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Lower Baseline Plasma Cortisol and Prolactin together with Increased Body Temperature and Higher mCPP-Induced Cortisol Responses in Men with Pedophilia

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There is some evidence that hormonal and serotonergic alterations may play a role in the pathophysiology of paraphilias. The aims of the present study were to examine: 1) baseline plasma cortisol, plasma prolactin, and body temperature; and 2) cortisol, prolactin, body temperature, as well as behavioral responses to meta-chlorophenylpiperazine (mCPP) and placebo in pedophiles and normal men. Pedophiles showed significantly lower baseline plasma cortisol and prolactin concentrations and a higher body temperature than normal volunteers. The mCPP-induced cortisol responses were significantly greater in pedophiles than in normal volunteers. In normal volunteers, mCPP-induced a hyperthermic response, whereas in pedophiles no such response was observed. mCPP induced different behavioral responses in pedophiles than in normal men. In pedophiles, but not in normal men, mCPP increased the sensations "feeling dizzy," "restless," and "strange" and decreased the sensation "feeling hungry". The results suggest that there are several serotonergic disturbances in pedophiles. It is hypothesized that the results are compatible with a decreased activity of the serotonergic presynaptic neuron and a 5-HT2 postsynaptic receptor hyperresponsivity.

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The sexual abuse of children (pedophilia) represents a significant proportion of about 25% of all sexual offences (Moller and Bier-Weiss 1995). Between 100,000 and 500,000 children in the United States are thought to be sexually molested annually (Fuller 1989). Pedophilia is one of the sexual deviation disorders or paraphilias, which are diagnosable psychiatric syndromes characterized by recurrent fantasies about deviant sex, intense associated cravings, and stereotypic behavioral responses (Berlin and Meinecke 1981). The DSM-IV (APA 1994) describes the paraphilias as an impulse control disorder (ICD)(Cosyns 1999). Indeed, patients with paraphilias experience tension or arousal before committing the sexual act, experience pleasure during the act and feel a release of tension after the act (Cosyns

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1999). Pedophiles use varying degrees of persuasion, coercion, and physical force in their sexual assaults (sexual aggression), which may cause damage to the physical integrity of the victim (sexual violence) (Greenberg et al. 1996).

Although there is a substantial evidence in the historical and anthropological record of pedophilia, there has been little research on the biological pathophysiology of pedophilia. Alterations in the metabolism of serotonin (5-HT) may play a role in the pathophysiology of paraphilias (Kafka 1997). 1) 5-HT is involved in male sexual behavior; 2) serotonergic agents, such as selective 5-HT reuptake inhibitors (SSRIs), can ameliorate paraphilic sexual behaviour (review: Balon 1998; Greenberg et al. 1996; Zonana and Norko 1999); and 3) there is an extensive number of clinical and animal studies supporting the hypothesis that a dysfunction of the 5-HT neurotransmitter system is an important factor in the underlying pathology of impulse control disorders (ICD) and aggression/violence (Linnoila et al. 1983; Markowitz and Coccaro 1995; Kavoussi et al. 1997; McElroy et al. 1995; Coccaro 1999).

A number of studies report lower CSF 5-hydroxyindole-acetic acid (5-HIAA) in ICD and aggressive patients, such as impulsive offenders and fire setters (review: Virkkunen et al. 1989; Coccaro 1999). The prolactin responses induced by D-L-fenfluramine (an indirect 5-HT agonist which releases 5-HT) are significantly and inversely related with measurements of aggression (Coccaro et al. 1989; O'Keane et al. 1992). Several authors found inverse relationships between platelet 5-HT transporter binding and impulsivity/aggression (Simeon et al. 1992; Coccaro et al. 1996). Patients with episodic aggression show a significantly lower platelet [^{3}H]-5-HT uptake than controls (Brown et al. 1989).

Coccaro et al. (1997) described a positive correlation between the number of platelet 5-HT2A receptor sites and measures of aggression, in personality-disordered patients. Tryptophan depletion in subjects with preexisting aggressive traits induces increased aggression (Cleare and Bond 1995). The prolactin responses to buspirone, a 5-HT1A agonist, are reduced in violent compared to nonviolent parolees (Cherek et al. 1999). Thus, dysfunctions of the 5-HT neurotransmitter system may be related to the pathophysiology of ICDs, aggression and violence.

