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ORIGINAL INVESTIGATION

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# Relationship of disinhibition and aggression to blunted prolactin response to *meta*-chlorophenylpiperazine in cocaine-dependent patients

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**Abstract** *Rationale:* Considerable evidence indicates that serotonergic (5-HT) mechanisms may mediate central effects of cocaine, and disinhibition and aggression. *Objective:* We investigated whether prolactin (PRL) response to *meta*-chlorophenylpiperazine (*m*-CPP), a mixed 5-HT agonist/antagonist, differed between abstinent cocaine-dependent patients and controls and whether *m*-CPP challenge responses were related to measures of disinhibition and aggression. *Methods:* Thirty-five cocaine-dependent African-American subjects who were abstinent for at least 2 weeks and 33 African-American controls underwent assessments of disinhibition and aggression and a challenge with 0.5 mg/kg of oral *m*-CPP. *Results:* The PRL response to *m*-CPP was compared between cocaine patients and controls and between subgroups categorized high or low based on disinhibition and aggression measures. Hierarchical regressions were used to determine whether behavioral measures predicted ΔPRL (peak PRL−baseline PRL). The PRL response to *m*-CPP was significantly diminished in cocaine patients compared to controls. The blunting was more robust in cocaine patients with high disinhibition and aggression. Among cocaine patients, the high-disinhibition subgroup showed greater blunting than the low-disinhibition subgroup and there was a trend for the high-aggression subgroup to be more blunted than the low-aggression subgroup. The subgroups of controls did not differ from each other. A combination of disinhibition and aggression measures significantly predicted ΔPRL in cocaine patients. *Conclusion:* The results indicate that cocaine-dependent patients show disturbances in postsynaptic 5-HT function during early abstinence. It appears that the 5-HT disturbances are more pronounced in the subgroup of cocaine patients with high disinhibition and aggression.

**Keywords** Serotonin · *m*-CPP · 5-HT · Cocaine · Substance abuse

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## Introduction

There is growing evidence to indicate that serotonergic (5-HT) mechanisms may be involved in mediating the reinforcing effects of cocaine (McMahon and Cunningham 2001; Muller et al. 2003). Acutely, cocaine binds to the 5-HT transporter and strongly inhibits 5-HT uptake (Castanon et al. 2000; Cunningham et al. 1996). Chronic administration of cocaine seems to downregulate several subtypes of postsynaptic 5-HT receptors, possibly as a compensatory mechanism to increased synaptic 5-HT (Heidbreder et al. 1999; King et al. 2002). Studies with selective 5-HT receptor ligands suggest the contribution of 5-HT1A, 5-HT1B, 5-HT2A, 5-HT2C, and 5-HT3 receptors to the reinforcing effects of cocaine (Burmeister et al. 2004; Cervo et al. 2002; Davidson et al. 2002; Fletcher et al. 2002; Neumaier et al. 2002). Moreover, manipulations of the brain 5-HT system can modulate the effects of cocaine under a variety of experimental conditions (Batki et al. 1993; Burmeister et al. 2003; Aronson et al. 1995; Satel et al. 1995; Walsh and Cunningham 1997).

Neuroendocrine and behavioral responses to a challenge with 5-HT agents have been widely employed to study human central 5-HT function in neuropsychiatric disorders (Kahn et al. 1990; Murphy et al. 1989). While the challenge responses appear to be altered in alcoholics (Buydens-Branchey et al. 1997; Farren et al. 1995; George et al. 1997; Krystal et al. 1996), data in cocaine abusers are limited and inconsistent. Buydens-Branchey et al. (1997) found that 31 cocaine-dependent patients showed a significantly blunted prolactin (PRL) response compared to 14 controls following challenge by *meta*-chlorophenylpiperazine (*m*-CPP), a mixed 5-HT-receptor agonist/antagonist. However, another study found no differences in neuroendocrine responses to *m*-CPP between 19 cocaine abusers and 11 controls (Handelsman et al. 1998). Results from studies using other 5-HT probes are also conflicting. While Lee and Meltzer (1994) reported that no differences in PRL or cortisol responses to MK-212, a 5-HT agonist, between cocaine abusers and controls in one study, another study employing sequential *d*,*l*-fenfluramine challenges found that PRL response was blunted in cocaine abusers and appeared to normalize with extended abstinence (Buydens-Branchey et al. 1998). The discrepancy in findings could be related to differences in the challenge protocols, 5-HT probes, or the samples studied.

Behavioral disinhibition and aggression are key components of several psychiatric disorders including substance abuse. Substantial evidence indicate that 5-HT dysfunction may underlie these behaviors (Coccaro et al. 1995; Goveas et al. 2004; Linnoila et al. 1983; Roy et al. 1988; Stanley et al. 2000; Twitchell et al. 2001). Neuroendocrine challenge protocols in substance abusers have tended to confirm this relationship, although the direction of association has not been uniform (O'Keane et al. 1992; Moss et al. 1990; Fishbein et al. 1989; Handelsman et al. 1998; Buydens-Branchey et al. 1997; New et al. 2004). Neuroimaging studies using 5-HT probes have extended these findings by revealing that deficits in specific brain regions may be associated with disinhibited aggression (New et al. 2002; Siever et al. 1999).There is some evidence to indicate that there might be neurobiological differences between subgroups of substance abusers. Supportive data have primarily distinguished type I and type II alcoholics (von Knorring et al. 1985; Cloninger 1987; George et al. 1997); however, similar differences have also been observed in cocaine abusers (Buydens-Branchey et al. 1997). Cocaine abusers consistently score higher on measures of disinhibition and report greater irritability compared to controls (Moeller et al. 1994). We have previously shown that alterations in platelet 5-HT transporters, a peripheral measure of 5-HT function, were related to disinhibition and aggression in cocaine abusers (Patkar et al. 2003). Therefore, measures of disinhibition and aggression appear to be appropriate clinical measures to subgroup cocaine abusers.

The objectives of the present study were to examine whether central 5-HT function, as measured by PRL response to *m*-CPP, differs between cocaine-dependent patients and controls and whether 5-HT function differs between subgroups of cocaine-dependent subjects characterized by high and low scores on disinhibition and aggression.

We selected *m*-CPP as our pharmacological 5-HT probe because it has been widely used to explore central 5-HT receptor function in healthy as well as psychiatrically ill subjects (Kahn and Wetzler 1991; Murphy et al. 1991; Yatham and Steiner 1993). *m*-CPP offers greater specificity for postsynaptic 5-HT receptors than other 5-HT probes such as *l*-tryptophan, 5-hydroxytryptophan, and fenfluramine, which exert significant effects at the presynaptic level (Broocks et al. 2001). *m*-CPP binds to 5-HT receptors in the following descending rank order of affinities (pKds): $5\text{-HT}_{2C}(7.7)>5\text{-HT}_{3}(7.0)>5\text{-HT}_{2A}(6.7)>5\text{-HT}_{1B}(6.6)>5\text{-HT}_{1A}(6.5)>5\text{-HT}_{7}(6.4)>5\text{-HT}_{1D}(5.8)>5\text{-HT}_{6}(5.6)$ (Monsma et al. 1993; Sleight et al. 1995). *m*-CPP also has considerably lower affinity for the human 5-HT transporter (<4.0) and for dopamine receptors (Hoyer et al. 1994). The effects of *m*-CPP on PRL, ACTH/cortisol, and temperature have been attributed to partial agonist activity at the $5\text{-HT}_{2C}$ receptor (Aulakh et al. 1992; Calogero et al. 1993; Frankel and Cunningham 2004; Murphy et al. 1991). The 0.5-mg/kg dose of *m*-CPP has become the commonly used dose for oral administration in challenge paradigms due to the tendency of higher doses to produce variable side effects (Gijsman et al. 2004).

