Altered Response to Meta-Chlorophenylpiperazine in Anorexia Nervosa: Support for a Persistent Alteration of Serotonin Activity After Short-Term Weight Restoration

Guido K. Frank,1 Walter H. Kaye,1* Theodore E. Weltzin,2 James Perel,1 Howard Moss,3 Claire McConaha,1 and Christine Pollice1

1 University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania
2 University of Wisconsin, Madison, Wisconsin
3 Temple University, Philadelphia, Pennsylvania

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Abstract: Objective: Patients with anorexia nervosa (AN) have disturbances of appetite and behaviors, such as dysphoria, inhibition, and obsessions, that could be related to altered serotonin activity. To investigate such relationships, we administered meta-chlorophenylpiperazine (m-CPP), a relatively serotonin-specific drug. Methods: To avoid the confounding effects of malnutrition or weight loss, we studied 12 patients with restricting-type AN between 5 and 17 days after a return to a normal weight and while on a stable dietary intake. We compared them to 12 healthy control women (CW). m-CPP was administered double blind and placebo controlled. Results: Although weight restored, AN women had lower body weight and increased ratings for depression and obsessionality compared with CW. After m-CPP, AN women had an elevation in mood and a reduction in body image distortion when compared with placebo. After m-CPP, groups had similar cortisol, adrenocorticotropin (ACTH), and growth hormone responses whereas AN women had an uncertain reduction in prolactin response. Discussion: These data support other studies that suggest that altered serotonin activity persists after weight restoration in AN patients. The finding that m-CPP temporarily improved mood and reduced body image distortions supports the hypothesis that altered serotonin activity may contribute to the pathophysiology of AN. © 2001 by John Wiley & Sons, Inc. Int J Eat Disord 30: 57–68, 2001.

Key words: anorexia nervosa; serotonin; m-CPP; OCD
INTRODUCTION

Anorexia nervosa (AN) is characterized by a refusal to maintain body weight over a minimal weight normal for age and height; an intense fear of gaining weight or becoming fat, even though underweight; and a disturbance in the way in which one's body weight, size, or shape is experienced (e.g., the person claims to “feel fat” even when emaciated. American Psychiatric Association [APA], 1994).

Alterations of the serotonin neurotransmitter system may contribute to the pathophysiology of AN (Brewerton & Jimerson, 1996; Wolfe, Metzger & Jimerson, 1997; Walsh & Devlin, 1998). An increase in intrasynaptic serotonin reduces food consumption (Leibowitz & Alexander, 1998; Blundell, 1984). Several serotonin receptors and sites for serotonergic action involved in feeding and satiety have been identified (Simansky 1996; Leibowitz & Alexander, 1998). Altered brain serotonin activity could play a role in increased satiety and weight loss in AN patients. In addition, more than 50 years of investigations suggest that anorexics tend to be inhibited, rigid, perfectionistic, and obsessional (Palmer & Jones, 1939). Such traits may be premorbid and persist after recovery (Kaye et al., 1992; Casper, 1990, Srinivasagam et al., 1995).

Underweight anorexics may have diminished serotonin activity (Walsh & Devlin, 1998; Kaye, Gendall, & Stober, 1998). In contrast, increased levels of cerebrospinal fluid (CSF) 5-hydroxy indoleacetic acid (5-HIAA), the major metabolite of serotonin, has been found after long-term recovery that could be a premorbidly existing trait. Low levels of CSF 5-HIAA are associated with impulsive and aggressive behavior (Asberg, Traskman, & Thoren, 1976; Van Praag, 1983; Linnoila et al., 1983), whereas behaviors in anorexic patients tend to be the opposite of those in impulsive and aggressive patients.