However, no research has examined the sensitivity of central serotonergic postsynaptic receptors in pedophiles using direct 5-HT agonists, such as m-chlorophenylpiperazine (mCPP). mCPP, the major metabolite of trazodone, is one of the most widely used 5-HT challenge agents in psychiatric research (Kahn et al. 1992; Maes and Meltzer 1996). mCPP rapidly crosses the blood brain barrier and has an affinity for multiple 5-HT receptor sites, e.g., 5-HT1A, 5-HT1D, 5-HT2A, and 5-HT2C (Hamik and Peroutka 1989; Kahn and Wetzler 1991) but binds most potently at the 5-HT2C site (Schoeffter and Hoyer 1989). mCPP increases prolactin, adrenocorticotropic hormone (ACTH), and corticosterone/cortisol in rodents, monkeys, and humans (Fuller 1981; Aloi et al. 1984; Yatham and Steiner 1993; Meltzer and Maes 1995). These effects are probably mediated through postsynaptic 5-HT1A and 5-HT2A/5-HT2C receptors (Meltzer and Maes 1995). mCPP administration increases body temperature (Murphy et al. 1989). These effects are probably mediated through 5-HT2 receptors, because stimulation of 5-HT1A receptors in man and rodents causes hypothermia (Gudelsky et al. 1986; Lesch et al. 1990), whereas stimulation of 5-HT2 receptors induces hyperthermic effects (Gudelsky et al. 1986).

Some other studies suggested an inverse relationship between the activity of the hypothalamic-pituitary-adrenal (HPA) axis and aggression. Thus, aggressive antisocial subjects had a significantly lower excretion of urinary free cortisol and lower CSF adrenocorticotropin hormone concentrations (ACTH) than controls (Virkkunen 1985; Virkkunen et al. 1994).

The aims of the present study were to examine: 1) mCPP-induced cortisol, prolactin, body temperature, and behavioral responses; and 2) baseline serum cortisol and prolactin concentrations as well as body temperature in pedophiles versus normal controls.

SUBJECTS AND METHODS

Subjects

Nineteen male subjects participated in this study, i.e., 11 normal volunteers and eight pedophiles. The patients were tested as part of an intake into a voluntary outpatient sex offender treatment program. Strict DSM-IV (American Psychiatric Association 1994) pedophilic disorder criteria were used to make the diagnosis of pedophilia (involving girl and/or boy victims). All subjects were evaluated by physical and clinical investigations (e.g., blood determinations such as sedimentation rate, serum electrolytes; thyroid function tests, such as assay of thyroid secreting hormone; renal and liver function tests; radiograph of heart and lungs; and ECG) to exclude subjects with any medical illnesses. All subjects were free of any medical drugs for at least two months prior to blood sampling. No one was a regular drinker or had ever been taking illegal or major psychotropic drugs, such as antidepressants and antipsychotic agents.

Patients and normal volunteers were screened for present, past, and family history of mental disorder by means of the structured interview according to the DSM-III-R. Normal volunteers with current or past history of psychiatric disorder and those with family history in first degree relatives were excluded from this study. Consequently, one subject was excluded from this study. We excluded patients with other axis-I diagnoses beside paraphilia, such as major depression, anxiety disorders, including obsessive compulsive disorder,

psychosis, organic mental disorder, and substance use disorder.

The description of the study samples is as follows: the mean (±SD) age of the normal controls is 32.5 (± 8.2) years and that of pedophiles 36.0 (±19.7) years ($F = 0.3$, $df = 1/17$, $p = .6$). Body mass index (BMI), i.e., body weight in kg/body length in m^2, of the normal controls is 25.0 (±2.5) and in pedophiles 26.3 (±4.7) ($F = 0.7$, $df = 1/16$, $p = .6$). Three of the pedophiles also suffered from other paraphilias NOS; two of these pedophiles showed a personality disorder NOS, i.e., the first showed features of avoidant, dependent and borderline personality, and the second showed features of dependent and narcissistic personality. The remaining patients had no axis-II diagnoses.

Methods

Each subject was tested on two occasions, i.e., on Day 1, the placebo condition and on Day 2, the mCPP condition. The pedophile outpatients and normal men arrived at the Clinical Research Center (CRC) between 8:00 a.m and 8:10 a.m. After insertion of an intravenous cannula at 8:30 a.m., i.e., 45 min for baseline (or T-45), three blood samples were collected 15 min (T-30) and 45 min (T0) later. At T0 (immediately after the T0 blood collection) subjects received either a single oral dose of mCPP (0.5 mg/kg at Day 2) or indistinguishable placebo (at Day 1) in a single blind order. Thereafter, blood samples were obtained and tympanal temperature was measured at 30 min intervals over a three hour period (from T30 to T180). Blood was stored in plastic tubes at −70°C until thawed for plasma cortisol and prolactin (in all blood samples) and mCPP assays (in T30, T60, T90, T120, T150, and T180).

Behavioral effects were self-reported by means of a 15-item visual analogue scale (VAS), which was completed at baseline (T0), 90 min (T90), and 180 min (T180) later (Maes and Meltzer 1996). Table 2 shows the description of the 15 VAS items. This VAS scale and other VAS scales have repeatedly been employed in challenge neuroendocrine research in order to assess the behavioral effects of the challenge substance on an item-by-item basis (for example: Maes and Meltzer 1996). Subjects remained supine during the test period and they were not allowed to sleep, eat, or smoke. They wore street clothes during the study. The temperature in the experimental room was maintained at 22.0 ± 1.1°C.

