges using m-CPP, ipsapirone, or placebo. After administration of m-CPP, the ANOVA revealed significant effects for drug challenge (F = 15.72; df = 1,22; $p = .0007$), time (F = 2.9; df = 6,132; $p = .0109$), and the interaction of drug challenge with time (F = 5.95; df = 6,132; $p = .0001$). There was a statistical trend for the interaction of drug challenge and group (F = 3.07; df = 1,22; $p = .093$). In controls, plasma cortisol levels were significantly increased 180 min and 240 min after administration of m-CPP. In contrast, no significant increases or plasma cortisol levels were observed in the marathon group when the m-CPP challenge was compared to the placebo condition (Figure 3, upper part).

After administration of ipsapirone, the ANOVA revealed significant effects for drug challenge (F = 31.14; df = 1,20; $p = .0001$), time (F = 5.26; df = 6,120; $p = .0109$) and the interaction of drug challenge with time (F = 17.29; df = 6,120; $p = .0001$). The ANOVA did not reveal any significant main effects for group, for the interaction of drug challenge with group (F = 0.18; df = 1,20; p .68), or for the interaction of drug challenge × time × group. In comparison to placebo, plasma cortisol levels were significantly increased 90, 120, 180, and 240 min after administration of ipsapirone in both the marathon and the control group (Figure 3, lower part).

Figure 4 (upper part) shows the time-course of plasma prolactin following the administration of m-CPP and placebo, and the time-course of temperature following the administration of ipsapirone and placebo. After administration of m-CPP, the ANOVA revealed significant effects for group (F = 12.06; df = 1,21; $p = .0023$), drug challenge (F = 14.56; df = 1,21; $p = .0010$), time (F = 17.98; df = 6,126; $p = .0001$), the interaction of drug challenge with time (F = 17.20; df = 6,126; $p = .0001$), and the interaction of group, drug challenge,

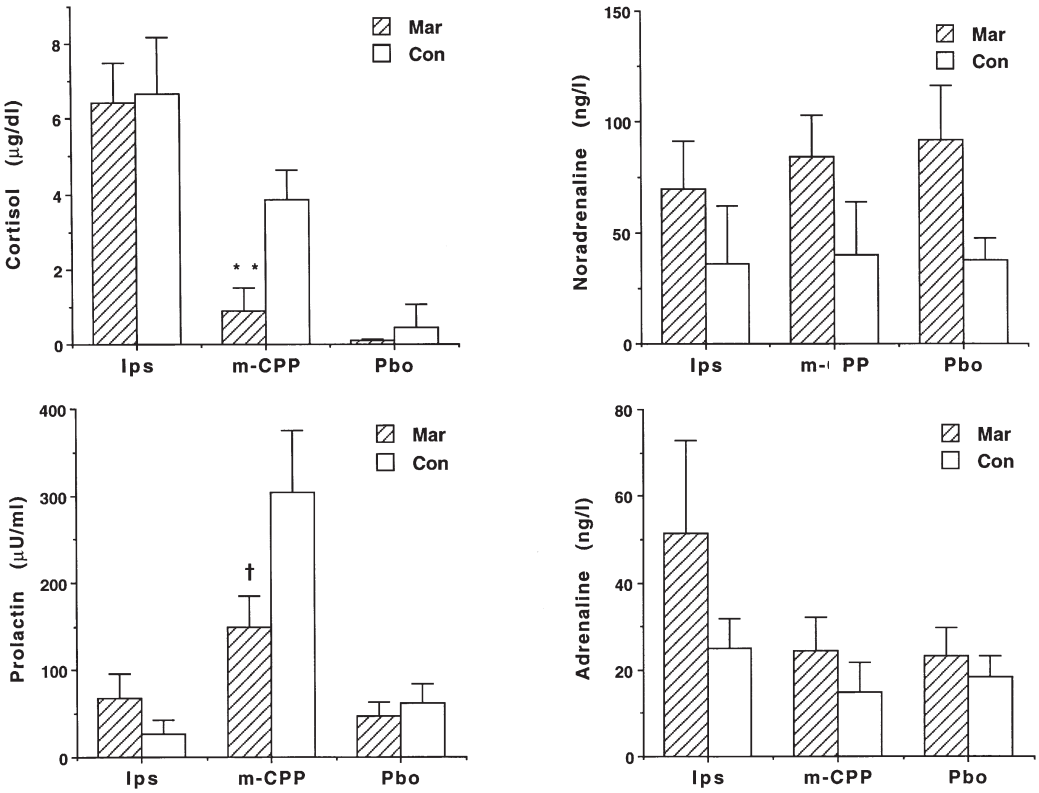

Figure 2. Maximum increase of plasma cortisol, prolactin, norepinephrine, and adrenaline in marathon runners (Mara, $n = 12$) and healthy controls (Con, $n = 12$) following the administration of ipsapirone, m-CPP, and placebo. Comparisons between marathon runners and controls were done with the Wilcoxon–Mann-Whitney test. *$p < .05$; **$p < .01$; † trend ($p = .089$).