One tool that can be used to investigate the relationships between brain serotonin activity and behavior is meta-chlorophenylpiperazine (m-CPP). m-CPP binds as an agonist at the 5HT1C and 5HT2C (Graeff, 1996), as an antagonist at the 5HT2B (Thomas, Gager, Holland, Brown, & Wood, 1996), and as a partial agonist at the 5HT2A (Willins & Meltzer, 1997) and 5HT3 (Hoyer, Neijt, & Karpf, 1989; Kahn & Wetzler, 1991) receptor sites in the brain. m-CPP may also act at presynaptic serotonin transporter sites in humans (Baumann, Mash, & Staley, 1995). It binds potently to alpha-2 adrenergic receptors, but weakly to dopamine and muscarinic cholinergic receptors (Hamik & Peroutka, 1989). m-CPP is a relatively selective serotonin agonist that can be used to assess serotonin functional activity in humans.

To reduce the confounding effects of malnutrition and low weight, we studied a group of subjects who had previously been underweight with AN and who, at the time of this study, had been restored to a normal body weight in an inpatient treatment program. We studied anorectic patients who restricted, but did not binge.

METHODS

Subjects

Subjects (all female) were hospitalized for treatment on the Eating Disorders Unit of Western Psychiatric Institute and Clinic, University of Pittsburgh, and gave informed consent for the study. All subjects were medication free for at least 30 days prior to any study.
Twelve patients with AN (short-term weight-restored anorexics) were recruited. At the time of admission to the Eating Disorders Unit, they had met criteria for AN as described in the 4th ed. of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; APA, 1994) and were at 74 ± 6% of average body weight (ABW, range 62–81% ABW). These anorexic patients gained weight in the hospital (21 ± 6% of ABW, range 13–32% ABW) over 71 ± 16 days (range 56–104 days). Anorexics were studied 12 ± 4 days (range 5–17 days) after attaining their target weight (95 ± 2% ABW, range 92–99% ABW). At the time of the study, all AN subjects were consuming 40 to 60 kcal/kg of caloric intake per day. All were food restrictors. None binged, but 3 purged by vomiting or abusing laxatives prior to hospitalization. All anorexic patients were amenorrheic on admission and none had resumption of menses at the time of this study.

Twelve healthy control women (CW) were admitted to a clinical laboratory on the same inpatient unit the night prior to the study. None had significant current or past psychiatric or medical diseases or any symptoms of an eating disorder according to DSM-IV criteria. All had normal menstrual cycles and were studied during the early follicular phase of the menstrual cycle.

Study Design

Subjects were not permitted to eat or smoke from midnight until the study was completed. At 7:30 a.m., an intravenous catheter was inserted in an antecubital vein and kept open with a heparinized 5% dextrose solution. After 1 hr of adaptation, blood samples were obtained at −30, −15, and at 0 min. Then the subject ingested capsules containing 0.5 mg/kg m-CPP or placebo. Blood samples were obtained at 15, 30, 60, 90, 120, 150, 180, and 240 min. After blood sampling was complete, the intravenous catheter was removed.

Subjects were given m-CPP and placebo in random order. For AN subjects, there were 3 ± 3 days between studies. For CW, there were 3 ± 2 days between studies.

Assessments of Mood and Behavior

Standardized Assessments of Depression, Anxiety, and Obsessive-Compulsive Disorder (OCD)

Both groups of subjects were interviewed within a week of this study by a trained rater who was a Ph.D. psychologist. This trained rater administered the Hamilton Anxiety and Depression Rating Scales. Obsessive-compulsive features were assessed by a trained rater who administered the Yale-Brown Obsessive Compulsive Scale (YBOCS; Goodman et al., 1989, Goodman et al., 1989) after excluding core anorexic traits as described by Kaye et al. (1992).