Cortisol was assayed by means of a fluorescence immunoassay (Abbott NV, Diagnostic Division, Belgium) method with the TDx (Abbott NV). The sensitivity of the assay was 0.2 μg/dL. The cross-reactivity of this assay was: 11-deoxycortisol 9.9%; corticosterone 6.3%; cortisone 2.3%; and tetrahydrocortisol 1.1%. Prolactin was determined by means of an ELISA method (Abbott NV) on a IMx analyzer. The sensitivity of the assay was 0.60 ng/mL. Body temperature was monitored using an electronic thermometer (Vital Check Monitor 4200; IVAC, CA). Plasma mCPP was analyzed by an HPLC procedure as described previously (Suchow et al. 1996).

Detection was performed using an electrochemical detector instead of an UV detector. The oxidation potential of the detector was set at 1000 mV. The method enabled the analysis of mCPP at a sensitivity of 1 ng/mL plasma. The analytical intra-assay coefficient of variation (CV) was 5.2%, respectively.

Statistics

The independence of classification systems has been ascertained by means of analysis of contingence (χ^2-test). Relationships between variables were assessed by means of Pearson's product moment correlation coefficients. Group mean differences were assessed with analyses of variance (ANOVA). Repeated measure (RM) design ANOVAs (regression method) or analyses of covariance (ANCOVAs) were employed to examine the within-subject variability with the baseline (T0), post-placebo, and mCPP (labeled "drug" effects) values (from T30 to T180; labeled "time" factor) as time factors, the between-subject variability with the two diagnostic groups as factors, and two-way interactions between drug × diagnostic groups and time × diagnostic groups. Tests on simple effects were carried out in order to examine significant main effects or significant interaction patterns (Howell 1982). Comparisons among treatment means and diagnosis were carried out with the Dunn test (Howell 1982).

RESULTS

Baseline Cortisol, Prolactin, and Body Temperature

ANOVAs performed on the values obtained during the placebo day showed that plasma cortisol ($F = 7.2$, $df = 1/153$, $p = .0008$) and prolactin ($F = 5.5$, $df = 1/153$, $p = .002$) were significantly lower in patients than in controls, whereas body temperature was significantly ($F = 27.1$, $df = 1/153$, $p < 10^{-4}$) higher in pedophiles (36.22 ± 0.45°C) than in controls (35.81 ± 0.53°C) (see also Figures 1, 2, and 3 for the baseline concentrations).

mCPP-Induced Hormonal and Body Temperature Responses

Figure 1 shows the cortisol time-response curves in both normal controls and pedophiles both before and after mCPP administration. RM design ANOVA showed a significant effect of time ($F = 3.6$, $df = 6/221$, $p = .002$), a significant drug effect ($F = 62.0$, $df = 1/221$, $p < 10^{-4}$), a significant time × diagnostic group interaction ($F = 2.5$, $df = 6/221$, $p = .02$) and a significant drug × diagnostic group interaction ($F = 7.3$, $df = 1/221$, $p = .007$).