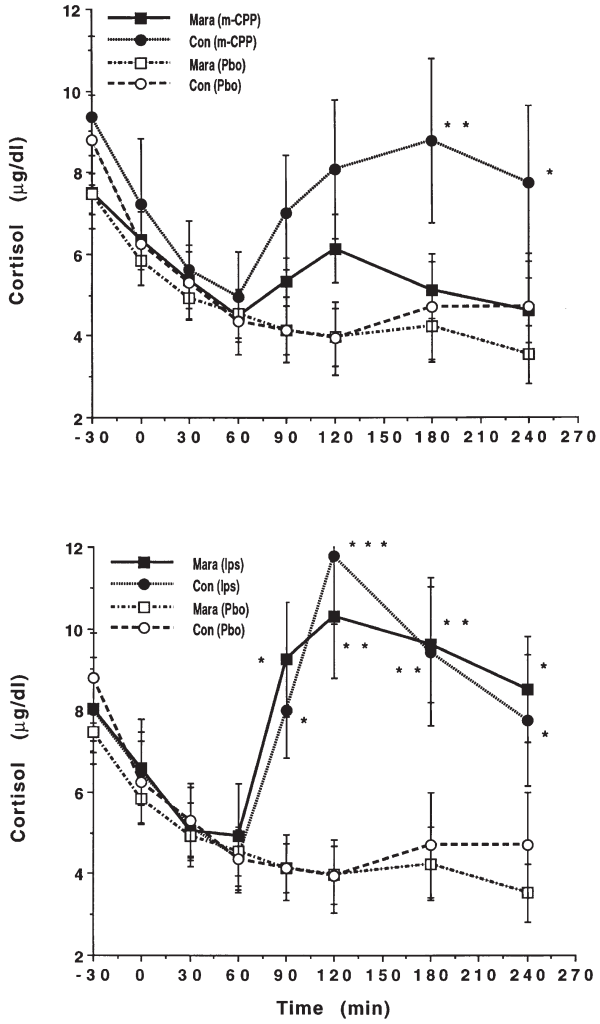

Figure 3. Time course of plasma cortisol in marathon runners (Mara, $n = 12$) and healthy controls (Con, $n = 12$) following the administration of m-CPP (upper part), ipsapirone (lower part), and placebo (upper and lower part). Drugs were administered at time point = 0 min. Comparisons were done by ANOVA: *ipsapirone or m-CPP vs. placebo, $p < .05$; **$p < .01$; ***$p < .001$).

