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Fluoxetine, but not Tricyclic Antidepressants, Potentiates the 5-Hydroxytryptophan-Mediated Increase in Plasma Cortisol and Prolactin Secretion in Subjects with Major Depression or with Obsessive Compulsive Disorder

Herbert Meltzer, M.D., Bijan Bastani, M.D., Karuna Jayathilake, M.S., MA, and Michael Maes, M.D., Ph.D.

It has been suggested that the clinical efficacy of chronic treatment with selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine and perhaps all antidepressants is due to their ability to enhance serotonergic activity. The effects of chronic treatment with fluoxetine or tricyclic antidepressants on the L-5-hydroxytryptophan (200 mg, L-5-HTP; PO)–induced increases in plasma cortisol and prolactin (PRL) concentrations were studied in patients with major depression or obsessive compulsive disorder (OCD). Administration of L-5-HTP increased plasma cortisol and PRL levels in medicated and unmedicated patients with major depression or OCD. The L-5-HTP–induced cortisol and PRL responses were significantly higher in fluoxetine-treated than in tricyclic-treated or unmedicated major depressed patients. The latter two groups did not differ significantly in their cortisol or PRL responses to L-5-HTP. The L-5-HTP–induced increases in cortisol and PRL in fluoxetine-treated patients with major depression or OCD were not significantly different. The results suggest that fluoxetine, but not tricyclic antidepressants, potentiates 5-HT receptor–mediated stimulation of cortisol and PRL secretion in humans, consistent with available evidence that fluoxetine treatment, but not tricyclic antidepressants, increases central serotonergic activity in patients with MD or OCD by a presynaptic mechanism. ***[Neuropsychopharmacology 17:1–11, 1997]*** *© 1997 American College of Neuropsychopharmacology*

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Several lines of evidence suggest an involvement of the neurotransmitter serotonin (5-HT) not only in the pathophysiology or pathogenesis of major depression, but also in the pathophysiology of obsessive compulsive disorder (OCD). There is some evidence that the pathophysiology of major depression is related to the following disturbances in 5-HT activity: (1) a deficient presynaptic 5-HT activity; (2) upregulation or sensitization of central postsynaptic 5-HT_{2A} receptors; (3) downregulation or desensitization of postsynaptic 5-HT_{1A} receptors; and (4) some combinations of the above or abnormalities in other 5-HT receptor subtypes, such as 5-HT_{2C}, 5-HT_3 (for review, see Maes and Meltzer 1995).

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In addition, various antidepressant treatments, such as tricyclic antidepressants, monoamine oxidase inhibitors (MAOIs), selective 5-HT reuptake inhibitors (SSRIs), and electroconvulsive treatment (ECT) may act by stimulating serotonergic activity, thus compensating for a relative 5-HT hyporesponsivity (for review: Blier et al. 1990; Chaput et al. 1991; Maes and Meltzer 1995).

The firmest evidence for the role of 5-HT in OCD remains the efficacy of SSRIs, such as fluoxetine, fluvoxamine, and clomipramine in the treatment of OCD, whereas the classical antidepressants are less effective or ineffective in that condition (Greist et al. 1995; Stein et al. 1995). Neuroendocrine challenge studies have provided some evidence that OCD may be accompanied by a 5-HT postsynaptic receptor subsensitivity. For example, OCD patients show blunted prolactin (PRL) or cortisol responses to 5-HT agonists such as D-fenfluramine, MK-212, and m-chlorophenylpiperazine (mCPP) (Bastani et al. 1990; Zohar et al. 1987; Hollander et al. 1991; Lucey et al. 1992). In addition, administration of metergoline, a 5-HT antagonist, worsened OCD symptoms in patients who had improved with clomipramine (Benkelfat et al. 1989). Because ipsapirone-induced cortisol responses, which reflect postsynaptic 5-HT_{1A} receptor function, did not differ between OCD and normal subjects (Lesch et al. 1991), the results with mCPP and MK-212 in OCD suggest a postsynaptic 5-HT_{2C} receptor hyporesponsivity in OCD. This thesis, however, is not consistent with other neuroendocrine and behavioral findings. First, Charney et al. (1988) reported a small, but statistically significant, increase in PRL secretion following L-tryptophan (L-TRP) administration. Second, behavioral studies in OCD patients show that administration of mCPP exacerbates obsessive symptoms (Zohar et al. 1987; Hollander et al. 1991). In conclusion, the precise nature of the serotonergic disturbances in OCD remains elusive, although there is some evidence for an involvement of 5-HT in that condition.

From the above, it may be concluded that the serotonergic disturbances observed in major depression and OCD are probably different, although treatment with SSRIs, such as fluoxetine, is effective in both conditions. In addition, typical antidepressants appear to be more efficacious for the treatment of major depression than OCD. Therefore, it is of importance to examine: (1) the functional effects of SSRIs, such as fluoxetine, on serotonergic neurotransmission both in major depression and OCD; and (2) the effects of tricyclic antidepressants versus fluoxetine on serotonergic function in major depression.