## Materials and methods

### Subjects

This study was conducted with approval from the Institutional Review Board of Thomas Jefferson University, Philadelphia, PA, in accordance with the Helsinki Declaration of 1975 under a research IND from the FDA. Thirty-five subjects were recruited from individuals attending a publicly funded outpatient cocaine treatment program. Following a complete description of the study, written informed consent was obtained from all subjects. The Structured Clinical Interview (SCID) for DSM-IV Axis I Disorders (First et al. 1997) was then administered to volunteers. Those with an Axis I diagnosis of cocaine dependence were included. Subjects who were dependent on cocaine but used or abused other substances (except nicotine) were included only if their primary drug was cocaine. Individuals with a diagnosis of schizophrenia, major depression, bipolar disorder, schizoaffective disorder, a serious medical illness, or pregnancy were excluded as were those who were referred from the criminal justice system or were receiving psychotropic medications in the previous 4 weeks. Urine drug screens and breath alcohol levels were obtained for all subjects. Nearly 92% of the patient population in our treatment program were African-American, and the study sample was restricted to African-American subjects to represent the clinical population.

Thirty-three African-American controls were recruited from those responding to local advertisements. Consent and screening procedures were similar to those followed

for cocaine subjects. Control subjects were excluded if they had a history of substance abuse or dependence (except nicotine), a major psychiatric disorder (schizophrenia, major depression, or bipolar disorder), a positive urine drug screen, or were taking psychotropic medications in the previous 4 weeks.

## Behavioral assessments

Subjects and controls were assessed using a battery of psychological tests. The instruments were selected based on evidence of a significant biological basis for disinhibition and aggression (Lesch and Merchdorf 2000) and on previous studies linking scores on these scales to indices of 5-HT function (Buydens-Branchey et al. 1997; Coccaro et al. 1996). These included the Buss–Durkee Hostility Inventory (BDHI) (Buss and Durkee 1957), the Sensation Seeking Scale: form V (SSS) (Zuckerman 1993), the Beck Depression Inventory (BDI) (Beck and Steer 1987), and the Fagerstrom Test for Nicotine Dependence (FTND) (Heatherton et al. 1991).

The BDHI is a 75-item questionnaire used to measure aggression. It is composed of eight subscales. The motor aggression factor is composed of four subscales (direct, indirect, verbal, and irritability), while the hostility factor is composed of two subscales (resentment and suspiciousness). The remaining subscales measure guilt and negativism. Reliability and validity have been established for the instrument (Buss and Durkee 1957). The SSS (form V) is a widely used 40-item self-report questionnaire that measures various dimensions of sensation-seeking behavior. It provides a total sensation-seeking score as well as scores on four subscales assessing disinhibition, thrill and adventure seeking, experience seeking, and boredom susceptibility. The SSS has been validated in biological studies (Fulker et al. 1980). The BDI is a 21-item self-report questionnaire used to assess depressive symptoms. The FTND is a widely used and validated six-item questionnaire used to assess severity of smoking (Heatherton et al. 1991).

## The *m*-CPP challenge test

### *Procedure*

The same protocol was followed for subjects and controls. All subjects had their medical health documented by history, physical examination, and laboratory tests. To minimize any effects of recent substance use on PRL levels, subjects underwent the *m*-CPP challenge procedure after at least 2 weeks of abstinence from illicit drugs and alcohol. The 2-week abstinence period was documented by monitoring urine and breath alcohol thrice a week including test day. The urine drug screens were negative on the day of the procedure. Women were studied in the initial follicular phase of the menstrual cycle. This phase was defined clinically as the 10-day period following the end of menstrual phase. Subjects were instructed to have a low monoamine diet for 3 days prior to the procedure. On test day, subjects were asked to come in the morning after an overnight fast (except water). Subjects were placed in a semirecumbent position, and their vital signs were assessed. A peripheral indwelling catheter was inserted for blood collection. Subjects were not allowed to eat, drink, or smoke during the procedure. Two baseline blood samples were drawn at 30-min intervals, and 0.5 mg/kg of oral encapsulated *m*-CPP (Sigma-Aldrich, St. Louis, MO) was administered. Six serial blood samples were obtained for PRL levels at 30-min intervals along with measurement of vital signs. The time schedule for blood draw included the period of increase in neuroendocrine parameters in previous studies (Kahn et al. 1992).

### *PRL determination*

Blood samples were centrifuged within 2 h of collection; the sera were separated and frozen at −70°C. Samples were identified by code numbers for blinding purposes. PRL was assayed using the Active PRL DSL-4500 Immunoradiometric Assay Kit (Diagnostic Systems Laboratories, Webster, TX). This assay employs a standardized two-site immunoradiometric assay technique (Miles et al. 1974) to provide quantitative estimates of PRL in the serum. The assay sensitivity was 0.1 ng/ml, and specificity tests carried out by the manufacturer indicate that other hormones were unlikely to cross-react with the PRL antibody. The interassay and intraassay coefficients of variation were 11% and 4.0%, respectively.

### *m-CPP determination*

*meta*-Chlorophenylpiperazine was assayed by high performance liquid chromatography (HPLC) method according to techniques described by Suckow et al. (1990). The *m*-CPP levels were determined at 60, 120, and 180 min after ingestion of *m*-CPP. Peak plasma levels of *m*-CPP were compared between subjects and controls.

## Statistical analyses

Cocaine-dependent subjects and controls were compared on baseline measures using two-tailed *t* tests and chi squared tests as appropriate. PRL response curves were compared between subjects and controls employing analysis of covariance (ANCOVA) with repeated measures to assess the main effects of group and time and their interaction. Unequally distributed baseline variables between the two groups were used as covariates. For all multivariate tests, the Greenhouse–Geisser correction was applied if the data did not meet assumptions of sphericity.

To examine whether *m*-CPP challenge response differed across subgroups, cocaine patients and controls were first compared across the total BDHI and SSS scores. The

approach to dealing with potential type I error associated with multiple tests (12 subscales of BDHI and SSS) was to perform a test of overall significance using total scores on the BDHI and SSS, as recommended by Cohen and Cohen (1983). Only in case of a significant result ($p<.05$) or trend ($p<.10$) for the main scale were tests of significance performed for the subscales. Subjects and controls were subdivided into high/low subgroups based on a median split of BDHI total scores (aggression). The PRL responses were compared across the four subgroups using ANCOVA with repeated measures. The same set of analyses was performed dividing cases and controls on a median split of the disinhibition subscale of the SSS to examine the association of disinhibition with *m*-CPP challenge responses.

The maximum change in PRL after *m*-CPP (ΔPRL) was calculated by subtracting the baseline PRL values from the peak PRL response following *m*-CPP (120 min). Correlations between ΔPRL and BDHI and SSS scores were performed using bivariate correlations. Hierarchical regression analyses were performed with ΔPRL as the independent variable and BDHI and disinhibition scores as predictor variables covarying for effects of demographics and depression to examine the relationship of aggression and sensation seeking with PRL responses. All data are reported as mean±standard deviation unless specified otherwise.

