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# Neurobiology of Tryptophan Depletion in Depression: Effects of *m*-Chlorophenylpiperazine (mCPP)

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*This study utilized neuroendocrine and mood responses to intravenous (IV) infusion of the serotonin (5-HT) agonist* m-*chlorophenylpiperazine (mCPP) to evaluate central 5-HT function in depressed patients undergoing acute tryptophan (TRP) depletion. Twenty-two drug-free patients with DSM-III-R major depression participated. Each patient underwent two randomized, double-blind TRP depletion tests, one sham and one active. At the estimated time of maximum TRP depletion, each patient received an IV infusion of mCPP 0.1 mg/kg. Blood was obtained for serum cortisol, prolactin, and growth hormone. Multiple rating scales were used to assess mood. The cortisol response to IV mCPP was significantly greater during TRP depletion than during sham depletion, and free plasma TRP was negatively correlated with the cortisol response during TRP depletion. These findings are consistent with the hypothesis that acute TRP depletion in drug-free depressed patients induces a compensatory up-regulation of postsynaptic 5-HT receptors, most likely of the 5-HT$_{2A/2C}$ subtype. Such changes suggest a mechanism by which acute and potent manipulations of 5-HT function in depressed patients could be used to effect rapid clinical improvement.* ***[Neuropsychopharmacology 17:342–350, 1997]***


KEY WORDS: *Depression; Serotonin; Tryptophan;* m-*Chlorophenylpiperazine; 5-HT$_2$ receptor; Antidepressants*

The role of serotonin (5-hydroxytryptamine, 5-HT) in the pathogenesis of depression remains a subject of intense investigation (Maes and Meltzer 1995). One of the most widely used experimental approaches to this issue has been the pharmacological challenge paradigm, which involves administering some provocative agent whose effects are mediated by 5-HT systems (Yatham and Steiner 1993). Numerous studies, using the 5-HT precursors tryptophan (TRP) (Price et al. 1991) and 5-hydroxytryptophan (5-HTP) (Meltzer et al. 1984), the 5-HT releaser fenfluramine (Mann et al. 1995), and the direct 5-HT agonist *m*-chlorophenylpiperazine (mCPP) (Anand et al. 1994), have demonstrated differences in the neuroendocrine responses of depressed and healthy comparison subjects. At the clinical level, the antidepressant efficacy of selective serotonin uptake inhibitors (SSUIs) constitutes a prima facie validation of this approach.

In recent years there has been increasing interest in the converse of 5-HT provocation, i.e., 5-HT antagonism or depletion. Acute depletion of the 5-HT precursor

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TRP has been most frequently used for this purpose. In recently remitted depressed patients receiving SSUIs, TRP depletion causes a clinically significant return of depressive symptoms (Delgado et al. 1990); this effect is not seen in patients remitted on norepinephrine uptake inhibitors (Delgado et al. in press). In drug-free depressed patients, TRP depletion has no immediate effect on mood, but one-third of patients are improved and one-fourth are worse on the following day, after TRP repletion; these changes are predictive of response to subsequent treatment (Delgado et al. 1994). Interestingly, TRP depletion has only mildly dysphoric (Young et al. 1985; Smith et al. 1987) or no mood effects (Abbott et al. 1992; Park et al. 1994; Moreno et al. 1995; Weltzin et al. 1995; Barr et al. 1997) in healthy volunteers, although more prominent depressive symptoms are induced in drug-free euthymic individuals with a past personal (Moreno et al. 1995) or family (Benkelfat et al. 1994) history of mood disorders.