Psychiatric Assessment of Behavioral Response to m-CPP and Placebo

Ratings of psychological state on the morning prior to the m-CPP or placebo challenge and after the administration of m-CPP and placebo were done by two methods. First, behavioral states were assessed by two psychiatrists (TEW and WHK) who were blind to whether m-CPP or placebo had been administered. These assessments were done at baseline and at 90 and 180 min after m-CPP or placebo administration. These psychological ratings were adapted from those previously described in the literature (Asberg, Montgomery, Perris, Schalling, & Sedvall, 1978; Murphy, Pickar, & Alterman, 1982; Overall & Gorham, 1962). At each time point, the following psychological states were assessed
using a 6-point scale: anxiety, depression, euphoria, body image distortion, and obsessive thinking. In this scale, 0 denotes the absence of a behavior. The numbers 1 through 6 denote increasingly more pronounced symptoms with each number anchored by a descriptive phrase. Peak changes were determined by taking the largest deviation from baseline at either 90 or 180 min after ingestion of m-CPP or placebo and subtracting the baseline score. For body image distortion, we devised a similar 0–6-point scale of relative intensity and preoccupation with fears of being fat (0, not present; 2, feels fat, but can believe possibility that really is not too fat; 4, feels too fat, unshakable belief that she is too fat, but able to concentrate on other thoughts; 6, relentless and continuous preoccupation with feeling too fat, unshakable belief that she is too fat, unable to concentrate on other thoughts).

**Subject Self-Assessment of Behavioral Response to m-CPP and Placebo**

Second, subjects self-rated their moods at baseline and at 30-min intervals for 12 hr after receiving m-CPP or placebo on a 24-item self-rating scale with extremes from 0 (*not present*) to 6 (*very marked*).

**Assays**

Methods used to measure plasma cortisol (Kao, Voina, Nichols, & Horton, 1975), adrenocorticotropic (ACTH), growth hormone (Odell, Rayford, & Ross, 1967), and prolactin (Sinha, Selby, Lewis, & Vanderlaan, 1973) have been previously described. The sensitivity and interassay coefficient of variation (CV) for cortisol were 1 μg/dl and 2.69, respectively; for ACTH, 5 pg/ml and 1.56, respectively; for growth hormone, 5 ng/ml and 2.30, respectively; and for prolactin, 1 ng/ml and 2.86, respectively.

**Statistical Procedures**

Statistical analysis was carried out using BMDP statistical software (Dixon, 1985). Hormonal concentrations for ACTH, cortisol, growth hormone, and prolactin were analyzed by using the following methods. First, baseline levels (determined by averaging hormone concentration for the day of m-CPP and placebo for the three prechallenge blood draws \([×30, −15, and 0 \text{ min}]\)) were compared using group *t* tests for between-group comparisons (anorexics vs. controls). Second, to determine the increase in hormone secretion in response to m-CPP, the area under the curve (AUC) was calculated using the trapezoidal method. The AUC for the placebo condition was then subtracted from the m-CPP condition. Third, an analysis of variance (ANOVA) with a repeated measures design was used to determine the response to drug (m-CPP vs. placebo) in the two diagnostic groups (anorexics vs. controls), with respect to mean response and trends over time.

Psychological symptoms were analyzed using the following methods. First, diagnostic group differences for baseline and peak change (peak minus baseline) assessments were done using group *t* tests and ANOVA using the baseline values as covariates (ANCOVA). Second, drug condition difference for peak change and peak change compared with baseline were determined separately for each diagnostic group using paired *t* tests. Third, repeated measures ANOVA was used to examine group and drug effects over time for self-ratings of mood. However, nonnormally distributed values were also assessed using Mann-Whitney *U* tests and exact significant levels. Values are expressed as *M ± SD.*
RESULTS

Short-term recovered anorexics weighed significantly less and were younger than control subjects (Table 1). In the past, short-term recovered anorexics, in comparison to controls, had a significantly lower lifetime low percent body weight and a trend toward having a lower lifetime high percent body weight. Subjects had similar ages of menarche.

Plasma m-CPP Concentrations

Plasma m-CPP levels were obtained at 60, 120, 180, and 240 min for 9 anorexics and 11 controls. A repeated measure ANOVA showed no difference between plasma m-CPP levels for Drug × Time interaction between these two groups ($df = 3.54$, $F = 1.22$, $p = .31$).

Hormonal Response

In terms of mean baseline values (combining the three baseline values for the day of the m-CPP and the day of the placebo), the anorexics had significantly reduced prolactin and cortisol levels and a trend toward elevated growth hormone compared with the controls (Table 2).