## Results

### Sample characteristics

Out of 131 AA cocaine-dependent patients screened, a total of 35 subjects participated in the *m*-CPP procedure. Excluded subjects were: 40 patients with current major psychiatric disorder or receiving psychotropic medications or referred from the criminal justice system, 46 patients who did not meet the criteria for 2-week or greater continuous abstinence from cocaine before the *m*-CPP challenge, 4 patients with serious medical disorders, 3 patients who withdrew due to side effects of *m*-CPP, and 3 subjects whose blood samples could not be analyzed for technical reasons. Thirty-three AA controls were recruited after screening 94 volunteers and excluding 35 persons who either had a positive urine drug screen or were unable to provide a urine sample, 18 individuals who had a diagnosis of major psychiatric disorder or were taking psychotropic medications, 2 persons with unstable medical illnesses, 4 individuals who withdrew due to *m*-CPP-related side effects and 2 persons whose blood samples could not be analyzed. The subjects [22 (63%) male] and controls [22 (66%) male] did not differ significantly in gender or age (subjects=34.33±4.7, controls=33.06±4.15). However, cocaine subjects (82%) were significantly more likely to be unemployed compared to controls (34%) ($\chi^2=34.6$, $df=1$, $p<.001$). Similarly, significant differences were observed in marital status between patients (71% single) and controls (44% single) ($\chi^2=5.22$, $df=1$, $p<.01$). Nearly 85% of subjects fulfilled all seven DSM-IV criteria for cocaine dependence. Subjects were abstinent for 15.6±3.7 days prior to the *m*-CPP procedure.

A significant proportion of the cocaine-dependent subjects had additional current or lifetime substance abuse diagnoses, reflecting the patient population in clinical settings. Nicotine was the most common drug (82%) followed by alcohol (36%), marijuana (24%), and opioids (12%). About 30% of controls smoked and none used alcohol during the study period. The mean FTND scores were significantly higher among cocaine subjects (4.82±2.11) compared to controls (2.11±2.36) ($t=6.64$, $df=67$, $p<.01$), indicating that cocaine patients were more severely nicotine-dependent compared to controls.

### Aggression and sensation seeking: cocaine subjects vs controls

As summarized in Table 1, cocaine patients obtained significantly higher scores on BDHI total score and the subscale scores measuring assault, indirect aggression, irritability, and resentment. Although the patients obtained significantly higher total scores on SSS compared to controls, this difference was attributable to significantly higher scores on the disinhibition subscale of the SSS in cocaine subjects compared to controls. No significant group differences were observed for the remainder of the subscales of the SSS. We also examined and found no

**Table 1** Comparison of measures of aggression and sensation seeking among cocaine patients and controls

| Assessment measures | Subjects (*n*=68) | | |
|---|---|---|---|
| | Cocaine (*n*=35) | Controls (*n*=33) | *t** |
| Buss–Durkee Hostility Inventory (BDHI) | | | |
| Assault | 3.48±.95 | 2.47±.90 | 4.58*** |
| Guilt | 2.14±.81 | 2.30±.85 | .82 |
| Indirect aggression | 3.54±1.14 | 2.69±.88 | 3.49** |
| Verbal aggression | 3.65±.1.21 | 3.33±1.06 | 1.19 |
| Irritability | 3.65±1.16 | 2.83±.81 | 3.47** |
| Negativism | 2.82±.92 | 2.38±.87 | 2.01 |
| Resentment | 3.48±.93 | 2.77±.95 | 3.94** |
| Suspicion | 3.51±1.26 | 2.97±1.10 | 1.96 |
| Total score | 22.94±6.02 | 18.4±5.06 | 3.49** |
| Sensation Seeking Scale (SSS) | | | |
| Disinhibition | 5.11±1.06 | 3.91±1.13 | 3.24** |
| Experience | 4.22±1.16 | 4.25±2.18 | .05 |
| Thrill/adventure | 4.65±1.18 | 4.30±1.21 | 1.83 |
| Boredom | 2.94±.96 | 2.91±1.05 | .12 |
| Total score | 17.08±3.82 | 15.22±3.59 | 2.10* |

Two-tailed tests; *df* values ranged from 63–66. Criterion for test of significance was performed using a Bonferroni correction
***$p<.001$; **$p<.01$; * $p<.05$

significant relationships between demographic characteristics, including age, gender, employment, and marital status, and scores on the BDHI and SSS ($\chi^2$<1.84 and $r$<.11 for all comparisons, $p$>.05 in each case) among patients and controls. Despite excluding individuals with major depression, cocaine subjects displayed higher scores on the BDI (14.94±10.21) than controls (6.57±3.75) ($t$=6.82, $df$=66, $p$<.001).

## PRL response to *m*-CPP: cocaine subjects vs controls

*Within-group comparisons* Repeated measures analysis of variance (ANOVA) of the response curves showed a significant time effect on PRL levels in both cocaine patients ($F$=34.7, $df$=2.4, $p$<.001) and controls ($F$=17.37, $df$=2.4, $p$<.001).

*Between-groups comparisons* Baseline PRL levels (average of the two baseline PRL values measured from blood draws 30 min apart) trended to be higher in cocaine patients (8.51±3.55) than controls (7.40±2.88) ($t$=1.48, $df$=66, $p$=.07). There were no significant differences in peak *m*-CPP concentrations between cocaine patients (27.3±6.1 ng/ml) and controls (25.1±4.6 ng/ml) ($t$=1.09). We compared the response curves between subjects and controls using baseline PRL and FTND scores as covariates. As shown in Fig. 1, repeated measures ANCOVA demonstrated a significant blunting in the PRL response in cocaine subjects compared to controls [$F$(1,65)=21.93, $p$<.001].

## PRL response to *m*-CPP: relationship to aggression and sensation seeking

The strongest differences between patients and controls were observed on the total BDHI and SSS-disinhibition scores. Based on the median value of the total BDHI and disinhibition subscale of the SSS scores, the cocaine patients were divided into high and low on aggression (median=24) and disinhibition (median=5). The controls were also similarly subgrouped based on median split of BDHI (median=17) and disinhibition (median=4) scores. The median values for BDHI and SSS did not differ significantly from the mean values in cocaine subjects and controls (Table 1).