These findings cannot be readily explained by a simple 5-HT deficit theory of depression or a simple 5-HT enhancement theory of antidepressant action (Blier and de Montigny 1994). Instead, the effects of TRP depletion in depressed patients appear to reflect an interaction of disease, disease state, and medication status. This raises the possibility that factors other than the presumed decrease in available 5-HT could contribute to the observed actions of TRP depletion. Based on studies in laboratory animals (Clemens et al. 1980; Trulson et al. 1976; Sharif et al. 1989; Stockmeier and Kellar 1989; Engleman et al. 1991; Callahan and Cunningham 1994) and healthy human volunteers (Anderson et al. 1990; Delgado et al. 1989; Walsh et al. 1995), it was hypothesized that acute TRP depletion would result in a compensatory up-regulation of postsynaptic 5-HT receptors, which could account for the bimodal distribution of mood changes previously observed (Delgado et al. 1994). To evaluate this possibility, acute TRP depletion was induced in depressed patients by administration of an amino acid (AA) mixture after a low-TRP diet, followed by intravenous (IV) infusion of mCPP to assess postsynaptic 5-HT receptor function (Anand et al. 1994; Murphy et al. 1991). The compensatory up-regulation hypothesis predicts that neuroendocrine and perhaps other responses to mCPP will be enhanced during acute TRP depletion.

## METHODS

### Subjects

The study was conducted at the Clinical Neuroscience Research Unit of the Connecticut Mental Health Center. Twenty-two depressed patients (16 women, six men; mean ± SD age, 43.5 ± 9.7 years; age range, 29–66) participated after giving written voluntary informed consent. They were determined to be free of serious medical illness on the basis of a complete physical, neurological, and laboratory examination. All patients met DSM-III-R criteria for a principal diagnosis of major depression as determined by a semi-structured interview conducted by a research psychiatrist (unipolar = 18, bipolar = 4; melancholic = 7, nonmelancholic = 15; nonpsychotic = 21, psychotic = 1). Both inpatients ($n$ = 7) and outpatients ($n$ = 15) were included in the study. The 20 patients who subsequently completed antidepressant treatment trials were categorized as marked ($n$ = 11), partial ($n$ = 4), or nonresponders ($n$ = 5) using previously described criteria (Delgado et al. 1990, 1994).

### Preparation of AA Mixture and mCPP

The AA mixture consisted of 15 amino acids with (sham test) or without (active test) TRP 2.3 g supplementation (Delgado et al. 1990, 1994; Young et al. 1985). The active AA mixture lowers plasma TRP levels by inducing synthesis of labile protein stores. Free TRP in blood and tissue is incorporated into these newly synthesized proteins, resulting in the decline of plasma TRP levels (Young et al. 1989). The TRP supplementation in the sham test abolishes this effect.

The mCPP infusion was prepared by dissolving mCPP 10 mg (Bristol-Myers Squibb, Princeton, NJ) in normal saline 10 ml and passing the solution under sterile conditions through a 0.22 micrometer polymer filter. A portion was obtained for pyrogen and sterility testing and the remainder frozen at −20°C until the day of testing. Infusions were carried out using a Harvard Apparatus pump (South Natick, MA).

Patients were studied during a placebo period preceding a single-blind antidepressant drug trial. At the time of testing, patients had been receiving placebo for at least 2 weeks and had been free of psychotropic drugs (except for low-dose benzodiazepines for severe agitation and insomnia) for at least 3 weeks (fluoxetine at least 5 weeks).

Each patient underwent two double-blind TRP depletion tests, one sham and one active, separated by 1 week. The sequence of the tests was randomly determined. On the day before each test session, patients were given a 160 mg/d, low-TRP diet (Delgado et al. 1990, 1994), supplemented by three identical-appearing capsules, each containing either TRP 500 mg (sham test) or placebo (active test). Patients then fasted overnight and through the end of the test session the next day. On the day of the test session, patients were placed in a dedicated testing room and IV catheters were inserted bilaterally into antecubital veins at 8:00 A.M. to permit drug administration and blood sampling. The AA mixture was given orally at least 60 min later (time −300 min).

Five hours after ingestion of the AA mixture, at the estimated time of maximum TRP depletion (Delgado et

al. 1990, 1994), each patient received an IV infusion of mCPP 0.1 mg/kg (time 0), given over 20 min (Anand et al. 1994). The test session ended 2.5 h later (time 150 min). Patients underwent a final behavioral evaluation the day after the test session at 9:00 A.M.