By repeated measures ANOVA, there was no difference for prolactin for Drug × Time × Group ($df = 8,176$, $F = 1.12$, $p = .35$). However, calculation of net AUC (the difference

<table>
<thead>
<tr>
<th>Results</th>
<th>Controls</th>
<th>Anorexics</th>
<th>$t$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>21 ± 3</td>
<td>17 ± 2</td>
<td>4.85</td>
<td>.0001</td>
</tr>
<tr>
<td>Percent ABW</td>
<td>101 ± 9</td>
<td>95 ± 2</td>
<td>2.44</td>
<td>.03</td>
</tr>
<tr>
<td>Percent high ABW</td>
<td>105 ± 8</td>
<td>97 ± 14</td>
<td>1.75</td>
<td>.1</td>
</tr>
<tr>
<td>Percent low ABW</td>
<td>93 ± 6</td>
<td>69 ± 8</td>
<td>8.15</td>
<td>.0001</td>
</tr>
<tr>
<td>Age of onset</td>
<td>15 ± 3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age of menarche</td>
<td>14 ± 2</td>
<td>13 ± 1</td>
<td>1.24</td>
<td>NS</td>
</tr>
<tr>
<td>Y-BOCS</td>
<td>3 ± 3</td>
<td>22 ± 5</td>
<td>9.64</td>
<td>.0001</td>
</tr>
<tr>
<td>Hamilton Depression</td>
<td>1 ± 3</td>
<td>15 ± 10</td>
<td>4.48</td>
<td>.001</td>
</tr>
<tr>
<td>Hamilton Anxiety</td>
<td>4 ± 3</td>
<td>13 ± 5</td>
<td>4.91</td>
<td>.0001</td>
</tr>
</tbody>
</table>

Note: ABW = average body weight; YBOCS = Yale-Brown Obsessive Compulsive Scale.

Table 2. Comparison of 12 normal control women and 12 short-term weight-restored women with anorexia nervosa

<table>
<thead>
<tr>
<th>Hormones</th>
<th>Controls</th>
<th>Anorexics</th>
<th>$t$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline prolactin (ng/ml)</td>
<td>8.1 ± 3.0</td>
<td>4.2 ± 2.6</td>
<td>3.31</td>
<td>.003</td>
</tr>
<tr>
<td>Prolactin (ng/ml/240 min AUC)</td>
<td>743 ± 509</td>
<td>345 ± 353</td>
<td>2.22</td>
<td>.04</td>
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<tr>
<td>Baseline cortisol (μg/dl)</td>
<td>16.9 ± 7.1</td>
<td>11.8 ± 3.6</td>
<td>2.23</td>
<td>.04</td>
</tr>
<tr>
<td>Cortisol (μg/dl/240 min AUC)</td>
<td>643 ± 615</td>
<td>460 ± 373</td>
<td>.88</td>
<td>NS</td>
</tr>
<tr>
<td>Baseline ACTH (pg/ml)</td>
<td>19.6 ± 6.2</td>
<td>15.9 ± 5.9</td>
<td>1.48</td>
<td>NS</td>
</tr>
<tr>
<td>ACTH (pg/ml/240 min AUC)</td>
<td>1002 ± 1782</td>
<td>696 ± 1026</td>
<td>.50</td>
<td>NS</td>
</tr>
<tr>
<td>Baseline growth hormone (ng/ml)</td>
<td>1.3 ± 1.7</td>
<td>3.5 ± 3.8</td>
<td>1.82</td>
<td>.09</td>
</tr>
<tr>
<td>Growth hormone (ng/ml/240 min AUC)</td>
<td>176 ± 245</td>
<td>79 ± 231</td>
<td>1.00</td>
<td>NS</td>
</tr>
</tbody>
</table>

Note: AUC = area under the curve; ACTH = adrenocorticotropic.
between the response to m-CPP and the placebo response) revealed that short-term weight-restored anorexics had a significantly blunted prolactin response after m-CPP compared with CW (Table 2).