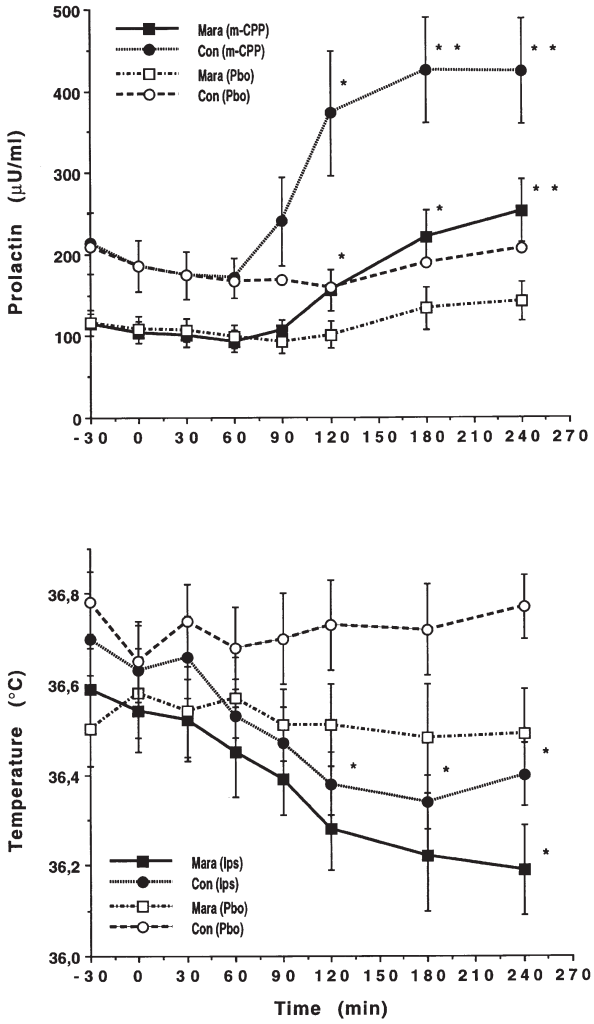

Figure 4. Time course of plasma prolactin following the administration of m-CPP and placebo and time course of temperature following the administration of ipsapirone and placebo in marathon runners (Mara, $n = 12$) healthy controls (Con, $n = 12$). Drugs were administered at time point = 0 min. Comparisons were done by ANOVA: *ipsapirone or m-CPP vs. placebo, $p < .05$; **$p < .01$). Prolactin levels were significantly higher in controls at all time points when compared to the marathon group (not indicated by asterisks).

and time (F = 3.7; df = 1,26; $p = .002$). In comparison to placebo, plasma prolactin levels were significantly increased 120, 180, and 240 min after administration of m-CPP in both the marathon and the control group. In addition, prolactin levels were significantly higher in controls at all time points as compared to the marathon group.

Figure 4 (lower part) shows the time-course of temperature following the administration of ipsapirone and placebo. After administration of ipsapirone, the ANOVA revealed significant effects for drug challenge (F = 27.08; df = 1,19; $p = .0001$), time (F = 12.37; df = 6,114; $p = .0001$), and the interaction of drug challenge with time (F = 6.42; df = 6,114; $p = .0001$). The ANOVA did not show any significant main effects for group, for the interaction of drug challenge with group, or for the interaction of drug challenge with time and group. In comparison to placebo, temperature was significantly reduced 120, 180, and 240 min after administration of ipsapirone in the control group; in marathon runners a significant reduction of body temperature was only observed 240 min after administration of ipsapirone (Figure 4).

Plasma Concentrations of m-CPP and Ipsapirone

Plasma concentrations of m-CPP and ipsapirone were measured across the challenge procedure. Maximum plasma m-CPP concentrations were observed 90 min after administration of the capsule both in marathon runners (25.54 ± 22.1 ng/ml) and in controls (19.3 ± 11.0 ng/ml). Ipsapirone reached its maximum plasma concentration 60 min after drug intake in the marathon group (27.94 ± 12.3 μg/l) and in the control group (38.81 ± 23.7 μg/l). ANOVA did not reveal any significant differences in plasma concentrations of m-CPP or ipsapirone between marathon runners and controls.

DISCUSSION

The major finding of this study is a significantly reduced cortisol response and a blunted prolactin response after administration of m-CPP in marathon runners. In contrast, ipsapirone induced a significant increase of cortisol of the same magnitude in both the marathon and the control group. Because other studies using various 5-HT antagonists have consistently shown that the effects of m-CPP on prolactin, CRH, ACTH, and cortisol are predominantly mediated by 5-HT_{2C} receptors (Aulakh et al. 1992; Calogero et al. 1993; Mazzola-Pomietto et al. 1995; Murphy et al. 1991; Pigott et al. 1993; Seibyl et al. 1991), our results are in agreement with the hypothesis that regular endurance training leads to a downregulation of central 5-HT_{2C} receptors. This conclusion is supported by the attenuated prolactin response in the marathon group, which is also mediated mainly by postsynaptic 5-HT_{2C} receptors (Aulakh et al. 1992; Murphy et al. 1991). Ipsapirone induces cortisol secretion via increased ACTH release and not by direct action on the adrenal gland (Przegalinski et al. 1989). The solid cortisol response after administration of ipsapirone in both groups does not support the assumption that the secretion of cortisol in marathon runners is impaired by peripheral adaptations on the pituitary–adrenal level.

The results from the three-factorial ANOVA show that a 0.4 mg/kg dose of m-CPP, which is 20% lower than in most other oral m-CPP studies, still elicits a significant neuroendocrine response as compared to placebo conditions. Analyses that include all time points can mask differences in maximal response that may occur at different time points. This might explain why the interaction of group with drug challenge and time was not significant for cortisol in the three-factorial ANOVA. Nevertheless, our results still must be interpreted with care.