*Comparisons of PRL responses between high-aggression/low-aggression subgroups* Analysis of covariance with repeated measures using baseline PRL and FTND scores was used to compare PRL response curves in the high-aggression ($n$=16) and low-aggression subgroups ($n$=19) of cocaine patients and control subgroups with high aggression ($n$=16) and low aggression ($n$=17). The analysis revealed a significant difference across the four groups [$F$(3,63)=8.56, $p$<.001]. The results are summarized in Fig. 2. The high aggression subgroup of cocaine patients showed a trend toward greater blunting of PRL response than the low aggression cocaine subgroup (mean difference=−1.2, 95% CI=−2.4 to.21, $p$=.08) and both low (mean difference=−3.13, 95% CI=−4.5 to −1.7, p<.001) and high (mean difference=−2.7, 95% CI=−4.1 to −1.3, p<.001) control subgroups. The low aggression cocaine subgroup showed a less pronounced but significant blunting compared to both subgroups of controls (mean difference ranged from −1.5 to −2.0, p<.05 to p<.01). The

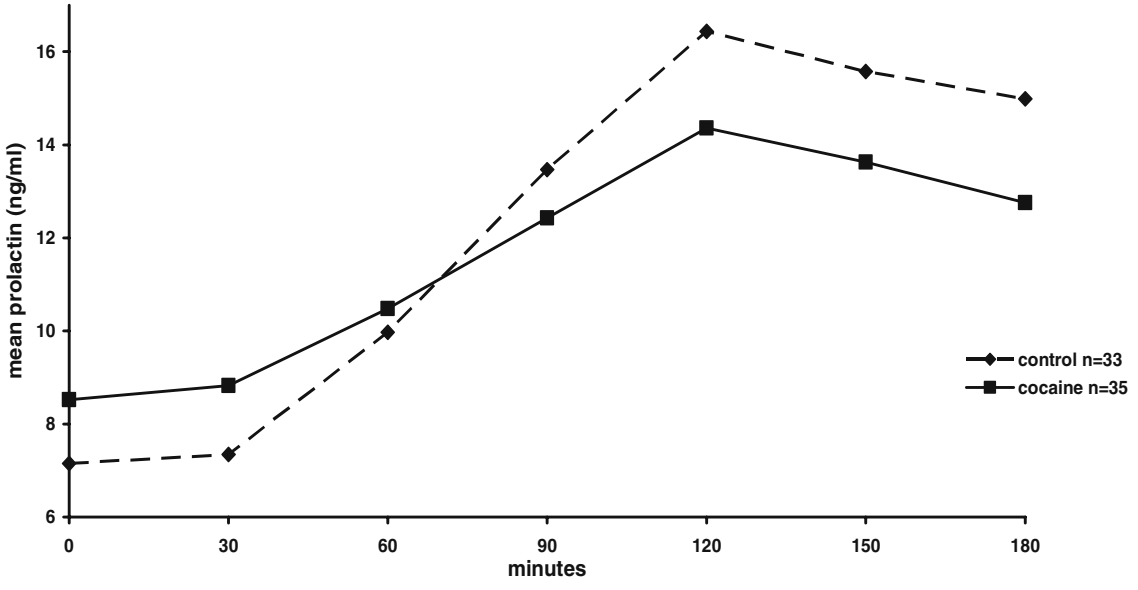


**Fig. 1** Prolactin response to *meta*-chlorophenylpiperazine in cocaine patients and controls. Serum prolactin (PRL) levels were evaluated every 30 min for 180 min, following *meta*-chlorophenylpiperazine stimulation in African-American cocaine-dependent subjects ($n$=35, *continuous line*) and non-drug-dependent controls ($n$=33, *dashed line*). Cocaine users showed significant blunting in PRL response compared to controls [analysis of covariance with repeated measures controlling for baseline PRL and smoking, $F$(1,65)=21.93, $p$<.001]. Time is reported on the $x$-axis; mean PRL levels are shown on the $y$-axis

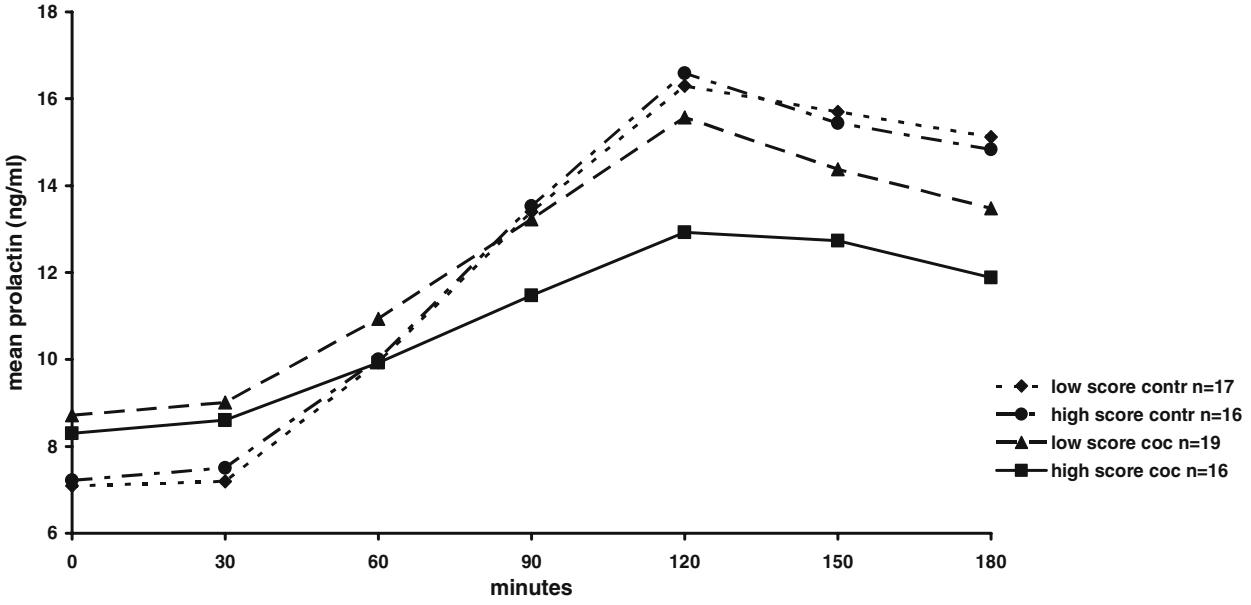


**Fig. 2** Prolactin response to *meta*-chlorophenylpiperazine: aggression subgroups. Cocaine-dependent subjects ($n$=35) and controls ($n$=33) were assessed using the Buss–Durkee Hostility Inventory to measure aggression and were subdivided into high/low subgroups based on a median split of the total scores. The prolactin (PRL) responses to *meta*-chlorophenylpiperazine stimulation were significantly different across the four subgroups [analysis of covariance with repeated measures controlling for baseline PRL and smoking, $F$ (3,63)=8.56, $p$<.001]. The high-aggression subgroup of cocaine patients ($n$=16, *continuous line*) showed a trend toward a greater blunted PRL response than the low-aggression cocaine subgroup ($n$=19, *dashed line*; $p$=.08) and a significant blunting compared to both high ($n$=16, *dashed-dotted line*; $p$<.001) and low ($n$=17, *dotted line*; $p$<.001) control subgroups. The low-aggression cocaine subgroup also showed blunting compared to both subgroups of controls ($p$<.05 vs low-aggression and $p$<.01 vs high-aggression controls, respectively). The high- and low-aggression subgroups of controls did not differ from each other ($p$=.49). Time is reported on the $x$-axis; mean PRL levels are shown on the $y$-axis