Blood samples for cortisol, prolactin, and growth hormone (GH) were drawn before the mCPP infusion at −315 min (i.e., −15 min before the AA mixture) and −5 min (i.e., 5 h after the AA mixture), and again at 45, 60, 90, and 150 min after the start of the infusion. Blood for plasma TRP was taken at −315 and −5 min. Vital signs (systolic and diastolic blood pressure, pulse, and oral temperature) were monitored, and behavioral ratings were administered at specified time points throughout the test day. Clinician-rated instruments included the modified 25-item Hamilton Depression Rating Scale (HDRS) (Mazure et al. 1986) and the Hamilton Anxiety Rating Scale (HARS) (Hamilton 1959). Patient-rated scales included the Beck Depression Inventory (BDI) (Beck et al. 1961), the 29-item Physical Symptoms Checklist (PSC) (Woods et al. 1986), and visual analog scales (VAS) (McCormack et al. 1988) describing 16 different mood states (talkative, happy, drowsy, nervous, sad, calm, depressed, anxious, energetic, fearful, mellow, high, angry, irritable, hungry, tired).

### Biochemical Methods

Plasma cortisol was measured with a radioimmunoassay (RIA) kit from Clinical Assays Inc. (Stillwater, MN), with intra- and interassay coefficients of variation (CVs) of 3% and 5%, respectively. Prolactin was assayed using an RIA kit from the same manufacturer, with intra- and interassay CVs of 6% and 11%. GH was determined by a double antibody RIA using material supplied by the National Institute of Arthritis, Metabolism, and Digestive Diseases, with intra- and interassay CVs of 5% and 7%. Total plasma TRP was assayed by high-performance liquid chromatography with fluorometric detection (HPLC-F). Free plasma TRP was assayed by obtaining the ultrafiltrate of plasma from cellulose-based filters (30,000 mol wt cutoff) at room temperature and subjecting the ultrafiltrate to the HPLC-F method (Delgado et al. 1990). The laboratory staff was blind to the sequence of active and sham TRP depletion.

### Data Analysis

To determine the effects of the TRP depletion alone, paired *t*-tests were performed on all variables using the −315 and −5 time points on the active and sham test days. To determine the effects of IV mCPP alone and during active and sham TRP depletion, multivariate analysis of variance (ANOVA) was applied to each variable in a test day × time model, using the −5 time point as the baseline and including responses at all subsequent time points. Effects of mCPP alone were determined by evaluating the main effect of time, whereas effects of TRP depletion on the response to mCPP were determined by evaluating the test day × time interaction. Huynh-Feldt-corrected significance values were reported when the sphericity assumption was not met. Peak change for neuroendocrine responses was calculated by subtracting the −5 time point baseline from the highest value after the mCPP infusion, with significance evaluated by paired or unpaired *t*-test, as appropriate. To minimize the effects of patients with spontaneous GH surges, GH data were analyzed with and without patients in whom GH was >3 ng/ml at baseline (Checkley 1980); since findings were identical with both methods, data from the entire sample are presented. Except as indicated, analyses were based on data from the test day only. Significance was set at $p < .05$ (two-tailed).

## RESULTS

### Effects of TRP Depletion on Responses to IV mCPP

Figure 1 shows that the cortisol response to IV mCPP was significantly greater during TRP depletion than during sham depletion ($F = 3.56$, $df = 4,80$, $p < .014$) (peak change, 12.9 ± 6.9 vs. 9.1 ± 7.1 μg/dl; $t = 3.05$, $df = 20$, $p < .006$). TRP depletion induced only nonsignificant increases in the PRL ($F = 1.34$, $df = 4,80$, $p < .272$) (peak change, 12.4 ± 12.0 vs. 8.8 ± 6.8 ng/ml; $t = 1.45$, $df = 20$, $p < .161$) and GH ($F = 0.51$, $df = 4,80$, $p < .664$) (peak change, 6.2 ± 9.0 vs 4.6 ± 6.3 ng/ml; $t = 0.79$, $df = 20$, $p < .441$) responses to IV mCPP. TRP depletion increased the PSC responses of irregular heart beat ($F = 5.51$, $df = 1,21$, $p < .029$) and urinary hesitancy ($F = 6.18$, $df = 1,21$, $p < .021$) to mCPP, although PSC total score response was unchanged. There were no effects on any other behavioral or physiological responses to mCPP.