The serotonergic effects of antidepressants in vivo can be evaluated by measuring hypothalamic-pituitary-adrenal (HPA) axis or PRL responses to L-5-hydroxytryptophan (L-5-HTP) (Lahti and Barsuhn 1980; Meltzer et al. 1984; Maes et al. 1987; Chaouloff 1993; Meltzer and Maes 1994). L-5-HTP causes a marked enhancement of corticosterone and PRL secretion in the blood of rats, and 200 mg L-5-HTP in nonenteric coated tablets reliably stimulates HPA axis hormone secretion and, to a lesser extent, PRL in humans (Lahti and Barsuhn 1980; Meltzer et al. 1981, 1984; Maes et al. 1987, 1989a, 1995; Fuller 1992; Meltzer and Maes 1994). There is evidence that the increase in plasma cortisol and PRL following L-5-HTP in rodents and man are modulated by at least three different postsynaptic receptors, the 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}, and 5-HT_3 receptors (for reviews see: Meltzer et al. 1982; Fuller and Snoddy 1990; Lesch et al. 1990; Fuller 1992; Jorgensen et al. 1992; Levy and Van der Kar 1992; Meltzer and Maes 1994). Significantly increased 5-HT precursor (L-TRP or L-5-HTP)–induced cortisol responses have been reported to occur in major depression (Meltzer et al. 1984; Maes et al. 1987, 1989a, 1989b, 1991, 1995). It is suggested that the greater L-5-HTP–induced cortisol responses may be attributed to an upregulation of hyperresponsiveness of postsynaptic 5-HT_{2A} receptors (Maes and Meltzer 1995).

Rodent studies using electrophysiological techniques indicate that treatment with SSRIs and tricyclic antidepressants induce a gradual increase in net 5-HT activity (Blier et al. 1988, 1990; Chaput et al 1991). Neuroendocrine challenge studies with 5-HTP in the rodent also suggest that treatment with fluoxetine is accompanied by a net increase in 5-HT activity and that the effects of tricyclic antidepressants are more variable (Lahti and Barsuhn 1980; Meltzer et al. 1984). Thus, fluoxetine enhanced 5-HTP–induced corticosterone responses, whereas tricyclic antidepressants were only weakly active at potentiating L-5-HTP effects or even antagonized these effects (Lahti and Barsuhn 1980; Fuller et al. 1975). Acute administration of fluoxetine has a significant stimulatory effect on 5-HTP–induced PRL secretion in rodents; chronic treatment with imipramine significantly increased L-5-HTP–induced PRL responses; amitriptyline significantly reduced these responses; and desipramine has no discernable effects (Meltzer et al. 1984). We previously reported that the L-5-HTP–induced increase in cortisol secretion was significantly decreased in 10 patients with major depression following treatment with nortriptyline, imipramine, amitriptyline, amoxapine, maprotiline, or trazodone (Meltzer et al. 1984).

The present study has been carried out to investigate: (1) the effects of chronic treatment with fluoxetine versus tricyclic antidepressants on L-5-HTP-induced cortisol and PRL responses in subjects with major depression; and (2) the effects of chronic treatment with fluoxetine on L-5-HTP-induced cortisol and PRL responses in patients with major depression versus OCD.

MATERIALS AND METHODS

Subjects

One hundred and twenty-three subjects participated in this study: 64 unmedicated, 14 tricyclic antidepressant-

treated, 16 fluoxetine-treated major depressed subjects, and 19 unmedicated and 10 fluoxetine-treated OCD patients. The demographic data of these subjects are listed in Table 1. Patients were admitted to the psychiatric ward of Case Western Reserve University or investigated on an outpatient basis in the General Clinical Research Center at the University Hospital. Diagnoses were made with the aid of the Research Diagnostic Criteria (RDC) (Endicott and Spitzer 1978) using the Schedule for Affective Disorders and Schizophrenia (SADS) interviews. Patients were rated on the Hamilton Scale, 17-item version (Hamilton 1960). Subjects with other axis-I diagnoses beside major depression or OCD were excluded from this study (e.g., organic mental disorders, schizophrenia, schizoaffective disorders, and substance abuse disorders, i.e., recent episode of a half year previous to admission to this study). None of the subjects were comorbid for both OCD and major depression. All patients had normal clinical investigations (e.g., blood determinations such as sedimentation rate, serum electrolytes, renal and liver function tests, pituitary-thyroid-axis hormones) and ECG.

All unmedicated patients were free of psychotropic drugs for at least 8 days before the challenge studies were conducted. Most subjects, however, had a washout period of 2 weeks or more. None of these subjects was treated with fluoxetine for at least 5 weeks prior to these studies. To exclude possible long-term effects from previous treatments with antidepressants on the results obtained in the unmedicated depressed subjects, we carried out some additional analyses on a subgroup of patients with a mean length of drug-free period of 28.1 (± 12.5) days. The mean dose of fluoxetine in the fluoxetine-treated major depressed subject was 44.6 (± 19.8) mg/day and in the OCD patients 60.0 (± 23.9) mg/day. Imipramine (n = 4; 150–300 mg/day), amitriptyline (n = 1; 300 mg/day), desipramine (n = 1; 150 mg/day), and nortriptyline (n = 8; 100–150 mg/day) were used to treat the 14 other medicated depressed patients. All patients had been treated for at least 4 weeks with the above SSRIs or TCAs.