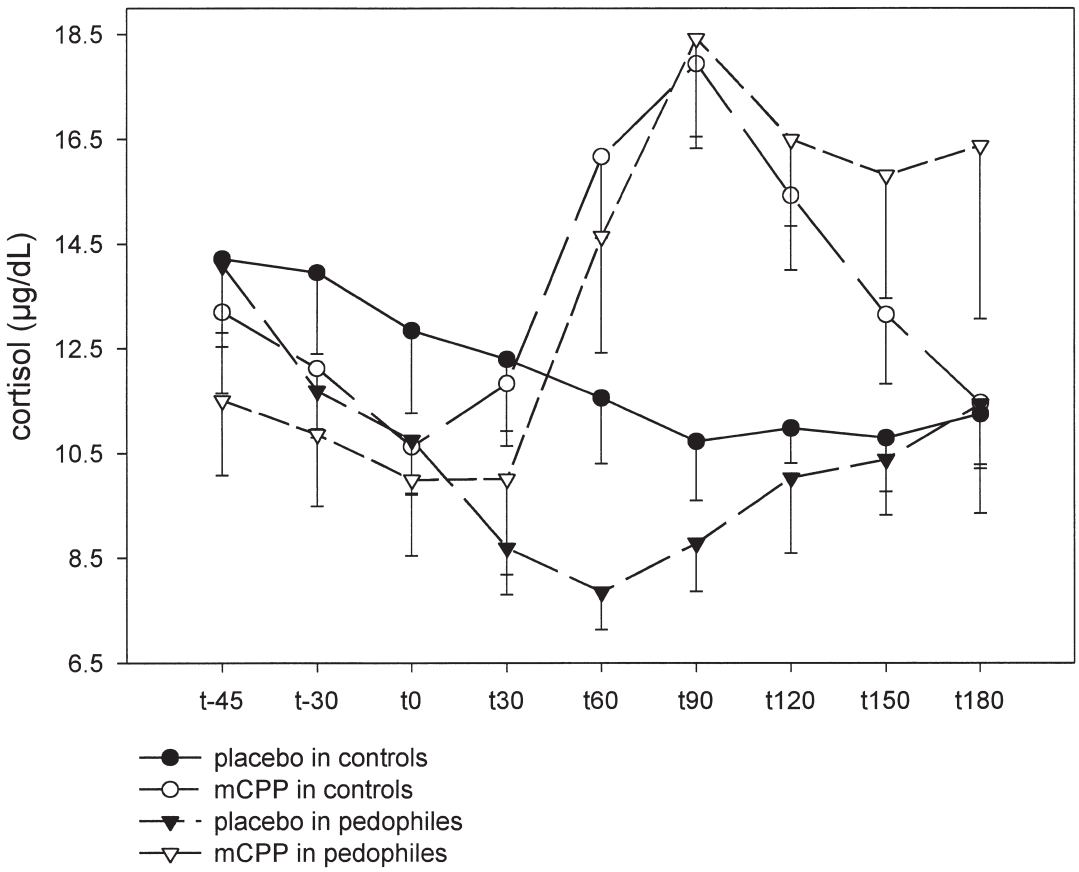

Figure 1. Effects of mCPP versus placebo (administered at t0) on plasma cortisol concentrations in male pedophiles and male healthy volunteers. Results are shown as mean (SEM).

These results show that both patients and controls demonstrated a significant cortisol response to mCPP compared to placebo and that the cortisol response was greater in pedophiles than in controls. The significant time × diagnostic group interaction may be explained by the prolonged increase in plasma cortisol at T120, T150, and T180 in pedophiles, whereas in controls peak plasma cortisol values occur at T90 and return to baseline at T180. In the mCPP condition (the placebo day values are excluded from the analyses), RM design ANOVA showed a significant effect of time ($F = 12.1$, $df = 6/102$, $p < 10^{-4}$) and a significant time × group interaction ($F = 2.3$, $df = 6/102$, $p = .04$).

Figure 2 shows the prolactin responses to placebo and mCPP in patients and controls. RM design ANOVA showed a significant effect of time ($F = 7.7$, $df = 6/221$, $p < 10^{-4}$), drug ($F = 99.8$, $df = 1/221$, $p < 10^{-4}$), a trend towards a significant drug × diagnostic group interaction ($F = 3.7$, $df = 1/221$, $p = .052$), and no significant time × diagnostic group interaction ($F = 1.7$, $df = 6/221$, $p = .1$). These results show that both patients and controls demonstrated a significant prolactin response to mCPP compared to placebo. The trend towards the significant drug × diagnostic group interaction may be explained by the greater effect of mCPP on plasma prolactin in patients versus controls.

Figure 3 shows the body temperature responses to placebo and mCPP in controls and patients. RM design ANOVA performed on body temperature showed a significant effect of time ($F = 4.8$, $df = 6/221$, $p = .0002$), drug ($F = 12.9$, $df = 1/221$, $p = .0006$), a significant drug × diagnostic group interaction ($F = 5.9$, $df = 1/221$, $p = .01$), but no significant time × diagnostic group interaction ($F = 0.6$, $df = 8/221$, $p = .8$). Analyses on simple effects showed a significant effect of mCPP on body temperature in controls ($F = 6.8$, $df = 1/17$, $p = .02$) but not in patients ($F = 0.18$, $df = 1/17$, $p = .7$). These results show that patients, but not controls, demonstrated a significant body temperature response to mCPP compared to placebo. Covarying for plasma cortisol in a RM design ANCOVA did not change the above results, i.e., the drug × diagnostic group interaction remained significant ($F = 15.1$, $df = 1/281$, $p = .0003$).