Regular exercise might be associated with adaptive changes on the hypothalamic level. Acute exercise is known to be a strong stimulus for the secretion of ACTH and cortisol (Luger et al. 1987; Oleshansky et al. 1990), and trained subjects show less activation of the hypothalamic–pituitary-adrenal axis as compared with untrained subjects at matched absolute workloads (Luger et al. 1987). An increase of basal ACTH and a diminished ACTH response to ovine corticotropin-releasing hormone (CRH) in highly trained runners has also been reported (Luger et al. 1987). In contrast, basal cortisol and ACTH levels were indistinguishable between elderly endurance athletes and sedentary controls, but cortisol responses to human CRH were significantly increased in the athlete group, and ACTH responses tended to be higher in this group (Heuser et al. 1991). These results show, that long-distance running does not lead to a decreased sensitivity for CRH on the pituitary–adrenal level.

M-CPP's effect on cortisol secretion seems to be directly related to CRH release from the nucleus paraventricularis, because it is suppressed in rats by pretreatment with anti-CRH rabbit serum (Calogero et al. 1990). M-CPP-induced cortisol release can also be blocked by dexamethasone and thus has been interpreted to result from increased ACTH release rather than being a primary adrenal action of m-CPP (Calogero et al. 1990). Because the nucleus paraventricularis receives neuronal inputs from various neurotransmitter systems including serotonergic pathways, the postulated downregulation of 5-HT_{2C} receptors by intensive endurance training might occur on the level of CRH secreting neurons or "above" the nucleus paraventricularis. In the same experiment, the cortisol response of the 5-HT_{1A} agonist 8-OH-DPAT was not completely blocked after pretreatment with anti-CRH rabbit serum or dexamethasone. It was concluded that 5-HT_{1A} agonists may also act at the pituitary level to stimulate ACTH release in vivo.

In both groups, oral administration of m-CPP in a dose of 0.4 mg/kg did not induce any significant behavioral effects. Eight out of 12 subjects did not notice any somatic or psychological symptoms during the m-CPP challenge. Presumably, we think that this dose of m-CPP might have been too low to detect subtle differences in serotonergic responsiveness as related to behavioral endpoints. In patients with panic disorder, the same oral dose of m-CPP led to marked sensations of anxiety, activation, altered self-reality, depression, dysphoria, and subjective functional deficit, and more than half of the patients experienced panic attacks or acute anxiety very similar to panic attacks (Broocks et al. 1998b). At the same time, patients with panic disorder are characterized by exercise avoidance and markedly reduced aerobic fitness (Broocks et al. 1997; Martinsen et al. 1989; Miyakoda et al. 1990; Roth 1989; Roth et al. 1986; Taylor et al. 1987). Abstinence from exercise seems to be a clinically relevant component of the phobic avoidance behavior. We have recently shown that aerobic exercise leads to significant clinical improve-

ment in patients with panic disorder (Broocks et al. 1998a). However, so far no clinical studies show that an exercise-induced remission of anxiety symptoms is associated with changes in serotonergic responsiveness. The results of the present study would support the assumption that exercise-induced downregulation of 5-HT_{2C} receptors could play an important role in mediating the anxiolytic and antidepressive effects of exercise. This hypothesis is also in keeping with observations from animal studies that periods of acute motor activity are associated with an increased turnover of serotonin in the mediobasal hypothalamus (Broocks et al. 1991). Similar to the action of serotonin reuptake inhibitors, repeated episodes of serotonergic stimulation could induce postsynaptic changes leading to decreased sensitivity for pharmacological or physiological serotonergic inputs.

The observation that responses to ipsapirone were not altered by long-distance running is in agreement with data from animal studies. Typical behaviors in rats such as "flat body posture, forepaw treading, and hyperphagia," which can be induced by 5-HT_{1A} receptor agonists, were not affected by training and/or acute exercise (Chaouloff 1994). On the other hand, it has been shown that administration of the 5-HT_{2A} receptor blocker ketanserin prevents exercise-elicited prolactin release (de Meirleir et al. 1985). This result suggests that exercise actually triggers 5-HT release and stimulation of those 5-HT_{2A} receptors controlling prolactin release. A clear-cut conclusion is difficult to draw, because it is not known whether ketanserin, at the doses used, affects only 5-HT_{2A} receptors. Two animal studies have reported that 5-HT_{2A}/5 HT_{2C} receptor blockade delayed the onset of exhaustion (Bailey et al. 1993a; Bailey et al. 1993b). In contrast, 5-HT_{2A}/5 HT_{2C} receptor stimulation increased treadmill fatigue (Bailey et al. 1992; Bailey et al. 1993b; Davis et al. 1993). On the other hand, downregulation of these subreceptors could well contribute to the delayed onset of fatigue after regular training. Semistarvation-induced hyperactivity in rats was inhibited by 5-HT_{2C} agonists and by alpha 2-adrenoceptor agonists (Wilckens et al. 1992). Taken together, these findings support the involvement of 5-HT_{2A} and 5-HT_{2C} receptors in the control of endurance.