### Effects of TRP Depletion Prior to mCPP

TRP depletion alone had no effect on neuroendocrine measures. HARS scores were slightly increased by TRP depletion (active, 16 ± 6 to 17 ± 8; sham, 17 ± 5 to 15 ± 4; $t = 2.52$, $df = 21$, $p < .02$), but HDRS and BDI scores were unaffected. TRP depletion caused increased VAS ratings of "anxious" ($t = 2.40$, $df = 21$, $p < .026$) and decreased VAS ratings of "energetic" ($t = 2.35$, $df = 21$, $p < .028$). Total scores on the PSC were unchanged by TRP depletion, but there were decreases in the specific items of blurred vision ($t = 2.37$, $df = 21$, $p < .027$), restlessness ($t = 2.94$, $df = 21$, $p < .008$), dry mouth ($t = 2.25$, $df = 21$, $p < .036$), and poor memory ($t = 2.84$, $df = 21$, $p < .01$) compared with sham depletion. Pulse was slightly increased by TRP depletion (active, 75 ± 10 to

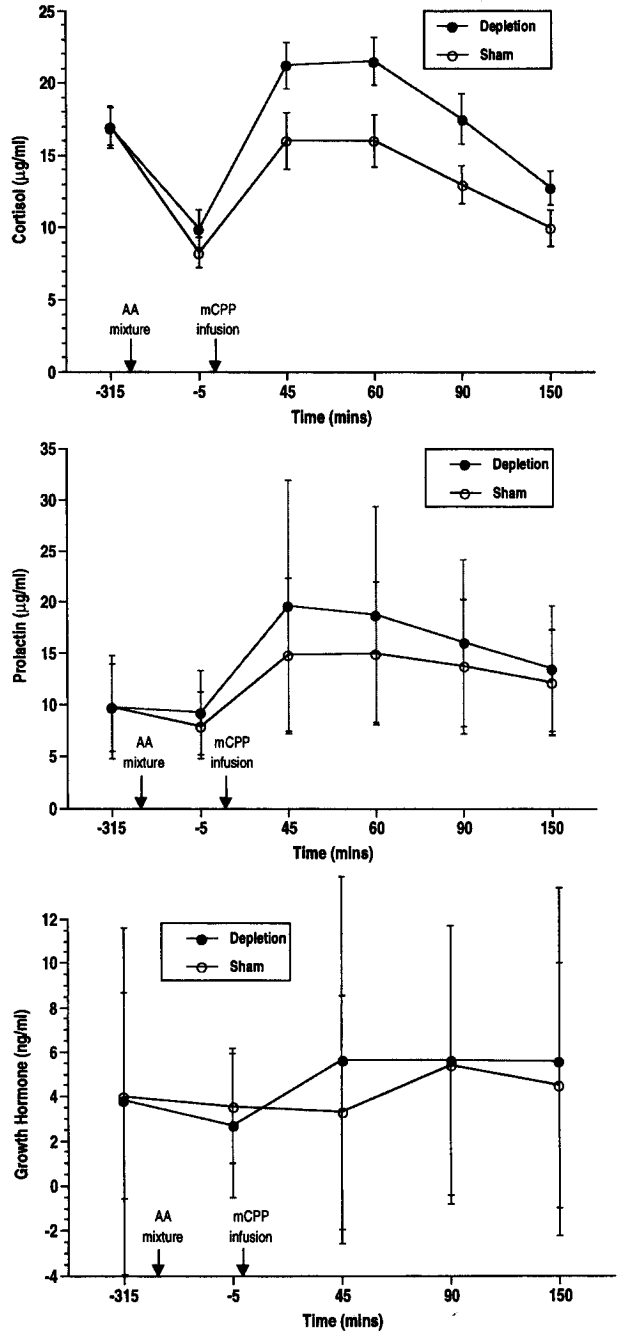


**Figure 1.** Mean responses of cortisol, prolactin, and growth hormone to IV mCPP during sham and active tryptophan (TRP) depletion in depressed patients ($n$ = 22). For cortisol, significant interaction of test day and time (F = 3.56, $df$ = 4,80, $p < .014$).