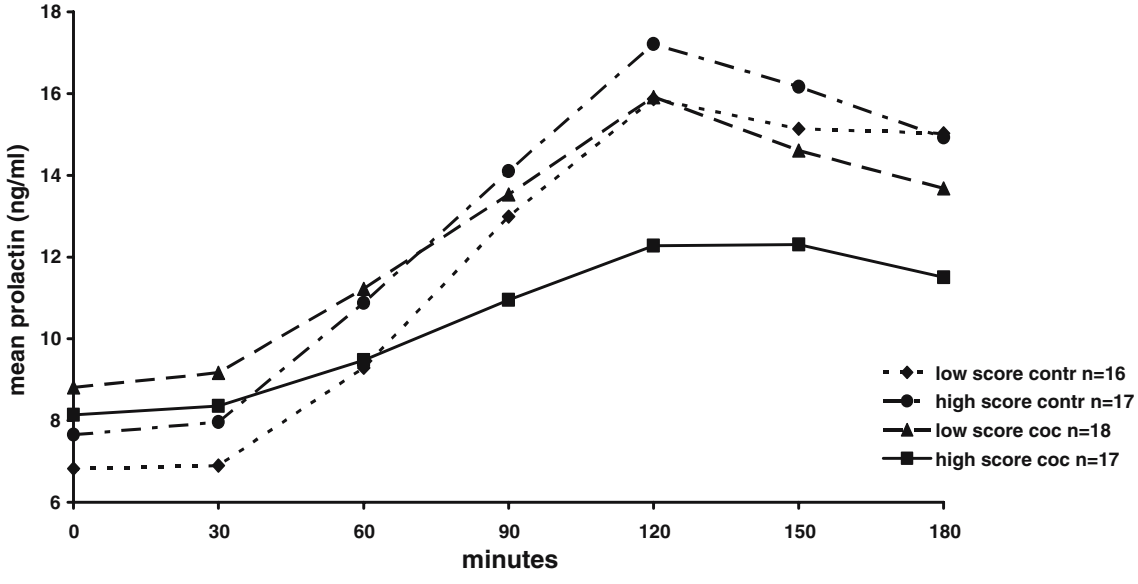


**Fig. 3** Prolactin response to *meta*-chlorophenylpiperazine: disinhibition subgroups. Cocaine-dependent subjects ($n$=35) and controls ($n$=33) were assessed using the Sensation Seeking Scale: form V and subdivided into high/low subgroups based on a median split of the scores at the disinhibition subscale. The prolactin (PRL) responses to *meta*-chlorophenylpiperazine stimulation were significantly different across the four subgroups [analysis of covariance with repeated measures controlling for baseline PRL and smoking, $F$ (3,63)=6.49, $p$<.001]. The high-disinhibition subgroup of cocaine patients ($n$=17, *continuous line*) showed a greater blunting of PRL response than the low-disinhibition cocaine subgroup ($n$=18, *dashed line*; $p$<.05) and both high ($n$=17, *dashed-dotted line*; $p$<.001) and low ($n$=16, *dotted line*; $p$<.001) control subgroups. The low-aggression cocaine subgroup showed a trend toward blunting compared to low-disinhibition controls ($p$<.06), but did not differ from the high-disinhibition control subgroup ($p$=.14). The high- and low-disinhibition subgroups of controls did not differ from each other ($p$=.84). Time is reported on the $x$-axis; mean PRL levels are shown on the $y$-axis

high and low aggression subgroups of controls did not differ from each other (mean difference=.46, 95% CI=−.88 to 1.82, $p$=.49).

*Comparisons of PRL responses between high/low sensation seeking subgroups* As seen in Fig. 3, repeated measures ANCOVA across the four subgroups showed a significant difference in PRL response curves between the high- ($n$=17) and low- ($n$=18) disinhibition subgroups of cocaine patients and high- ($n$=17) and low- ($n$=16) disinhibition subgroups of controls [$F$(3,63)=6.49, $p$<.001]. The high-disinhibition subgroup of cocaine patients showed a significantly greater blunting of PRL response compared to the low-disinhibition subgroup of cocaine patients (mean difference=−1.7, 95% CI=−3.1 to −2.8, $p$<.05) and both high (mean difference=−2.7, 95% CI=−4.2 to −1.1, $p$<.001) and low (mean difference=−3.0, 95% CI=−3.5 to −1.5, $p$<.001) control subgroups. The low-disinhibition subgroup of cocaine subjects showed a trend toward blunted PRL response compared to the low-disinhibition control subgroup (mean difference=−1.4, 95% CI=−2.7 to −.63, $p$=.06) but did not differ from the high-disinhibition control subgroup (mean difference=−.97, 95% CI=−1.9 to −1.1, $p$=.14). The high and low subgroups of controls (mean difference=−.13, 95% CI=−1.5 to 1.2, $p$=.84) did not differ from each other with respect to the PRL responses.

## Correlations between maximum change in PRL (ΔPRL) and behavioral measures in cocaine patients

ΔPRL values were significantly lower in cocaine patients compared to controls [$F$(1,67)=22.8, $p$<.001]. We have previously reported factor analysis of the SSS and BDHI to show that that the instruments assess separate dimensions of sensation seeking and hostility (Patkar et al. 2002). Since each instrument appears to measure separate components, we first performed correlations of total BDHI and SSS scores with ΔPRL (peak PRL−baseline PRL) in cocaine subjects ($n$=35). ΔPRL was negatively correlated with total BDHI scores ($r$=−.38, $p$<.05) and showed a trend of negative correlation with total SSS scores ($r$=−24, $p$=.10). We then correlated subscales of BDHI and SSS with ΔPRL. There was a significant negative correlation of BDHI subscales of indirect aggression ($r$=−38, $p$<.05) and irritability (−.31, $p$<.05) with ΔPRL. Correlations of other BDHI subscales were not significant. Only the disinhibition subscale of SSS was significantly correlated with ΔPRL ($r$=−.41, $p$<.02). ΔPRL was not correlated with peak $m$-CPP levels ($r$=.09).

Hierarchical regressions were performed to determine whether disinhibition and aggression contributed toward predicting ΔPRL. Step 1 entered the strongest correlate (disinhibition subscale scores), step 2 added the total BDHI scores, and step 3 examined whether age, sex, and Beck Depression scores entered as a block accounted for any additional variance. This analytic strategy permits examination of the strongest predictor first followed by examination of residual variance contributed to by any potentially significant variables, thereby avoiding errors that may be introduced by multiple comparisons. The results are summarized in Table 2.

**Table 2** Hierarchical regression to predict maximum change in PRL (ΔPRL) from aggression and disinhibition in cocaine-dependent patients

| ΔPRL (Outcome variable) | $\beta$ coefficient | 95% CI | $R^2$ variance | $F$ |
|---|---|---|---|---|
| Step 1: disinhibition subscale scores (SSS) | −.34 | −2.09–.11 | .18 | 3.93[a] |
| Step 2: total scores on BDHI | −.27 | −.26–.18 | .26 | |
| Step 3: age, sex, and Beck Depression scores | −.16 | −.07–.12 | .24 | |

[a] $F$(5,29)=3.93, $p$<.05

Overall, a combination of disinhibition subscale scores of the SSS and total BDHI scores significantly predicted ΔPRL. Disinhibition was the strongest predictor and contributed 18% of the variance in predicting ΔPRL, while total BDHI scores added 8% variance to the model. A combination of BDI scores, age, and sex did not improve prediction of ΔPRL, indicating that the blunted PRL associated with disinhibition and aggression was not accounted for by depressive symptoms, gender, or age.