Plasma mCPP Concentrations

Table 1 shows the mean (±SD) mCPP concentrations from T30 to T180. RM design ANOVA showed that in

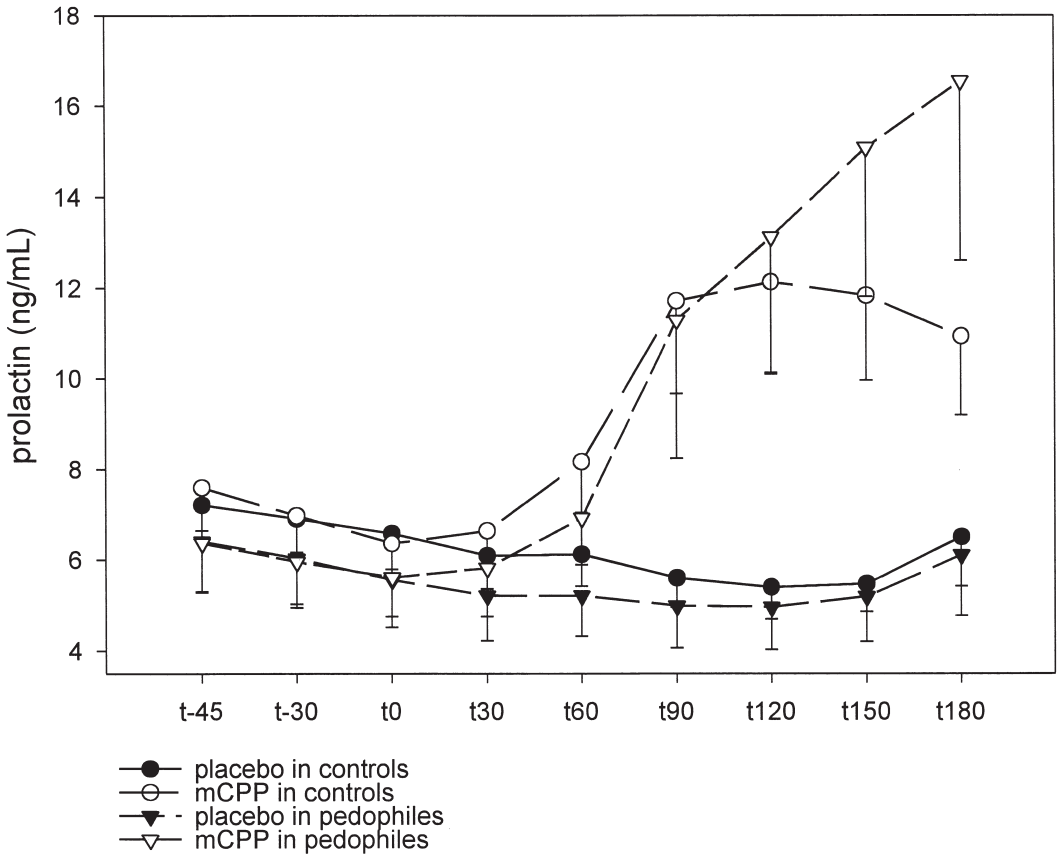

Figure 2. Effects of mCPP versus placebo (administered at t0) on plasma prolactin concentrations in male pedophiles and male healthy volunteers. Results are shown as mean (SEM).

both pedophiles and controls there were significant differences in mCPP concentrations between the time points (significant time effect: F = 11.1, df = 6/102, $p < 10^{-4}$) and that there were no significant differences in the time-concentration curves between both groups (no significant drug concentration × diagnostic group interaction: F = 0.6, df = 6/102, $p = .7$). Table 1 shows that there were no significant differences in the mCPP concentrations between pedophiles and controls at any of the time points. Correlation analyses showed significant time-relationships between plasma mCPP concentrations and plasma cortisol (r = 0.50, df = 1/94, $p < 10^{-4}$), prolactin (r = 0.54, df = 1/94, $p < 10^{-4}$), and body temperature (r = 0.47, df = 1/94, $p < 10^{-4}$; all results of intraclass correlation analyses, which were pooled over the subjects).

Significant Intercorrelations and Effects of Age

In subjects treated with mCPP, there were significant and positive intraclass correlations (pooled over the subjects) between plasma cortisol and prolactin (r = 0.52, df = 1/113, $p < 10^{-4}$), plasma cortisol and body temperature (r = 0.26, df = 1/113, $p = .004$), and between plasma prolactin and body temperature (r = 0.59, df = 1/113, $p < 10^{-4}$).

There were no significant correlations between age and baseline (i.e., expressed as area under the curve [AUC] from T0 to 180 min later), plasma cortisol (r = −0.22, $p = .6$), plasma prolactin (r = 0.39, $p = .1$), or body temperature (r = −0.06, $p = .8$). There were no significant correlations between age and the mCPP-induced (i.e., AUC from T0 to 180 min later) cortisol (r = −0.21; $p = .6$), prolactin (r = 0.07, $p = .7$), or body temperature (r = −0.09, $p = .7$) responses.

Effects of mCPP on the VAS Items

Table 2 shows the outcome of 15 RM design ANOVAs performed on the 15 VAS items. RM design ANOVAs showed that, in both pedophiles and controls, mCPP significantly decreased the VAS item scores on feeling hungry, sleepy, and irritated, and significantly increased the item scores on feeling sick, elated, and strange. The significant drug by group interactions observed for the VAS items feeling dizzy and restless may be explained by non-significant increases in patients and non-significant reductions in volunteers in these VAS item responses to mCPP.