80 ± 14 bpm; sham, 73 ± 10 to 73 ± 9 bpm; $t$ = 2.28, $df$ = 21, $p < .033$), but blood pressure and temperature were unaffected.

Total plasma TRP levels decreased by 86% during active TRP depletion (baseline, 10.9 ± 3.0 μg/ml; +5 h after the AA mixture, 1.5 ± 1.7 μg/ml; $t$ = 14.32, $df$ = 21, $p < .001$). Free plasma TRP levels declined by 70% (baseline, 1.8 ± 0.6 μg/ml; +5 h, 0.5 ± 0.6 μg/ml; $t$ = 5.50, $df$ = 21, $p < .001$). In contrast, during the sham test total plasma TRP levels increased by 78% (baseline, 12.4 ± 3.2 μg/ml; +5 h, 22.2 ± 11.0 μg/ml; $t$ = 4.63, $df$ = 21, $p < .001$) and free plasma TRP levels increased by 115% (baseline, 2.1 ± 0.6 μg/ml; +5 h, 4.4 ± 2.0 μg/ml; $t$ = 6.82, $df$ = 21, $p < .001$). Free plasma TRP was negatively correlated with the cortisol response to mCPP during TRP depletion ($r = -.43$; $p < .05$); there were no other correlations between total or free plasma TRP levels and peak neuroendocrine responses during sham or active TRP depletion.

### Effects of IV mCPP Alone

Intravenous mCPP alone caused significant increases in cortisol (F = 34.74, $df$ = 4,80, $p < .001$), PRL (F = 15.89, $df$ = 4,80, $p < .001$), and GH (F = 4.87, $df$ = 4,80, $p < .003$). mCPP increased scores on the HDRS (F = 4.98, $df$ = 2,42, $p < .011$) and the HARS (F = 5.22, $df$ = 2,42, $p < .009$), with no effect on the BDI or PSC total scores. VAS ratings of "nervous" (F = 4.24, $df$ = 3,63, $p < .024$), "anxious" (F = 6.64, $df$ = 3,63, $p < .003$), "irritable" (F = 4.37, $df$ = 3,63, $p < .021$), "high" (F = 8.13, $df$ = 3,63, $p < .002$), "fearful" (F = 8.40, $df$ = 3,63, $p < .001$), and "depressed" (F = 4.64, $df$ = 3,63, $p < .005$) were increased by mCPP. In contrast, mCPP caused decreased VAS ratings of "happy" (F = 7.36, $df$ = 3,63, $p < .001$), "calm" (F = 4.14, $df$ = 3,63, $p < .01$), "drowsy" (F = 4.58, $df$ = 3,63, $p < .016$), "talkative" (F = 5.78, $df$ = 3,63, $p < .003$), and "hungry" (F = 6.56, $df$ = 3,63, $p < .002$). mCPP increased heart rate (F = 3,47, $df$ = 4,84, $p < .011$), but did not affect blood pressure or temperature.

### Relationships between Neuroendocrine and Other Variables

Peak change neuroendocrine responses to IV mCPP during TRP depletion did not differ according to unipolar/bipolar, melancholic/nonmelancholic, or inpatient/outpatient status, although GH responses were nonsignificantly lower in melancholics ($t$ = 2.02, $df$ = 18; $p < .059$). Stratification of neuroendocrine responses by sex revealed that the increased cortisol response during TRP depletion was significant in females ($t$ = 2.18; $df$ = 13; $p < .048$), but not in males ($t$ = 1.95, $df$ = 6; $p < .108$). No other significant findings were noted. There was no relationship between peak change neuroendocrine responses and final response to antidepressant treatment.