## ΔPRL and gender

Although we controlled for menstrual phase in women, we also performed separate gender-specific analyses because of previous reports of possible gender differences in PRL response (New et al. 2004). We found that ΔPRL values were not significantly different among men ($n$=22) (5.23±3.08) and women ($n$=13) (6.85±2.64), among cocaine patients [$F$(1,34)=2.48, $p$=.12] or controls [men ($n$=22)=8.97±2.88, women ($n$=11)=9.28±3.34, $F$(1,32)=.08, $p$=.89]. Age was not correlated with ΔPRL in cocaine patients ($r$=−.08) or controls ($r$=−.10). Consistent with the overall group differences, ΔPRL values were significantly lower in cocaine-dependent men compared to healthy men [$F$(1,43)=20.2, $p$<.001] and among cocaine-dependent women compared to healthy women [$F$(1,23)=4.12, $p$<.05].

# Discussion

We found that the PRL response following $m$-CPP was significantly blunted in cocaine patients compared with controls. This is consistent with findings from a previous study of $m$-CPP challenge in cocaine abusers (Buydens-Branchey et al. 1997) that utilized a similar protocol and same dose of $m$-CPP. Furthermore, similar results were reported in cocaine abusers using another 5-HT probe, $d$, $l$-fenfluramine (Buydens-Branchey et al. 1999). In contrast,

another study using *m*-CCP found no differences in PRL responses between cocaine abusers and controls (Handelsman et al. 1998). However, that study used lower doses of *m*-CPP and studied a different clinical population compared with our study. The PRL-stimulating effects of *m*-CPP have been shown to be related to its 5-HT effects, in particular its agonist actions at the postsynaptic 5-$HT_{2C}$ receptors (Murphy et al. 1991; Thomas et al. 1996). Human studies have also indicated that doses of *m*-CPP used in challenge paradigms did not significantly alter dopamine or noradrenaline activity (Kahn et al. 1992; Silverstone et al. 1994). Therefore, it may be reasonable to attribute the blunted PRL response observed in cocaine abusers to disturbances in 5-HT function, possibly postsynaptic 5-$HT_{2C}$ receptor subsensitivity.

By categorizing patients into subgroups based on disinhibition and aggression, we found a differential response to *m*-CPP challenge, with more pronounced blunting in the high-disinhibition and high-aggression subgroups. This difference was observed only in cocaine patients and not in controls. Previous approaches to identify biological differences in substance abusers based on pharmacological challenges have also suggested that subgroups characterized by aggression may differ in neuroendocrine or behavioral responses (Buydens-Branchey et al. 1997; George et al. 1997). Taken together, these findings lend support to the concept that cocaine dependence may be heterogeneous and that biological differences may underlie some aspects of the clinical heterogeneity.

The data regarding women with substance abuse diagnoses and neuroendocrine challenge studies are limited despite 30–40% of crack cocaine abusers being women (Wong et al. 2002) and evidence that neural mechanisms underlying relapse may differ between male and female cocaine abusers (Tucker et al. 2004). We therefore included women in our study. Recent neuroimaging studies that have used *m*-CPP as a 5-HT stimulus have not shown a gender effect (New et al. 2002). For these reasons, we included women controlling for effects of menstruation in our sample. While the differences in the PRL responses between cocaine abusers and controls were stronger in men, they were also significant in women, indicating that the 5-HT disturbances related to chronic cocaine use seem to occur in both men and women.

The strong negative correlations of ΔPRL with disinhibition and aggression contributes to the evidence that 5-HT abnormalities may mediate behaviors characterized by poor impulse control. Only the disinhibition subscale was correlated with ΔPRL, suggesting that not all dimensions of sensation-seeking behavior may have 5-HT correlates. In contrast, both the hostility and motor aggression factors were negatively associated with ΔPRL. Of note, disinhibition was the stronger predictor of variance in ΔPRL compared to aggression; however, together both accounted for about 25% of variance in ΔPRL. This indicates that the 5-HT dysfunction in cocaine abuse is not fully accounted for by disinhibition and aggression, and other clinical and biological factors possibly related to cocaine use could be implicated. In this context, sequential challenges with *d*, *l*-fenfluramine have revealed that the PRL response tends to normalize with extended abstinence from cocaine, implying that cocaine use may also contribute to the 5-HT disturbances (Buydens-Branchey et al. 1999).

The present data should be interpreted in the context of certain limitations. Ideally, each subject would have undergone a placebo-controlled challenge on 2 separate days. The logistical constraints of an outpatient sample necessitated the modified paradigm. However, this design did not appear to compromise the data because the primary end points included neuroendocrine instead of behavioral measures, and the PRL estimations were performed by personnel blinded to the clinical information. Previous work has also shown that the effect of time and stress of challenge test accounts for a very small percentage of drug vs placebo PRL levels (Coccaro et al. 1989). We did not measure the cortisol response along with the PRL estimations because the two measures have been concordant in more than 90% of studies (Murphy et al. 1996). Another limitation is that the cocaine-dependent individuals had a history of using a variety of other substances. This reflects the "real-world" clinical population in treatment settings (Patkar et al. 2004). While we controlled for the effects of tobacco smoking and monitored for abstinence from drug and alcohol for 2 weeks, we cannot exclude the possibility that use of other substances could have affected the findings.

In conclusion, the present study demonstrates that cocaine-dependent patients have diminished PRL response to the mixed 5-HT agonist *m*-CPP. The blunted response is more pronounced in the subgroup of cocaine patients with high disinhibition and aggression. This indicates that disturbances in 5-HT function, possibly postsynaptic 5-$HT_{2C}$ receptor function, occur in subgroups of cocaine abusers characterized by high disinhibition and aggression. Further studies are necessary to clarify the extent to which the 5-HT disturbances signal a vulnerability to impulsive–aggressive behavior or are a consequence of cocaine dependence, and whether these disturbances predict response to treatment with 5-HT agents.

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## References

Aronson SC, Black JE, McDougle CJ, Scanley BE, Jatlow P, Kosten TR, Heninger CR, Price LH (1995) Serotonergic mechanisms of cocaine effects in humans. Psychopharmacology (Berl) 119:179–185

Aulakh CS, Hill JL, Murphy DL (1992) Effects of various serotonin receptor subtype-selective antagonists alone and on *m*-chlorophenylpiperazine-induced neuroendocrine changes in rats. J Pharmacol Exp Ther 263:588–595

Batki SL, Manfredi LB, Peyton J, Jacob P, Jones RT (1993) Fluoxetine for cocaine dependence in methadone maintenance: quantitative plasma and urine cocaine/benzoylecgonine concentrations. J Clin Pharmacol 13:243–250

Beck AT, Steer RA (1987) Beck depression inventory. The psychological corporation. Harcourt Brace Jovanovich, San Antonio

Broocks A, Meyer T, Gleiter CH, Hillmer-Vogel U, George A, Bartmann U et al (2001) Effect of aerobic exercise on behavioral and neuroendocrine responses to meta-chlorophenylpiperazine and to ipsapirone in untrained healthy subjects. Psychopharmacologia 155:234–241

Burmeister JJ, Lungren EM, Neiswander JL (2003) Effects of fluoxetine and d-fenfluramine on cocaine-seeking behavior in rats. Psychopharmacology (Berl) 168:146–154

Burmeister JJ, Lungren EM, Kirschner KF, Neiswander JL (2004) Differential roles of 5-HT receptor subtypes in cue and cocaine-seeking behavior in rats. Neuropsychopharmacology 29:660–668

Buss AH, Durkee A (1957) An inventory for assessing different kinds of hostility. J Consult Psychol 21:343–348

