Testmeal Responses Following m-Chlorophenylpiperazine and L-Tryptophan in Bulimics and Controls

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A wealth of data support a role for serotonin (5-HT) function in the mediation of satiety responses, that are impaired in patients with bulimia nervosa. Testmeal results are presented in which 26 bulimic patients and 17 normal controls were given in randomized, double-blind-fashion, placebo, and the 5-HT agents m-chlorophenylpiperazine (m-CPP, 0.5 mg/kg p.o.) and L-tryptophan (L-TRP, 100 mg/kg I.V.). Three and one-half hours after drug administration, subjects were allowed to eat and lib from a standardized testmeal of 3,500 calories, after which postprandial vomiting was not allowed. M-CPP, but not L-TRP, significantly decreased meal size in the combined group, the controls, and to a lesser extent, the bulimics ($p \leq .06$). Maximum m-CPP

concentrations were inversely correlated to the number of calories consumed in the total group. Following m-CPP, there were significant decreases in carbohydrate, protein, and fat intake in the total group of subjects. There were also trends for decreased carbohydrate and protein intake in the bulimics following m-CPP. There were trends for both m-CPP and L-TRP to reduce fat intake in the controls. Differences in the effects between m-CPP and L-TRP are likely due to differential involvement of 5-HT receptor subtypes at presynaptic and postsynaptic sites. These studies in humans confirm reports in animals that m-CPP decreases food intake, including carbohydrates, protein, and fat in a mixed testmeal.

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Serotonergic manipulations are known to result in marked changes in feeding behaviors, particularly satiety responses (Blundell 1977, 1984, 1986; Blundell and Latham, 1978, 1980, 1982; Latham and Blundell 1979; Samanin et al. 1982; Silverstone and Goodall 1986; Garattini et al., 1988, 1989), which are dysfunctional in bulimic patients (Owen et al. 1985; Chiodo and Latimer 1986; Kissileff et al. 1986). Pharmacologic enhancement of 5-HT neurotransmission in animals and

man generally leads to increased satiety (Blundell 1984, 1986), with the exception of 5-HT_{1A} receptor activation that induces feeding in animals in specific paradigms (Dourish et al. 1985, 1986, 1988). Conversely, attenuation of 5-HT neurotransmission by various methods leads to decreased satiety and increased food consumption and weight gain (Blundell and Latham 1978, 1980, 1982; Blundell 1984, 1986). The effects of 5-HT on feeding are thought to be mediated centrally via the medial hypothalamus (Leibowitz and Shor-Posner 1986; Leibowitz et al. 1988; Leibowitz 1990), although there is some evidence that peripheral mechanisms may play a part (Pollock and Rowland 1981; Davies et al. 1983; Fletcher and Burton 1984).

Patients with bulimia nervosa have several disturbances which suggest dysregulation of 5-HT function, including affective dysregulation, anxiety, impulsivity, and addiction (Brewerton et al. 1986, 1989, 1990a, 1990b, 1992c in press; Jimerson et al. 1990).

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Given these relationships, we studied the feeding responses in normal weight patients with bulimia nervosa and with healthy controls following challenge with the 5-HT precursor L-tryptophan (L-TRP) and the 5-HT agonist m-chlorophenylpiperazine (m-CPP) as well as placebo (both IV solution and capsules). A more detailed discussion of the neuroendocrine and neuropharmacological aspects, including side-effect profile, of these drugs as challenge agents has been studied (Brewerton et al., 1988, 1990a, 1990b, 1992c; Murphy et al., 1991).

SUBJECTS AND METHODS

The demographic features of the normal weight bulimic patients and the age and weight-matched female normal controls have been described (Brewerton et al. 1992b), but will be briefly reviewed and are in Table 1. There was not complete overlap between the m-CPP and L-TRP patient and control groups. All subjects were studied after at least four weeks off all medications, including birth control pills. At the time of admission, all patients met DSM-III criteria (American Psychiatric Association, 1980) for bulimia; retrospectively, all patients were also found to meet DSM-III-R criteria (American Psychiatric Association 1987) for bulimia nervosa. None of the patients with bulimia met present or past DSM-III criteria for anorexia nervosa. Normal controls were selected on the basis of an absence of present or past major psychiatric illness as determined by the SADS-L (Spitzer and Endicott 1975). There was no significant difference in the weights of patients as compared to controls (Table 1). All subjects were in good general health, not pregnant, and free of significant medical illness on the basis of a thorough medical evaluation including a physical examination, EKG, and appropriate laboratory tests. In addition, controls were eliminated on the basis of a lifetime family history of any psychiatric disorder or obesity in a first degree relative. Each subject received an oral and written explanation of the purposes, procedures, and potential hazards of the project, and then gave informed consent.