Drug × Time × Group interaction was not significant for ACTH (df = 8,168, F = 0.61, p = NS), cortisol (df = 8,176, F = .26, p = NS), or growth hormone (df = 8,176, F = 1.17, p = .32). The AUC for cortisol, ACTH, and growth hormone response was similar between groups (Table 2).

**Mood and Behavioral Response**

**Standardized Assessments of Depression, Anxiety, and OCD**

Compared with CW, the AN subjects had significantly elevated baseline ratings on the Hamilton Anxiety and the Hamilton Depression Rating Scale and on the YBOCS (Table 1).

**Psychiatric Assessment of Behavioral Response to m-CPP and Placebo**

Data were nonnormally distributed and Mann-Whitney U tests were applied for group comparisons. The mean baseline assessments on the morning before administration of m-CPP or placebo showed that the AN subjects, compared with CW, had significantly higher scores for anxiety (2.0 ± 1.1 vs. 0.6 ± 0.7, U = 16.0, p = .001), depression (1.9 ± 1.2 vs. 0.3 ± .05, U = 13.0, p < .001), body image distortion (2.4 ± 1.4 vs. 0 ± 0, U = 12.0, p < .001), and obsessional thoughts (1.7 ± 1.6 vs. 0.1 ± 0.3, U = 32.5, p = .02).

We calculated change scores (peak score after m-CPP or placebo minus the baseline score). Given the marked baseline differences in mood between anorexics and controls, only the change scores are presented (Figure 1). After administration m-CPP compared with placebo, anorexic subjects had a significantly greater reduction in body image distortions (U = 33.0, p = .02). Between groups, after m-CPP compared with placebo, anorexics tended to be less anxious compared with controls (U = 43.0, p = .06), were less depressed (U = 36.0, p = .04), and had decreased body image distortions (U = 12.0, p < .001). After a conservative Bonferroni correction for multiple comparisons, body image distortions were still significantly reduced (p < .004).

**Subject Self-Assessment of Behavioral Response to m-CPP and Placebo**

For subject self-rating of changes in mood and behavior, repeated measures ANOVAs showed a significant Group × Drug × Time difference for only two of the self-ratings of behavioral states. That is, after m-CPP, anorexics had an increase in elation (df = 7,154, F = 2.48, p = .02) and feeling strange (df = 7,154, F = 3.58, p = .001).

Compared with the CW (n = 12), the AN women (n = 12, Table 3) had significantly higher baseline values for feeling anxious (t = 3.09, p = .01), depressed (t = 3.02, p = .01), irritable (t = 2.61, p = .02), difficulty concentrating (t = 2.43, p = .02), and sad (t = 3.10, p = .01).

We compared differences between baseline value and change at 120 min after m-CPP versus the change at 120 min after placebo within groups. For anorexic patients, the peak effects of m-CPP on elation occurred at 120 min (Table 3; t = 2.31, p = .03). At 120 min after administration of m-CPP, anorexics had a significant increase in feeling strange (t = 2.62, p = .02). For healthy women, there were no significant m-CPP minus placebo changes from baseline at 120 min (Table 3).

We compared between-group differences in terms of change at 120 min after m-CPP minus the change at 120 min after placebo. We found that anorexics had significantly
greater elation \((t = 2.46, p = .03)\) and felt more strange \((t = 2.52, p = .03)\). This effect persisted when taking into account the baseline values as covariates \((F = 5.41, p = .03\) for elation, \(F = 7.95, p = .01\) for strange). In addition, AN women also felt less anxious after taking baseline values into account as covariates \((F = 4.26, p = .05)\). After a conservative correction for multiple testing (Bonferroni), a tendency toward increased elation \((p = .07)\) still persisted. In part, values were normally and nonnormally distributed. Nonparametric testing resulted in significant group differences between AN patients and CW after m-CPP for being less anxious \((U = 32.5, p = .02)\), more elated \((U = 36, p = .04)\), and a tendency for an increased feeling of strange or unreal \((U = 39.5, p = .06)\). After Bonferroni correction for multiple testing, there was at a trend toward significance for anxiety \((p = .1)\).