Analyses on simple effects performed on the item feeling hungry showed a significant suppressant effect of

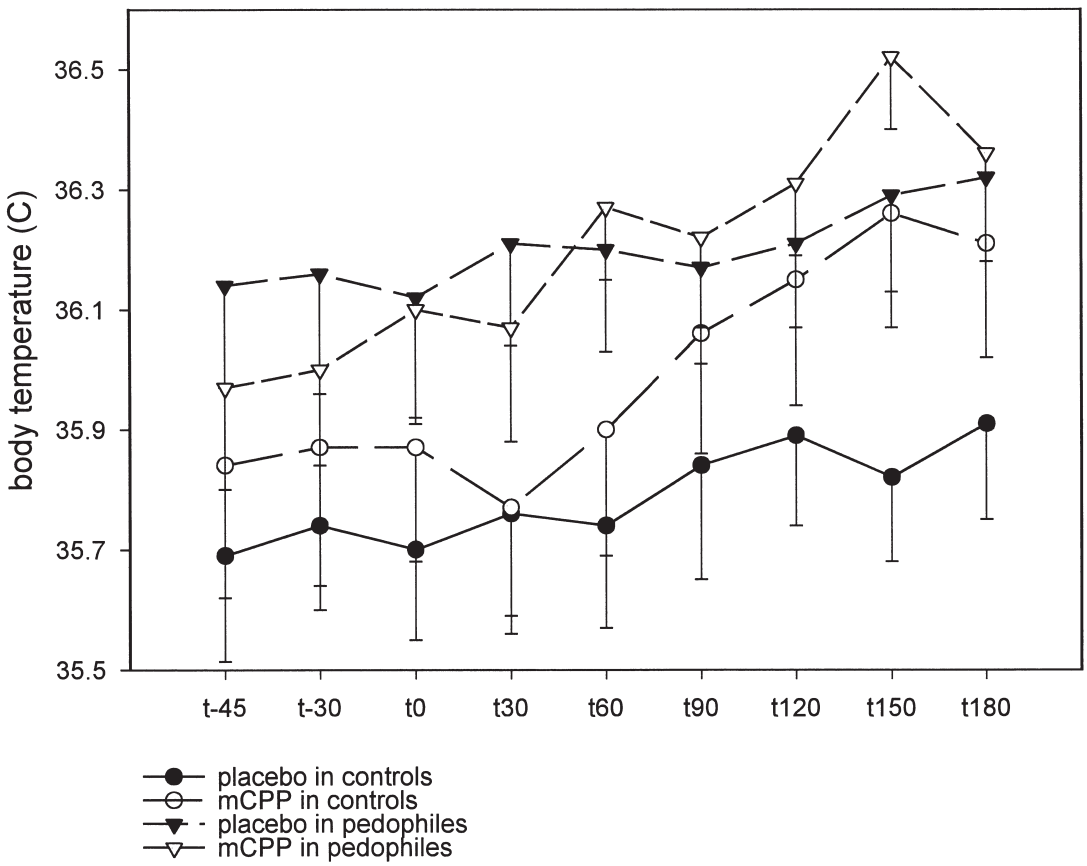

Figure 3. Effects of mCPP versus placebo (administered at t0) on body temperature in male pedophiles and male healthy volunteers. Results are shown as mean (SEM).

mCPP in patients (F = 8.3, df = 1/17, p = .009) and no significant effects in controls (F = 0.7, df = 1/17, p = .6). Analyses of simple effects performed on the VAS item feeling strange showed a significant enhancing effect of mCPP in pedophiles (F = 4.5, df = 1/17, p = .04) and no significant effects in controls (F = 0.08, df = 1/17, p = .8).

DISCUSSION

The major findings of this study are: 1) the mCPP-induced cortisol responses are significantly greater in pedophiles than in normal men; and 2) serum cortisol and prolactin are significantly lower and body temperature significantly higher in pedophiles.

To the best of our knowledge, this is a first study showing that the mCPP-induced cortisol responses are significantly greater and prolonged in pedophiles than in normal men. The mCPP-induced prolactin responses showed a trend toward a significant drug × diagnostic diagnostic group interaction (p = .052). The less pronounced differences in mCPP-induced prolactin versus cortisol responses may be explained by a number of factors: 1) Figure 2 (the mCPP-induced prolactin responses) suggests that the peak prolactin response to mCPP occurs later in pedophiles than in controls and possibly even beyond the 3-hour test period. Thus, a

Table 1. Mean Plasma Meta-Chlorophenylpiperazine (mCPP) Concentrations from T30 to T180

Time point	T30	T60	T90	T120	T150	T180
Mean (SD) in ng/mL	10.3 (8.2)	21.4 (15.8)	24.4 (19.0)	30.8 (33.1)	29.7 (29.0)	26.7 (21.9)
F (df = 1/17)[a]	0.00	0.02	0.00	0.2	0.19	0.05
p	.9	.9	.97	.6	.7	.8

[a]All results of analyses on simple effects, which were performed at each time point and which examined the differences in mCPP concentrations between pedophiles and controls. The results show that there were no significant differences in mCPP concentrations between patients and controls at any of the time points.