All subjects were studied at the National Institute

of Mental Health Clinical Center Eating Disorders Unit after overnight bedrest and a 14 hour fast (except for water). In addition, 20 of the 26 bulimic subjects were inpatients at the time of the study, and had been abstinent from bingeing and vomiting for at least four weeks. Inpatients were treated on a highly structured, locked, inpatient unit with supervised meals and bathroom use. The daily caloric intake for all inpatients was prescribed and consisted of approximately 30 kcal/kg. All meals were prepared and checked by experienced dieticians for an appropriate balance of macronutrients, minerals, and vitamins. Patients were not allowed to exercise and were checked periodically by nursing staff to prevent excessive activity. All subjects also observed limited activity levels and a low monoamine, alcohol free, low caffeine diet for at least 72 hours prior to the study. Subjects who smoked were not allowed to do so on the days of the study. A 20 gauge intravenous catheter attached to a heparinized double stopcock was inserted by 9:00 A.M. on each of the procedure days. Double-blind administration of m-CPP (0.5 mg/kg p.o.), L-TRP (100 mg/kg IV), or placebo was performed on separate days in random order of at least 48 hours apart. Each subject had an infusion of saline, or L-TRP, and the same number of capsules (placebo or m-CPP), except for six patients with indwelling venous lines who received only capsules on each day of two days (placebo or m-CPP). Plasma levels of m-CPP and L-TRP were measured by high pressure liquid chromatography (Miller and Devane 1986; Larsson et al. 1988).

The Hamilton Depression Scale (HAMD) (Hamilton 1960) was administered by one of the authors (TDB), and subjects completed the Beck Depression Inventory (BDI) (Beck 1961) on the morning of each study day. Subjects completed a side-effects check list throughout the procedure.

All subjects were given a standardized testmeal consisting of 3,500 calories, including 50% carbohydrates, 30% fat, and 20% protein, presented between three and a half hours and four hours post drug administration. Subjects were instructed "to eat as much or as little as desired" in "as long or as short a period of time as desired." No vomiting was allowed. Outcome measures included meal size, duration, and macronu-

Table 1. Demographic Characteristics of Bulimics and Controls

	Bulimics		Controls	
	m-CPP (n = 26)	L-TRP (n = 23)	m-CPP (n = 15)	L-TRP (n = 16)
Age (yr)	24.7 ± 4.8	24.1 ± 4.8	26.4 ± 5.3	26.8 ± 5.3
Weight (kg)	54.7 ± 4.9	55.3 ± 5.2	57.5 ± 6.3	57.5 ± 6.2
ABW (%)	92.7 ± 7.9	92.4 ± 7.7	95.6 ± 7.7	95.5 ± 7.8

* m-CPP indicates m-chlorophenylpiperazine; L-TRP, L-tryptophan; and ABW, average body weight. Data are given as mean ± SD.

Figure 1. Testmeal size following m-CPP. Bulimic subjects ($p \leq .06$), controls ($p \leq .05$) and the total group of subjects ($p \leq .02$) ate significantly less following m-CPP than following placebo.

trient content (i.e., protein, carbohydrate, and fat). Macronutrients were calculated as both absolute amount in grams as well as percentage of total intake.

Data Analysis

Before analysis, all data were tested for normal distribution and homogeneity of variance using the Statisti-

cal Analysis System (SAS) Proc Univariate. All data were parametric and were analyzed across groups using the unpaired t -test, and were analyzed within groups using the paired t -test. All variances are reported as SD. Peak drug concentrations and depression ratings (HAMD and BDI) were correlated with all testmeal variables using Pearson γ . A priori, it was decided to test each drug separately versus placebo, and the data were ana-

Figure 2. Macronutrient content following m-CPP in all subjects ($n = 41$). In the total group of subjects m-CPP in comparison to placebo significantly reduced carbohydrate ($p \leq .002$, paired t -test), protein ($p \leq .01$), and fat intake ($p \leq .02$).