### Effects of TRP Depletion and IV mCPP on Mood

Evaluation of HDRS, HARS, and BDI scores at the end of the test day and the morning after showed them to be distributed normally. ANOVAs of scores on these measures at all time points during the entire test day and

the morning after revealed no interactive effects of TRP depletion and IV mCPP. There was a nonsignificant tendency for partial responders to show improvement the day after sham and worsening the day after active TRP depletion on the HARS ($F = 2.16$, $df = 8,68$, $p < .053$) and the HDRS ($F = 2.05$, $df = 8,68$, $p < .109$)

## DISCUSSION

As predicted, TRP depletion increased neuroendocrine (viz., cortisol) responses to IV mCPP. Cortisol responses were inversely correlated with free plasma TRP, which is known to correlate with brain 5-HT levels in animal studies (Young et al. 1989; Moja et al. 1989). These findings are consistent with the hypothesis that changes in brain 5-HT levels induced by the TRP depletion were related to the enhanced cortisol response. Although statistically significant increases were also observed in certain subjective somatic responses to mCPP during TRP depletion (irregular heart beat and urinary hesitancy), it is more striking that behavioral and physiological effects were negligible. The bimodal distribution of mood responses previously reported (Delgado et al. 1994) after dietary TRP repletion of drug-free depressed patients undergoing TRP depletion was not seen in this study of mCPP after TRP depletion.

Attributing the present findings to changes at specific 5-HT receptors requires caution because of mCPP's complex receptor interactions. Binding affinity has been shown for $5\text{-HT}_{2C} > 5\text{-HT}_3 > 5\text{-HT}_{2A} > 5\text{-HT}_{1B} > 5\text{-HT}_{1A}$ receptors (Hoyer et al. 1994), as well as for $\alpha_2$-adrenergic receptors (Hamik and Peroutka 1989), and both agonist and antagonist properties have been demonstrated. Additionally, mCPP may bind to the 5-HT transporter and inhibit 5-HT uptake (Baumann et al. 1993). The $5\text{-HT}_{2C}$ receptor appears to mediate many of the functional effects of mCPP (Murphy et al. 1991; Aulakh et al. 1995). In rats, mCPP-induced PRL secretion is mediated by $5\text{-HT}_{2C}$ receptors, but corticosterone effects seem to involve other mechanisms (Aulakh et al. 1992). In humans, the $5\text{-HT}_{2A/2C}$ antagonist ritanserin partially attenuates mCPP's PRL effects and completely antagonizes its cortisol effects (Seibyl et al. 1991), whereas the $5\text{-HT}_3$ antagonist BRL 46470 has no effect (Silverstone and Cowen 1994).

TRP depletion alone had no effect on core depressive symptoms, replicating the findings of Delgado et al. (1994) in an independent sample of drug-free depressed patients. Other behavioral effects were also modest, comprising a slight increase in anxiety and decrease in energy, whereas several subjective somatic and cognitive symptoms (blurred vision, restlessness, dry mouth, poor memory) actually showed less change with active than with sham depletion. Although TRP depletion caused a slight increase in heart rate, it had no effect on basal cortisol, PRL, or GH secretion.

Similarly, the effects of IV mCPP alone were comparable to those previously observed in drug-free depressed patients not undergoing concurrent sham or active TRP depletion (Anand et al. 1994). In the present study, these effects included changes in neuroendocrine (increased cortisol, PRL, and GH), behavioral (increased nervousness, anxiety, depression, irritability, fear, and high, and decreased happiness, calm, drowsiness, talkativeness, and hunger), and physiological (increased heart rate) measures.