Buydens-Branchey L, Branchey M, Fergeson P, Hudson J, McKernin C (1997) The meta-chlorophenylpiperazine challenge test in cocaine addicts: hormonal and psychological responses. Biol Psychiatry 41:1071–1086

Buydens-Branchey L, Branchey M, Hudson J, Rothman M, Fergeson P, McKernin C (1998) Effect of fenfluramine challenge on cocaine craving in addicted male users. Am J Addict 7:142–155

Buydens-Branchey L, Branchey M, Hudson J, Rothman M, Fergeson P, McKernin C (1999) Serotonergic function in cocaine addicts: prolactin responses to sequential D,L-fenfluramine challenges. Biol Psychiatry 45:1300–1306

Calogero AE, Bagdy G, Moncada ML, D'Agata R (1993) Effect of selective serotonin agonists on basal, corticotrophin-releasing hormone- and vasopressin-induced ACTH release in vitro from rat pituitary cells. J Endocrinol 136:381–387

Castanon N, Scearce-Levie K, Lucas JJ, Rocha B, Hen R (2000) Modulation of the effects of cocaine by 5-HT1B receptors: a comparison of knockouts and antagonists. Pharmacol Biochem Behav 67:559–566

Cervo L, Rozio M, Ekalle-Soppo CB, Carnovali F, Santangelo E, Samanin R (2002) Stimulation of serotonin 1B receptors induces conditioned place aversion and facilitates cocaine place conditioning in rats. Psychopharmacology (Berl) 163:142–150

Cloninger CR (1987) Neurogenic adaptive mechanisms in alcoholism. Science 236:410–416

Coccaro EF, Siever LJ, Klar HM, Maurer G, Cochrane K, Cooper TB et al (1989) Serotonergic studies in patients with affective and personality disorders. Arch Gen Psychiatry 47:587–599

Coccaro EF, Kavoussi RJ, Hauger RL (1995) Physiological responses to d-fenfluramine and ipsapirone challenge correlate with indices of aggression in males with personality disorders. Int Clin Psychopharmacol 10:177–179

Coccaro EF, Kavoussi RJ, Sheline YI, Berman ME, Csernansky JG (1996) Impulsive aggression in personality disorder correlates with tritiated paroxetine binding in the platelet. Arch Gen Psychiatry 53:531–536

Cohen J, Cohen P (1983) Applied multiple regression/correlation analysis for the behavioral sciences, 2nd edn. Erlbaum, Hillsdale, pp 545

Cunningham KA, Bradberry CW, Chang AS, Reith ME (1996) The role of serotonin in the actions of psychostimulants, molecular and pharmacological analyses. Behav Brain Res 73:93–102

Davidson C, Lee TH, Xiong Z, Ellinwood EH (2002) Ondansetron given in the acute withdrawal from a repeated cocaine sensitization dosing regimen reverses the expression of sensitization and inhibits self-administration. Neuropsychopharmacology 27:542–553

Farren CK, Ziedonis D, Clare AW, Dinan TG (1995) D-Fenfluramine-induced prolactin responses in post-withdrawal alcoholics and controls. Alcohol Clin Exp Res 19:1578–1582

First MB, Gibbon M, Spitzer RL, Williams JBW (1997) Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-IV): clinician version. American Psychiatric, Washington, DC

Fishbein DH, Lozovsky D, Jaffe JH (1989) Impulsivity, aggression, and neuroendocrine responses to serotonergic stimulation in substance abusers. Biol Psychiatry 25:1049–1066

Fletcher PJ, Grottick AJ, Higgins GA (2002) Differential effects of the 5-HT(2A) receptor antagonist M100907 and the 5-HT(2C) receptor antagonist SB242084 on cocaine-induced locomotor activity, cocaine self-administration and cocaine-induced reinstatement of responding. Neuropsychopharmacology 27:576–586

Frankel PS, Cunningham KA (2004) M-Chlorophenylpiperazine (mCPP) modulates the discriminative stimulus effects of cocaine through actions at the 5-HT2C receptor. Behav Neurosci 118:157–162

Fulker DW, Eyseneck SBG, Zuckerman M (1980) The genetics of sensation seeking. J Pers 14:261–281

George DT, Benkelfat C, Nutt DJ, Hill JL, Phillips MJ, Wynne D et al (1997) A comparison of behavioral and biochemical responses to meta-chlorophenylpiperazine in subtypes of alcoholics. Am J Psychiatry 154:81–87

Gijsman HJ, Cohen AF, van Gerven JM (2004) The application of the principles of clinical drug development to pharmacological challenge tests of the serotonergic system. J Psychopharmacol 18:7–13

Goveas JS, Csernansky JG, Coccaro EF (2004) Platelet serotonin content correlates inversely with life history of aggression in personality-disordered subjects. Psychiatry Res 126:23–32

Handelsman L, Kahn RS, Sturiano C, Rinaldi PJ, Gabriel S, Schmeidler JP et al (1998) Hostility is associated with a heightened prolactin response to meta-chloropiperazine in abstinent cocaine addicts. Psychiatry Res 80:1–12

Heatherton TF, Kozlowski LT, Frecker RC (1991) The Fagerstrom test for nicotine dependence: a revision of the Fagerstrom tolerance questionnaire. Br J Addict 86:1119–1127

Heidbreder CA, Oertle T, Feldon J (1999) Dopamine and serotonin imbalances in the left anterior cingulate and pyriform cortices following the repeated intermittent administration of cocaine. Neuroscience 89:701–715

Hoyer D, Clarke DE, Fozard JR, Hartig PR, Martin GR, Mylecharane EJ et al (1994) International Union of Pharmacolgy classification of receptors for 5-hydroxytryptamine (serotonin). Pharmacol Rev 46:157–203

Kahn RS, Wetzler S (1991) M-Chloropiperazine as a probe of serotonin function. Biol Psychiatry 30:1139–1166

Kahn RS, Wetzler S, Asnis GM, Kling MA, Suckow RF, van Praag HM (1990) Pituitary hormone responses to meta-chlorophenylpiperazine in panic disorder and healthy control subjects. Psychiatry Res 37:24–35

Kahn RS, Knott P, Gabriel S, DuMont K, Mastroianni L, Davidson M (1992) Effect of m-chlorophenylpiperazine on plasma homovanillic acid concentrations in healthy subjects. Biol Psychiatry 32:1055–1061

King GR, Pinto G, Konen J, Castro G, Tran S, Hilburn C (2002) The effects of continuous 5-HT(3) receptor antagonist administration on the subsequent behavioral response to cocaine. Eur J Pharmacol 449:253–259

Krystal JH, Webb E, Cooney N, Kranzler HR, Southwick SW, Heninger GR et al (1996) Serotonergic and noradrenergic dysregulation in alcoholism: m-chlorophenylpiperazine and yohimbine effects in recently detoxified alcoholics and healthy comparison subjects. Am J Psychiatry 153:83–92

Lee MA, Meltzer HY (1994) Blunted oral body temperature response to MK-212 in cocaine addicts. Drug Alcohol Depend 35:217–222

Lesch KP, Merchdorf U (2000) Impulsivity, aggression and serotonin: a molecular psychobiological perspective. Behav Sci Law 18:581–604