Figure 3. Maximum m-CPP concentrations were correlated with the total number of calories consumed in the total group ($n = 41$, $r = -0.33$, $p < .03$). There was a trend for this in the controls ($n = 16$, $r = -0.45$, $p < .07$), but not the bulimics.

lyzed as such. Different sample sizes and incomplete overlap among subjects from drug to drug also indicated separate analyses. This strategy has been used in reporting neuroendocrine results (Brewerton et al. 1992c). In addition, the outpatient bulimics were combined with the inpatient bulimics because there were no significant differences in any of the testmeal parameters between these two groups, and these patients served to increase the power of the statistics for treatment and diagnosis effects.

RESULTS

M-CPP versus Placebo

Testmeal duration was not significantly different between m-CPP and placebo in the bulimics (m-CPP: 24.5 ± 11.7 min), the controls (m-CPP: 18.1 ± 6.3 min), or the total group. In the total group of subjects, meal size (kcal) was significantly reduced following m-CPP compared to placebo ($n = 41$, $p < .02$). In addition, meal

Figure 4. Testmeal size following L-TRP. There were no significant differences in testmeal size for the bulimics, the controls, or the total group of subjects following L-TRP as compared to placebo.

size was significantly reduced following m-CPP in the controls alone (736 ± 373 versus 887 ± 330 cal, $p \leq .05$, paired t -test), and there was a similar trend in the bulimics alone (584 ± 314 versus 725 ± 337 cal, $p \leq .06$) (Figure 1).

In the total group, m-CPP reduced the carbohydrate ($p \leq .002$, paired t -test), protein ($p \leq .01$), and fat intake ($p \leq .02$) in comparison to placebo (Figure 2). Maximum m-CPP concentrations were significantly correlated with the total number of calories consumed ($r = -0.33$, $p < .03$) (Figure 3) and fat intake ($r = -0.33$, $p = .033$). A trend was noted for a significant correlation with carbohydrate intake as well ($r = -0.27$, $p = .08$).

There was a trend for bulimics to eat less carbohydrate (gms) after m-CPP than placebo ($p < .1$). There was also a trend for bulimics to eat less protein (in both absolute gms and % total intake) after m-CPP than placebo ($p \leq .1$), and there was a trend for controls to eat less fat (gms) after m-CPP ($p < .1$).

There were no significant correlations between maximum m-CPP concentrations and any of the testmeal measures in the patients alone. However, in the controls, there was a trend for maximum m-CPP concentrations to be inversely correlated with the total number of calories eaten ($n = 16$, $r = -0.45$, $p < .07$) (Figure 3), as well as the number of grams of protein ($r = -0.44$, $p < .09$) and fat consumed ($r = -0.45$, $p < .08$).

L-TRP versus Placebo

There were no significant differences in testmeal duration or size in the bulimics, the controls (Figure 4) or the total group. There were no significant differences in macronutrient selection in the total group of subjects. However, there was a trend for bulimics to eat less protein (% total cal) ($p \leq .09$) and for controls to eat less fat (gms) after L-TRP ($p \leq .1$) (Figure 5). In comparison to placebo, there was a significant difference in change in fat intake (gms) after L-TRP between bulimics and controls ($p \leq .05$), (i.e., overall, bulimics ate more fat [4.5 ± 16.8 gms] and controls ate less [-3.9 ± 8.4 gms]). There were no significant correlations between maximum L-TRP concentrations and any of the testmeal measures in the patients, the controls, or the combined groups. There was a trend for maximum L-TRP concentrations to be correlated with fat intake in the patients alone ($n = 23$, $r = 0.36$, $p = .088$).