Table 2. The mCPP-Induced Behavioral Responses, as Measured by Means of the VAS Items

VAS items:	Drug (df = 1/85)		Drug × group (df = 1/85)	
No: feeling	F	*p*	F	*p*
1: hungry	8.9	.004	3.1	.07
2: sleepy	4.0	.04	0.0	.9
3: sick	7.8	.006	0.4	.5
4: dizzy	0.7	.6	5.4	.02
5: calm	0.5	.6	2.2	.1
6: active	2.1	.1	2.4	.1
7: anxious	0.0	.8	1.2	.3
8: irritated	4.4	.03	0.03	.8
9: sad	3.3	.07	0.4	.5
10: elated	3.9	.04	0.3	.6
11: good	0.2	.7	0.4	.6
12: restless	0.04	.8	4.5	.03
13: strange	5.0	.03	3.1	.08
14: arousal	2.6	.1	0.8	.6
15: relaxed	0.2	.6	0.4	.5

longer (>3 hours) test time could have revealed significant differences in the prolactin responses; and 2) 5-HT1A postsynaptic receptor stimulation may contribute to mCPP-induced prolactin secretion. Indeed, pindolol, a partial 5-HT1A receptor agonist, blocks the ability of mCPP to stimulate prolactin secretion in humans, whereas ritanserin, a 5-HT2A/2C receptor antagonist, blocks the mCPP-induced prolactin and cortisol responses (Meltzer and Maes 1995). Thus, depending upon differences in 5-HT1A functioning between pedophiles and controls, the prolactin responses to mCPP may be less specific for 5-HT2A/2C receptor stimulation than the cortisol responses.

There is evidence for a possible involvement of postsynaptic 5-HT1A receptors in the pathophysiology of ICD and aggression/violence (Kavoussi et al. 1997; Cherek et al. 1999; Sanchez 1999). The increased mCPP-induced hormonal responses may indicate an upregulation of 5-HT2A/2C postsynaptic receptors in pedophiles. As far as pedophilia is related to ICD and violence/aggression (see Introduction), our findings are in agreement with previous reports on increased number of platelet 5-HT2A receptors in aggression (Coccaro et al. 1997). The platelet 5-HT2A receptor is essentially identical to the corresponding structure in central 5-HT synapses (Cook et al. 1994). However, other studies reported no significant association between platelet 5-HT2A receptor sites and measures of aggression (McBride et al. 1994), whereas Blumensohn et al. (1995) reported a reduction in the number of platelet 5-HT2A binding sites in delinquent adolescents.

We found that the mCPP-induced body temperature responses were significantly blunted in pedophiles. At first sight, these results do not corroborate the thesis that pedophilia is associated with 5HT2A/C receptor hyperresponsivity. As explained in the Introduction, mCPP-induced increases in body temperature are mediated, in part, through 5-HT2 postsynaptic receptors (Gudelsky et al. 1986). Nevertheless, we found significant and positive correlations between the changes over time between serum cortisol/prolactin and body temperature. The different mCPP-induced responses in cortisol/prolactin versus body temperature may be explained by a number of factors: 1) increased cortisol secretion may have diminished the mCPP-induced body temperature responses; however, even after adjusting for the possible effects of cortisol in ANCOVAs, the blunted mCPP-induced body temperature responses in pedophiles remained significant; 2) stimulation of 5-HT1A receptors in human and rodents causes hypothermia (Gudelsky et al. 1986; Lesch et al. 1990); since mCPP has a moderate affinity for 5-HT1A receptors (Hoyer 1988), an altered number or affinity of pre- or postsynaptic 5-HT1A receptors could have modified the body temperature responses to mCPP; and 3) since baseline body temperature is significantly increased in pedophiles, a physiological ceiling in the temperature responses to mCPP could explain the lack of a temperature response to mCPP administration in those patients.