Linnoila M, Virkkunen M, Scheinen M, Nuutila A, Rimon R, Goodwin FK (1983) Low cerebrospinal fluid 5-hydoxyindolacetic acid concentration differentiates impulsive from non-impulsive violent behavior. Life Sci 33:2609–2614

McMahon LR, Cunningham KA (2001) Antagonism of 5-hydroxytryptamine(2a) receptors attenuates the behavioral effects of cocaine in rats. J Pharmacol Exp Ther 297:357–363

Miles LE, Lipschitz DA, Bieber CP, Cook JD (1974) Measurement of serum ferritin by a 2-site immunoradiometric assay. Anal Biochem 61:209–224

Moeller FG, Steinberg JL, Petty F, Fulton M, Cherek DR, Kramer G et al (1994) Serotonin and impulsive/aggressive behavior in cocaine dependent patients. Prog Neuropsychopharmacol Biol Psychiatry 18:1027–1035

Monsma FJ Jr, Shen Y, Ward RP, Hamblin MW, Sibley DR (1993) Cloning and expression of a novel serotonin receptor with high affinity for tricyclic psychotropic drugs. Mol Pharmacol 43:320–327

Moss HB, Yao JK, Panzak GL (1990) Serotonergic responsivity and behavioral dimensions in antisocial personality disorder with substance abuse. Biol Psychiatry 28:325–338

Muller CP, Carey RJ, Huston JP (2003) Serotonin as an important mediator of cocaine's behavioral effects. Drugs Today 39:497–511

Murphy DL, Mueller EA, Hill JL, Tolliver TJ, Jacobson FM (1989) Comparative anxiogenic, neuroendocrine, and other physiologic effects of m-chlorophenylpiperazine given intravenously or orally to healthy volunteers. Psychopharmacology (Berl) 98:275–282

Murphy DL, Lesch KP, Aulakh CS, Pigott TA (1991) Serotonin-selective arylpiperazines with neuroendocrine, behavioral, temperature and cardiovascular effects in humans. Pharmacol Rev 43:47–55

Murphy DL, Aulakh C, Mazzolo-Pomietto P, Briggs NC (1996) Neuroendocrine responses to serotonergic agonists as indices of the functional status of central serotonin neurotransmission in humans: a preliminary comparative analysis of neuroendocrine endpoints versus other endpoint measures. Behav Brain Res 73:209–214

Neumaier JF, Vincow ES, Arvanitogiannis A, Wise RA, Carlezon WA Jr (2002) Elevated expression of 5-HT1B receptors in nucleus accumbens effects sensitizes animals to cocaine. J Neurosci 22:10856–10863

New AS, Hazlett EA, Buchsbaum MS, Goodman M, Reynolds D, Mitropoulo V et al (2002) Blunted prefrontal cortical 18-fluorodeoxyglucose positron emission tomography response to meta-chlorophenylpiperazine in impulsive aggression. Arch Gen Psychiatry 59:621–629

New AS, Trestman RF, Mitropoulou V, Goodman M, Koenigsberg HH, Silverman J et al (2004) Low prolactin response to fenfluramine in impulsive aggression. J Psychiatr Res 38:223–230

O'Keane VO, Moloney E, O'Neill H, O'Connor A, Smith R, Dinan TG (1992) Blunted prolactin responses to d-fenfluramine in sociopathy: evidence for subsensitivity of central serotonergic function. Br J Psychiatry 160:643–646

Patkar AA, Berrettini WH, Hoehe M, Thornton CC, Gottheil E, Hill KP (2002) Serotonin transporter polymorphisms and measures of impulsivity, aggression, and sensation seeking among African-American cocaine-dependent individuals. Psychiatry Res 110:103–115

Patkar AA, Gottheil E, Berrettini WH, Hill KP, Thornton CC, Weinstein SP (2003) Relationship between platelet serotonin uptake sites and measures of impulsivity, aggression, and craving among African-American cocaine abusers. Am J Addict 12:432–437

Patkar AA, Thornton CC, Mannelli P, Hill KP, Gottheil E, Vergare MJ et al (2004) Comparison of pretreatment characteristics and treatment outcomes for alcohol-, cocaine-, and multisubstance-dependent patients. J Addict Dis 23:93–109

Roy A, Adinoff B, Linnoila M (1988) Acting out hostility in normal volunteers: negative correlation with levels of 5HIAA in cerebrospinal fluid. Psychiatry Res 24:187–194

Satel SL, Krystal JH, Delgado PL, Kosten TR, Charney DS (1995) Tryptophan depletion and attenuation of cue-induced craving for cocaine. Am J Psychiatry 152:778–783

Siever LJ, Buchsbaum MS, New AS, Speigel-Cohen J, Wei T, Hazlett EA et al (1999) d,l-Fenfluramine response in impulsive personality disorder assessed with [18F] fluorodeoxyglucose positron emission tomography. Neuropsychopharmacology 20:413–423

Silverstone PH, Rue JE, Franklin M, Hallis K, Camplin G, Laver D et al (1994) The effects of administration of mCPP on psychological, cognitive, cardiovascular, hormonal and MHPG measurements in human volunteers. Int Clin Psychopharmacol 9:173–178

Sleight AJ, Carolo C, Petit N, Zwingelstein C, Bourson A (1995) Identification of 5-hydroxytryptamine7 receptor binding sites in rat hypothalamus: sensitivity to chronic antidepressant treatment. Mol Pharmacol 47:99–103

Stanley B, Molcho A, Stanley M, Winchel R, Gameroff MJ, Parsons B et al (2000) Association of aggressive behavior with altered serotonergic function in patients who are not suicidal. Am J Psych 157:609–614

Suckow RF, Cooper TB, Kahn RS (1990) High performance liquid chromatographic method for the analysis of plasma m-chlorophenylpiperazine. J Chromatogr 528:228–234

Thomas DR, Gager TL, Holland V, Brown AM, Wood MD (1996) m-Chlorophenylpiperazine (mCPP) is an antagonist at the cloned human 5-HT2B receptor. Neuroreport 17:1457–1460

Tucker KA, Browndyke JN, Gottschalk PC, Confrancesco AT, Kosten TR (2004) Gender-specific vulnerability for rCBF abnormalities among cocaine abusers. Neuroreport 15:797–801

Twitchell GR, Hanna GL, Cook EH, Stoltenberg SF, Fitzgerald And HE, Zucker RA (2001) Serotonin transporter promoter polymorphism genotype is associated with behavioral disinhibition and negative affect in children of alcoholics. Alcohol Clin Exp Res 25:953–959

von Knorring AL, Bohman M, von Knorring L, Oreland L (1985) Platelet MAO activity as a biological marker in subgroups of alcoholism. Acta Psychiatr Scand 72:51–58

Walsh SL, Cunningham KA (1997) Serotonergic mechanisms involved in the discriminative stimulus, reinforcing and subjective effects of cocaine. Psychopharmacology (Berl) 130:41–58

Wong CJ, Badger GJ, Sigmon SC, Higgins ST (2002) Examining possible gender differences among cocaine-dependent outpatients. Exp Clin Psychopharmacol 10:316–323

Yatham LN, Steiner M (1993) Neuroendocrine probes of serotonergic function: a critical review. Life Sci 53:447–463

Zuckerman M (1993) P-impulsive sensation seeking and its behavioral, psychophysiological and biochemical correlates. Neuropsychobiology 28:30–36