Placebo

Testmeal duration was significantly longer in the bulimics ($n = 26$, 24.3 ± 9.2 minutes) as compared to the controls ($n = 17$, 17.3 ± 6.1 min, $p \leq .05$, unpaired t -test) on the placebo day. There was also no statistically significant difference in meal size between bulimics (725 ± 337 cal) and controls (887 ± 330 cal) on the

Figure 5. Testmeal content following L-TRP. Bulimics ate less fat than controls following placebo ($p \leq .05$), and there was a trend for controls to eat less fat after L-TRP ($p \leq .1$).

placebo day (Figures 1, 4). There was a trend for bulimics to eat significantly less fat (23.7 ± 12.9 gms) than controls (31.0 ± 13.3 gms, $p \leq .1$) (Figure 4). There were no other significant differences in macronutrient content between bulimics and controls on the placebo study day.

Depression Ratings

No significant or near significant correlations were found between any of the testmeal measures and HAMD and BDI scores.

Side Effects

As previously reported (Brewerton et al. 1992c), mild nausea was the most common side effect for both agents. Maximum nausea ratings were significantly higher following both agents in comparison to placebo, but there were no significant differences between m-CPP and L-TRP. In addition, maximum ratings were not correlated to any of the testmeal measures.

DISCUSSION

M-CPP significantly decreased testmeal size in the total group of volunteers ($p \leq .002$) and the healthy controls alone ($p < .05$), and there was a trend for this effect in the bulimics alone ($p < .06$). This is compatible with reports in animals that m-CPP and other serotonergic agents decrease food intake (Samanin et al. 1982; Kennett et al. 1987, 1990; Kennett and Curzon 1988a, 1988b; Aulakl et al. 1989). Recent evidence indicates that m-CPP's effects on feeding are specifically mediated via 5-HT_{1C} receptors (Kennett and Curzon 1988a, 1988b; Kennett et al. 1990, 1991). The finding of a significant inverse correlation between m-CPP levels and total calories consumed is compatible with this hypothesis. In the total group of subjects, m-CPP induced decreases in food intake were nonspecific in that all macronutrients were suppressed to significant degrees; however, the strongest case could be made for its effect on carbohydrates, because this was the most robust finding.

Following the L-TRP challenge, bulimic patients ate slightly more, and controls ate slightly less after L-TRP, although these were not statistically significant differences. Nor were there differences in the total group. The lack of significant effect by intravenous L-TRP is similar to studies of oral L-TRP in humans in which few effects (Wurtman and Wurtman 1981a, 1981b; Silverstone and Goodall 1986) or no effects were observed (Hrboticky et al. 1985; Krahn and Mitchell 1985; Russ et al. 1991). These data add to considerable doubt about the extent to which L-TRP induced increases in 5-HT turnover actually cause enhanced 5-HT neurotransmission (Trulson 1985). Yet, L-TRP significantly enhanced

prolactin and cortisol secretion in these same patients, probably as a result of enhanced 5-HT function (Brewerton et al. 1992c).

Following placebo, bulimics ate fewer calories compared to controls, although this was a nonsignificant difference and was probably a result of restrained eating in the bulimic subjects, given the vomiting restriction.

The effects of the 5-HT agents on the macronutrient content of the testmeal differed somewhat by diagnosis. There was at least a trend for both m-CPP and L-TRP to reduce the percentage of protein ingested in the bulimics, but not the controls. M-CPP also reduced the grams of protein ingested in the bulimics, but not the grams of protein ingested in the controls. The case for a role of 5-HT in the direct regulation of protein intake is controversial and weak, and most of his work has been done in animals (Anderson 1979; Curtis-Prior 1983; Shor-Posner et al. 1986; Fernstrom 1987; Peters and Harper 1987), so these data are provocative.

There is a much stronger case for a role for 5-HT in the regulation of carbohydrate intake (Fernstrom 1987). Our finding of a lack of effect of L-TRP on carbohydrate intake in normal controls is contrary to studies in some (Latham and Blundell 1979; Gibbons et al. 1981), but not all animal studies (Peters et al. 1984). However, following m-CPP, carbohydrate intake was decreased in the total group of subjects and the bulimic patients. Furthermore, there was a trend for a significant inverse correlation between maximum m-CPP concentrations and carbohydrate intake in the total group of subjects. Other serotonergic agents, such as fenfluramine (Wurtman and Wurtman 1977; Burton et al. 1981; Li and Anderson 1984; Kim and Wurtman 1988a), fluoxetine (Wurtman and Wurtman 1977; Kim and Wurtman 1988b), the 5-HT reuptake inhibitor, CGS10686B (Kim and Wurtman 1988b), as well as the postsynaptic agonist MK-212 (Wurtman and Wurtman 1979), have all been shown to suppress carbohydrate ingestion in animals. There are no other studies in humans of m-CPP on food intake, but oral administration of L-TRP (Wurtman and Wurtman 1981a, 1981b; Silverstone and Goodall 1986) and fenfluramine (Wurtman and Wurtman 1977, 1981a, 1981b; Rogers et al. 1979; Hill and Blundell, 1990) have been reported to decrease carbohydrate intake in man.