Other monoaminergic neurotransmitter systems are also affected by chronic exercise. In the cerebrospinal fluid of depressed patients, concentrations of the serotonin metabolite 5-HIAA and the norepinephrine metabolite vanillylmandelic acid (VMA) were significantly higher after 4 hours of hyperactivity than in the same patients after bed rest (Post et al. 1973). Also, urinary and CSF MHPG was significantly higher during a day of increased motor activity in comparison with a day with usual ward activities in depressed patients (Beckmann et al. 1979). Semistarvation-induced hyperactivity was associated with highly significant increases in noradrenaline turnover as estimated by the main metabolite MHPG in the mediobasal hypothalamus of rats (Broocks et al. 1990). Other studies using chronic activity wheel running confirmed increased tissue concentration of 5-HT and NE at rest (Broocks et al. 1990; Broocks et al. 1991; Dishman 1997; Dunn et al. 1996). A protective effect of exercise against NE depletion in locus coeruleus cell bodies after footshock was also reported (Dishman 1997; Dunn et al. 1996). The concomitant reduction in escape latency was interpreted as consistent with an antidepressant effect. Wheel running also decreased the density of $GABA_A$ receptors in the corpus striatum while increasing open-field locomotion, consistent with an anxiolytic effect (Dishman 1997). Tyrosin hydroxylase activity has been shown to increase in the caudate of rats trained by voluntary running (Morgan et al. 1984). After a 12-week protocol of daily treadmill running, a significantly higher density of dopamine-2 receptors as labeled with (3H)-spiperone was found in the striatum of rats (Gilliam et al. 1984; MacRae et al. 1987). In humans, an increase of β-endorphin has been observed after strenuous aerobic exercise (Krüger and Wildmann 1986; Wildmann et al. 1986), and regular training potentiated the secretion of β-endorphin (Carr et al. 1981). However, improvements of mood did not correlate with the increase of plasma β-endorphin (Farrel 1982). Naloxon antagonized the exercise-induced lowering of pain threshold but had only a very limited effect on exercise-induced psychological changes (Janal et al. 1984; Markoff et al. 1982). Also, the blood–brain barrier is relatively impermeable to pituitary β-endorphin (Kalin et al. 1985).

At baseline, plasma levels of cortisol, adrenaline, and NE were not significantly different between the two groups. However, marathon runners had significantly lower mean plasma concentrations of prolactin in comparison with the untrained controls. This could be explained by the lower number of female subjects in the marathon group, because prolactin levels are generally lower in males (Murphy et al. 1989). However, it could also be shown, that the prolactin response to m-CPP does not differ in males and females (Murphy et al. 1989). Nevertheless, the unbalanced sex ratio is a clear methodological weakness of our study. Although female subjects did not undergo neuroendocrine testing during or 1 week before menstruation, they were not tested at corresponding stages of the menstrual cycle. This could also have had some influence on our results.

Data from the bicycle spiroergometry demonstrate that this sample of marathon runners, in fact, represented a very high fitness group. Athletes and controls performed the bicycle test with a comparable degree of exertion, which can be inferred from the fact that maximal heart rate, subjective ratings of exertion, and the respiratory exchange rate did not differ between the groups. Our results cannot answer the question of

whether moderate exercise will also alter 5-HT_{2C} receptor-related functions.

In conclusion, regular long-distance running seems to be associated with a significantly decreased cortisol—and possibly prolactin—response to m-CPP. In contrast, marathon athletes and untrained controls did not differ in their behavioral, hormonal, and temperature response to the administration of ipsapirone. In a recent meta-analysis on serotonergic agonists as indices of the functional status of central serotonin neurotransmission in humans (Murphy et al. 1996), six out of 13 studies showed a divergence of neuroendocrine and psychobehavioral responses to m-CPP. As a consequence, we should be careful to interpret altered neuroendocrine response measures alone as an indicator of an ubiquitous up- or downregulation of serotonergic receptors. Nevertheless, the fact remains that the neuroendocrine response to m-CPP seems to be affected by the degree of aerobic fitness when cortisol (and possibly prolactin) is used as endpoint measure. Exercise-induced downregulation of 5-HT_{2C} receptors in certain brain areas could be related to the anxiolytic and antidepressant effects of exercise.

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