Most previous studies specifically addressing the neurobiology of AA-induced TRP depletion have emphasized its effects on brain 5-HT metabolism. Studies in rats have shown that administration of a TRP-free AA mixture substantially reduces brain levels of TRP, 5-HT, and the 5-HT metabolite 5-hydroxyindoleacetic acid (5-HIAA) (Moja et al. 1989; Gessa et al. 1974). Similar reductions in cerebrospinal fluid levels of TRP and 5-HIAA are obtained in vervet monkeys (Young et al. 1989). Whereas there is no direct evidence that brain 5-HT levels are similarly reduced in humans, reductions in plasma TRP levels in human studies (Delgado et al. 1990, 1994; Young et al. 1985; Smith et al. 1987; Benkelfat et al. 1994; Barr et al. 1997), including the present one, are generally greater than those obtained in animals. Moreover, Zimmermann et al. (1993a, 1993b) showed that TRP depletion in humans decreases plasma and urine levels of melatonin and its metabolites, which are dependent on pineal 5-HT as an intermediate. Preliminary evidence indicates markedly decreased brain 5-HT metabolism after TRP depletion in healthy volunteers studied with positron emission tomography (PET) imaging of the labeled TRP analog $^{11}$C-α-methyltryptophan (Benkelfat C, Nishizawa S, Young SN, Leyton M, Plier P, de Montigny C, Mzengezza S, Diksic M, unpublished observations).

Several preclinical investigators have examined the effects of 5-HT depletion induced by other means on various aspects of 5-HT function. There is considerable evidence that postsynaptic 5-HT receptors manifest a compensatory up-regulation after depletion of synaptic 5-HT. In an early study, rats fed a TRP-free diet for 2 weeks showed enhanced corticosterone and PRL responses to 5-HTP with or without fluoxetine (Clemens et al. 1980). In rat brain, 5-HT receptor number is elevated by pretreatment with 5,7-dihydroxytryptamine (DHT, a toxin which selectively destroys 5-HT neurons), p-chorophenylalanine (PCPA, an inhibitor of TRP hydroxylase, the rate-limiting enzyme in 5-HT synthesis), or reserpine (a presynaptic monoamine depleting agent) (Sharif et al. 1989; Stockmeier and Kellar 1989). DHT also increases 5-HT receptor-mediated functional responses (Trulson et al. 1976; Engleman et al. 1991), effects which may not necessarily depend on increased

5-HT receptor number (Hensler et al. 1991). A recent study demonstrated enhancement of the postsynaptic 5-$HT_{2C}$ receptor-mediated discriminative stimulus properties of mCPP after PCPA (Aulakh et al. 1995). However, attenuation of some responses, particularly neuroendocrine, has also been reported (Seckl et al. 1990; Feldman et al. 1991). It should be noted that 5-$HT_2$ receptor regulation differs from that of other receptor subtypes, in that down-regulation occurs with both agonist and antagonist treatment (Leysen and Pauwels 1990). Some data also suggest that 5-$HT_{2A}$ receptors may not up-regulate after 5-HT depletion (Butler et al. 1990), but up-regulation is demonstrated by 5-HT $_{2C}$ receptors (Pranzatelli 1990).

Findings in healthy human subjects, although more limited, also support compensatory up-regulation. Delgado et al. (1989) found that 10 days of gradual TRP depletion with a 200-mg/day TRP-restriction diet led to enhancement of the PRL response to an IV TRP infusion. A 700-mg/day diet, which reduced total plasma TRP by an equivalent degree (15–20%), had no enhancing effect. Three weeks of a 1000–1200 kcal weight reduction diet has been shown to increase PRL responses to IV TRP (Anderson et al. 1990) and oral d-fenfluramine (Walsh et al. 1995). Effects in all of these studies were greater in females than in males. This was true of the present study as well, although in our sample it may simply reflect greater statistical power owing to a larger number of female subjects. A recent study utilizing administration of the AA valine to inhibit transport of TRP across the blood-brain barrier found that the PRL response to d-fenfluramine was diminished, rather than increased, in healthy male subjects (Willamson et al. 1995).