M-CPP also reduced the amount of fat intake in the total group and both agents reduced the grams of fat intake in the controls, but not the bulimics alone. In addition, fat intake was significantly and inversely correlated with maximum m-CPP concentrations in the total group of subjects. There was also a significant difference in change in fat intake (gms) after L-TRP between bulimics and controls (bulimics ate more fat and controls ate less). Bulimic subjects ate fewer grams of fat than controls in this setting, which is compatible with clinical observations that bulimics and other restrained

eaters avoid fat consumption. These results suggest that 5-HT may also play a role in modulating fat intake, perhaps via its effects on the opiate system (Marks-Kaugman 1982; Shor-Posner et al. 1985; Leibowitz and Shor-Posner 1986; Brewerton et al. 1992b).

Neither m-CPP, nor L-TRP produced significant differences in testmeal duration in the bulimics, the controls, or the total group. This has been demonstrated in animal studies to increase following enhancement of 5-HT function (Leibowitz et al. 1988). Meal duration may be a less sensitive measure of 5-HT's effects on human feeding, which is more complex and multi-determined. Not surprisingly, bulimics took significantly more time to eat than the controls, regardless of the drug. Patients knew that they were subject to possible observation during eating and that they would not be able to purge following the testmeal; this situation may have increased food-related anxiety and avoidance behavior (Katzman and Wolchik 1984; Johnson et al. 1986; Davis et al. 1988). The effects of the artificial nature of this eating paradigm on our results must be acknowledged.

Administration of the two agents may be important in interpreting our results. Although all agents were administered at the same time (10 A.M.), the plasma levels of the intravenously administered L-TRP peaked earlier than the orally administered m-CPP. L-TRP may therefore have had a more rapid onset of action and a longer interval until the testmeal was presented than m-CPP may have had. However, L-TRP still has to be metabolized to 5-HT, enter the vesicles and be released, whereas m-CPP has a direct action on receptor sites. On the other hand, peak neuroendocrine responses to IV L-TRP occurred approximately one and a half hours earlier than the peak neuroendocrine responses to oral m-CPP (Brewerton et al. 1992c). Other differences between m-CPP and L-TRP that could possibly explain diversity in feeding responses include presynaptic versus postsynaptic mechanisms, the subtype(s) of 5-HT receptor, the anatomic loci of action, comparative drug dose, and amount of prestudy fasting. It is impossible to determine the degree to which nausea contributed to the suppression of food intake. The effects of enhanced 5-HT function on other neurotransmitters (e.g., norepinephrine, acetylcholine, and peptides), such as the opiates (Brewerton et al. 1992b) and CCK-8 (Brewerton et al. 1992a; Lydiard RB et al. 1993), may also be important in understanding these results. Nevertheless, the observation that bulimics and controls demonstrated some diversity in their responses to both serotonergic agents is consistent with a serotonin dysregulation hypothesis of bulimia nervosa (Brewerton et al. 1986, 1989, 1991a, 1991b, 1992; Brewerton, in press; Jansen et al. 1989; Goldbloom and Garfinkel, 1990; Jimerson et al. 1990; Liebowitz, 1990).

In summary, this study determined that the serotonin receptor agonist m-CPP produced a significant

decrease in calorie intake in volunteers consuming a standardized test meal. Meal size was inversely correlated with peak m-CPP drug levels, and the drug effects were not significantly different for bulimic patients and for controls. Decreased food intake following m-CPP was relatively nonselective across macronutrients; the decrease in percentage was not significantly different for protein or fat, although the most robust decrease was for carbohydrates.

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