**Correlations**

There were no significant relationships for either short-term weight-restored anorexics or controls between the prolactin AUC and current weight, age, baseline assessments,
changes in anxiety, depression, elation, body image distortion, or obsessionality. In NC self-assessments, however, depression correlated positively with anxiety (.7, \( p = .01 \)), sadness (.8, \( p < .01 \)), and irritability (.7, \( p < .01 \)), and feeling strange correlated with feeling elated (.6, \( p = .06 \)). In short-term recovered anorexics, depression correlated with sadness (.9, \( p < .01 \)) and with irritability (.5, \( p = .07 \)), but not with anxiety; feeling strange was positively correlated with elation (.6, \( p = .02 \)) and with anxiety (.6, \( p = .053 \)).

**DISCUSSION**

After m-CPP administration, anorexics had evidence of a blunted prolactin response, but normal cortisol, ACTH, and growth hormone response. m-CPP was associated with increased elation and feeling strange in short-term weight-restored anorexics, as well as with a reduction in dysphoric mood and body image distortion. These data extend previous observations that suggest that anorexics have an alteration in brain serotonin activity that persists after weight recovery.

**Target Behavioral Symptoms**

After short-term weight restoration, anorexic patients had elevations of baseline symptoms of depression, anxiety, and obsessionality. m-CPP administration was associated with a reduction in dysphoric mood states. In fact, AN subjects had an elevation of mood on two separate scales (psychiatric rater and self-assessment). It is well recognized that restrictor anorexics are intense, serious, and inhibited people and that the response to m-CPP was particularly unusual for many of them. Clinically, we noticed that many of the AN subjects were less emotionally constricted and introverted on m-CPP.

We were surprised to find that some anorexic patients had a reduction of distortions of body image and the feeling of being too fat. No scales, to our knowledge, have been...
devised to assess changes in body image distortion in response to a drug challenge. The scale we devised has not been standardized. Still, we found that 9 of the 12 restricting-type anorexic subjects had less preoccupation with feeling too fat after administration of m-CPP. We are not certain whether this change was secondary to elevated mood or reduced inhibition or to some direct effect of the m-CPP on obsessions about body image distortion. Because the scale has not been standardized and because of the existence of a significant baseline difference, this finding has to be viewed with caution.

A previous study investigating m-CPP after weight restoration in AN patients found no behavioral alterations compared with CW (Hadigan, Walsh, Buttinger, & Hollander, 1995). Whereas in our study, weight-restored anorexics showed a decrease in depressive feelings, that study reported a tendency toward more depressed mood in both AN women and CW. In Hadigan et al.’s study, however, subjects were entered at a lower weight, they were not distinguished by anorexia subgroup, and different instruments were used for psychological assessment, which might have contributed to the observed differences. In addition, CW were not studied in the same phase of the menstrual cycle and gonadal hormone levels may have influenced the response to m-CPP (Rubinow, Schmidt, & Roca, 1998).

There has been interest in similarities between AN and OCD patients. Many OCD patients have increased obsessions and anxiety after oral or intravenous administration of m-CPP in most (Zohar, Mueller, Insel, Zohar-Kadouch, & Murphy, 1987; Hollander et al., 1992; Brooks et al., 1998), but not all, studies (Charney, Goodman, & Price, 1988; Goodman et al., 1995). These data suggest that although AN and OCD patients may have a similarity of certain symptoms, they have a difference in pathophysiology in regard to serotonin function. In addition, people with AN and bulimia nervosa (BN) may have differential responses to m-CPP after weight restoration. BN subjects had a dysphoric response to administration of m-CPP (Kaye, Greeno, et al., 1998) and short-term weight-restored bulimic-type anorexics had an increase in anger, tension, and distress after m-CPP (Brewerton et al., 1992; Brewerton & Jimerson, 1996).