The second major finding of this study is that baseline serum cortisol and prolactin were significantly lower and body temperature was significantly higher in pedophiles than in controls. As far as pedophilia is related to the violence/aggression dimension, our findings extend those of previous reports showing an inverse relationship between HPA-axis activity and aggression/violence (Virkkunen 1985; Virkkunen et al. 1994). A reduction in plasma cortisol in alcohol dependent patients as a function of a history of repeated episodes of domestic violence has been reported (Bergman and Brismar 1994). In non-human primates, however, a positive relationship was observed between plasma ACTH and aggression (Higley et al. 1992). In fact, the simultaneous occurrence of lowered serum cortisol and prolactin and increased body temperature could point toward decreased 5-HT presynaptic activity, which has been described to occur in ICD and violence/aggression (see Introduction). Indeed, 5-HT stimulates HPA-axis activity and prolactin secretion, while presynaptic 5-HT1A stimulation results in hypothermic responses (Lal and Martin 1980; Gudelsky et al. 1986).

It has been hypothesized that 5-HT exerts an inhibitory effect on aggressive/violent and impulsive behavior (Soubrie 1986; Eichelmann 1995; Geyer 1996; Kavoussi et al. 1997) and that lowered presynaptic 5-HT neurotransmission may diminish these inhibitory effects, thus, increasing impulsivity and aggression/violence (Cleare and Bond 1995; Coccaro 1999; Sanchez 1999). It has been argued that in other psychiatric disorders, e.g., major depression, postsynaptic 5-HT2A/2C receptor upregulation may reflect an adaptive process

to a presynaptic hypoactive serotonergic neuronal activity. Therefore, it may be hypothesized that pedophilia is accompanied by a postsynaptic 5-HT2A/2C upregulation which could be secondary to lowered presynaptic 5-HT neurotransmission. However, serotonergic denervation does not always induce 5-HT2 receptor upregulation (Leysen 1992). In addition, there are also reports that do not clearly fit into the low 5-HT hypothesis of ICD or violence/aggression (for example: Malick and Barnett 1976; Olivier et al. 1990).

The third major finding of this study is that mCPP significantly and differently influenced behavioral responses in pedophiles versus normal men. Thus, mCPP increases the VAS items feeling dizzy, restlessness, and feeling strange in pedophiles and not in normal men. mCPP significantly reduced the item feeling hungry in pedophiles, whereas no significant effects were established in normal men. These behavioral responses may be mediated by post-synaptic 5-HT2 receptors (Lee et al. 1992; Goodall et al. 1993; Kennett and Curzon 1991). Thus, alterations in post-synaptic 5-HT2 receptor functioning in pedophiles may explain the differences in the responses to mCPP in pedophiles versus controls. However, the alterations in the above VAS items may be too general to be attributed to alterations in 5-HT2 receptors.

In the present study, we did not find significant differences in plasma mCPP concentrations at any of the time points between pedophiles and normal men. Thus, the changes in the hormone and body temperature responses in pedophilia are not related to differences in mCPP pharmacokinetics between the study groups. Interestingly, we found significant and positive relationships over time (from T30 to T180) between the plasma mCPP concentrations and either the hormonal or body temperature responses. Another factor which may interfere with the interpretation of our results is that mCPP has catecholaminergic activities. Thus, mCPP is a dopaminergic receptor antagonist and may bind to α2-adrenoceptors (Hamik and Peroutka 1989). However, in experimental animals, mCPP (2.5 mg/kg) did not affect the turnover of noradrenaline or dopamine (Invernizzi et al. 1981; Fuller 1981; Samanin et al. 1979) and in humans, mCPP administration did not affect the plasma concentration of homovanillic acid, the major dopamine metabolite (Kahn et al. 1992) and 3-methoxy-4-hydroxyphenylglycol, the major noradrenaline metabolite (Asnis et al. 1992).

However, a first limitation of the present study is the small sample size (n = 8 pedophiles) and, consequently, the higher likelihood of both type I and type II errors of inference. In addition, the conclusions that a hyposerotonergic presynaptic neuron as well as 5-HT2 receptor abnormalities may play a role in pedophilia should be interpreted with caution since the serotonergic control of the cortisol, prolactin, and temperature responses may be more complex than postulated. The greater cortisol response to mCPP in pedophiles could merely be a reflection of the lowered negative feedback exerted by cortisol, i.e., if baseline cortisol concentrations are lower the mCPP-induced responses could be greater. However, given the temperature and prolactin data, this seems unlikely.

Other mechanisms may be important in explaining the hormonal and temperature changes in pedophiles, such as changes in the function and expression of other serotonergic receptors or downstream signaling effects. In addition, part of the cortisol response may be of adrenal origin. Measurements of ACTH would allow a further distinction between central and peripheral disorders. Finally, in the case of the 15 VAS items multiple comparisons have been used and, thus, some of the results could have been observed by chance.

In conclusion, the finding of the present study suggest that 5-HT could be a important neurotransmitter for pedophilia and that deficits in serotonergic neurotransmission may play a major role in pedophilia. 5-HT2A/C postsynaptic receptor upregulation and lowered presynaptic 5-HT activity deserve attention in future studies in pedophilia.

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