Previous investigators have speculated that 5-$HT_2$ receptors might be up-regulated in depressed patients, independent of any experimental manipulation, owing to a diminished availability of TRP to the brain (Meltzer et al. 1984; Maes et al. 1987). This hypothesis builds upon the observation in depressed patients of reductions in the plasma level of TRP or in the ratio of TRP to the other large neutral amino acids (LNAAs) with which it competes for transport across the blood-brain barrier (Coppen et al. 1973; Quintana 1992; Karege et al. 1994). In support of this is evidence that the cortisol response to 5-HTP is enhanced in depressed patients compared with healthy controls, possibly reflecting increased sensitivity of 5-$HT_2$ receptors (Meltzer et al. 1984; Maes et al. 1987). However, Maes et al. (1987) found that the cortisol response to 5-HTP did not correlate with reductions in plasma TRP or the TRP/LNAA ratio in depressed patients, and other studies have shown no evidence of enhanced behavioral or neuroendocrine responses to mCPP, a putative direct agonist at the 5-$HT_{2A/C}$ receptor (Kahn et al. 1990; Anand et al. 1994). Whereas the present study supports the hypothesis that diminished central availability of TRP can up-regulate 5-$HT_2$ receptors, it is not directly informative as to whether this occurs in depressed patients at baseline.

The present findings do provide a new perspective for understanding recent clinical studies with TRP depletion. As discussed above, TRP depletion results in depressive symptoms in SSUI-remitted depressed patients (Delgado et al. 1990), but not in untreated (Delgado et al. 1994) or norepinephrine uptake inhibitor-remitted depressed patients (Delgado et al. in press). Minimal effects are also seen in healthy volunteers (Abbott et al. 1992; Park et al. 1994; Moreno et al. 1995; Weltzin et al. 1995; Barr et al. 1997). Interestingly, SSUI-remitted obsessive-compulsive disorder patients experience depressive, but not obsessive-compulsive, symptoms with TRP depletion (Barr et al. 1994). SSUI treatment alone, however, does not confer vulnerability, since TRP depletion has little effect in SSUI-treated healthy subjects (Barr et al. 1997). At the same time, TRP depletion does appear to exacerbate symptoms in some drug-free conditions, such as premenstrual syndrome (Menkes et al. 1994), bulimia nervosa (Weltzin et al. 1995), and autism (McDougle et al. 1996), as well as in euthymic subjects with a past personal (Moreno et al. 1995) or family (Benkelfat et al. 1994) history of mood disorders.

Taken together, these studies suggest that 5-HT plays a more important role in the treatment of depression than in its pathogenesis: whereas potent enhancement of 5-HT function (e.g., by SSUI treatment) is capable of exerting antidepressant effects, potent disruption of 5-HT function does not worsen depression once it is established. Similar findings have recently emerged with respect to the norepinephrine system (Miller et al. 1996a, 1996b). Moreover, whereas enhanced 5-HT function may be necessary for some antidepressants to exert their clinical effects, it is not necessary for all antidepressants (Miller et al. 1996b; Delgado et al. in press), nor is it sufficient (Price et al. 1989). Maintenance of normal 5-HT function may be more important for mood regulation in the euthymic state in at-risk individuals and in some disorders other than depression, even though the clinical benefits of enhanced 5-HT function in such conditions may be more limited.

The present observation of an enhanced cortisol responsive to mCPP following acute TRP depletion presumably reflects increased sensitivity of postsynaptic 5-HT receptors, most likely of the 5-$HT_{2A/2C}$ subtype. Other functional responses to mCPP, also thought to be regulated by 5-HT, were not affected. We have recently observed a similar enhancement of the cortisol response to IV TRP after TRP depletion in an independent sample of 38 drug-free depressed patients (Price LH et al. in press). This evidence of increased receptor sensitivity could explain the earlier finding of clinical improvement in some patients when TRP depletion is followed

by repletion (Delgado et al. 1994). Importantly, no clinical or behavioral change was observed in either this or our other recent study, perhaps reflecting the importance of timing, other presynaptic factors (Price et al. 1990), or changes in other neuroregulatory systems in this effect. Nonetheless, these findings suggest a mechanism that might be developed to permit the use of acute and potent manipulations of 5-HT function to induce rapid clinical improvement in depressed patients.

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