### Hormones: Baseline and m-CPP Response

After m-CPP administration, AN patients, compared with CW, had blunted prolactin secretion by calculation of AUC, but not by repeated measures ANOVA. Other studies found a blunted prolactin response to m-CPP in ill and short-term weight-recovered anorexics (Brewerton & Jimerson, 1996; Hadigan et al., 1995). It is important to note that altered prolactin response has also been found in other disorders such as BN, OCD, and subjects with antisocial and borderline personality disorder (Charney, Goodman, & Price, 1988; Hollander et al., 1992; Moss, Yao, & Pauzak, 1990; Stein, et al., 1996).

We found that AN women had reduced baseline cortisol levels, but a normal cortisol response to m-CPP. Reduced basal cortisol concentrations after short-term recovery in AN patients have been noted elsewhere (Gold et al., 1986). Hadigan et al. (1995) found reduced cortisol response to m-CPP prior to but not after weight restoration. It could be speculated that the baseline reduction of cortisol in our study may have altered central 5-HT receptor densities (Lopez, Vazquez, Chalmers, & Watson, 1997), and thus affected the behavioral response to m-CPP. More unspecific serotonin challenges using d-fenfluramine in weight-recovered AN patients (mixed subtypes) did not show alterations in hormonal response compared with controls in one study (O’Dwyer, Lucey, & Russell, 1996), but blunted plasma cortisol after a test meal in another (Ward, Brown, Lightman,
Campbell, & Treasure, 1998). However, both studies did not control for d-fenfluramine plasma levels, and one study did not have a placebo condition.

**Limitations**

AN patients were significantly younger and weighed less than CW. However, these mean differences were small (4 years of age and 6% ABW), and no correlation was found between these demographic variables and outcome measures. AN women were studied soon after weight restoration, a time when they are hypermetabolic and must eat at least 50% more than controls in order to maintain their weight (Weltzin, Fernstrom, Hansen, McConaha, & Kaye, 1991). A hypermetabolic state might also have suppressed the prolactin response to m-CPP (Goodwin, Fairburn, & Cowen, 1987). All AN women were amenorrheic. Estradiol has been shown to stimulate prolactin synthesis (Chan, Means, & O’Malley, 1978), suppress the release of tuberoinfundibular dopamine (which inhibits prolactin, Crowley, 1982), and increase prolactin secretion through its effects on serotonergic neuronal activity (Johnson & Crowley, 1983). Reduced sex steroid activity could have contributed to reduced baseline prolactin and prolactin response to m-CPP.

After Bonferroni correction for multiple testing, only tendencies toward statistical significance persisted, except for body image distortions. However, the reported results consistently occurred in self and clinical rater reports and suggest decreased anxiety and depressive feelings and increased elation. A Type 1 error appears unlikely for the observed changes in response to m-CPP administration. Comorbid lifetime psychiatric diagnoses were not assessed so that the influence of other psychopathology on these results cannot be determined.

**CONCLUSIONS**

The mechanism responsible for elevated mood and/or reduced behavioral inhibition after m-CPP administration is uncertain. Several serotonin receptors have been implicated in the modulation of inhibition, anxiety, and obsessionality (Cowen, 1991; Peroutka et al., 1989; Fuller, 1992). A reduced prolactin response to m-CPP in the studied weight-restored AN women raises the possibility of a reduction in activity of the postsynaptic 5HT1C or 5-HT2C receptor. Data suggest that these receptors may be responsible for central prolactin response (Aulakh, Hill, & Murphy, 1992; Fone, Austin, Topham, Kennett, & Punhani, 1998; Gleason & Shannon, 1998) and for eating behavior and emotional states (Heisler, Chu, & Tecott, 1998; Sargent, Sharpley, Williams, Goodall, & Cowen, 1997). In the future, specific brain imaging studies have to identify receptors specifically involved in prolactin response.

It has been our experience that third and fourth party providers tend to conceptualize AN as a disorder primarily caused by psychosocial factors, despite its high morbidity and mortality. This study suggests that AN patients have disturbances that persist after weight recovery. These data contribute to the argument that patients with AN require medical and psychiatric intervention up to and beyond mere weight restoration.

**REFERENCES**

m-CPP and Anorexia Nervosa