Methods

Each subject was tested on two study days separated by at least 48 hours and with two different conditions, placebo or L-5-HTP (200 mg PO in nonenteric coated tablets) administration. On the day of these studies, following an overnight fast, an intravenous catheter was inserted in the antecubital vein at 9:00 A.M. At 9:30 A.M. the first of three baseline samples was obtained, and the other two were drawn at 15-minute intervals. After the third sample (T_0) patients ingested L-5-HTP or an indistinguishable placebo capsule. Hereafter, blood samples were obtained every 30 minutes over a 3-hour period. All subjects were restricted to bedrest during the study period; they were not allowed to eat or sleep. For the medicated patients, the morning dose of tricyclic antidepressants or fluoxetine was held.

Blood was stored in plastic tubes at −20° C until thawed for cortisol or PRL assay. Cortisol was determined by radioimmunoassay (kits from Diagnostic Products, Los Angeles, CA). The interassay coefficient of variation (CV) was 4.3% (mean = 13.3 g/dl, n = 13). PRL was assayed by means of a double antibody radioimmuno procedure using reagents from The National Institute of Arthritis and Metabolic Diseases. The interassay CV of duplicate determinations in the same assay was 3.5%.

Data Analysis

Relationships between variables were assessed by means of Pearson's product–moment or Spearman's rank-order correlations. Effects of L-5-HTP were analyzed by means of repeated-measures analysis of variance (ANOVA) with placebo/L-5-HTP treatment as repeated measures, medication status (unmedicated fluoxetine, tricyclics), and/or diagnosis (OCD versus major depression) as factors, and T_0 hormonal values as covariates. The latter are introduced as covariates to control for possible differences in basal cortisol values between the four conditions. Two indices of cortisol/PRL responses were used in this study: (1) the L-5-HTP–induced peak cortisol or PRL responses, that is, the highest hormone value obtained after administration of placebo or L-5-HTP; and (2) the area under the time by concentration curve from T_0 until 3 hours later (labeled as AUC), as computed using Simpson's rule. Peak and AUC hormonal responses were used in the ANCOVAs with basal cortisol T_0 covaried. Multiple comparisons

Table 1. Demographic Data of the Study Subjects

Diagnosis	Drug State	Male/Female Ratio	Age (years)	Body Mass Index
Major depression	Unmedicated	41/23	41.2 ± 13.4	25.4 ± 5.9
Major depression	Tricyclic	12/2	52.1 ± 9.1	26.7 ± 6.3
Major depression	Fluoxetine	7/9	40.7 ± 11.3	28.9 ± 9.2
OCD	Unmedicated	12/7	31.2 ± 11.1	24.2 ± 4.1
OCD	Fluoxetine	7/3	34.8 ± 7.8	25.4 ± 5.3

All results are expressed as mean ± SD.

among treatment means were assessed by means of Fisher's least-significant differences (LSD).

RESULTS

Demographic data

Table 1 lists the demographic data of the 123 subjects in this study. There were five study groups, which were categorized according to diagnosis (major depression versus OCD) and drug state (unmedicated, fluoxetine-, or tricyclic antidepressant–treated). Statistical analyses were performed on different study groups; (1) unmedicated, fluoxetine, and tricyclic antidepressant–treated major depressed subjects; and (2) unmedicated and fluoxetine–treated major depressed and OCD subjects. No significant differences in gender ratio were found between unmedicated, fluoxetine-, and tricyclic antidepressant–treated depressed patients ($\chi^2 = 4.0$, df = 2; $p = .13$). Depressed subjects on typical antidepresants were somewhat older than the unmedicated and fluoxetine-treated patients ($F = 8.5$, df = 2/151, $p = .0006$). No significant differences in gender-ratio were found between fluoxetine and unmedicated major depressed and OCD patients ($\chi^2 = 1.6$, df = 3, p = 0.7). No significant differences in age were found between unmedicated and fluoxetine-treated subjects with major depression or OCD ($F = 2.6$, df = 3/105, $p = 0.052$). There were no significant differences in body mass index (BMI) between the five categories ($F = 1.4$, df = 4/118, $p = .2$).

The mean (± SD) HDRS scores in the five study groups were (1) unmedicated major depressed subjects 17.4 (± 7.4); (2) tricyclic-treated major depressed patients 12.8 (± 8.5); (3) fluoxetine-treated major depressed subjects 10.4 (± 6.5); (4) unmedicated OCD patients 8.5 (± 5.0); and (5) fluoxetine-treated OCD patients 8.2 (± 4.8). The HDRS score was significantly lower in subjects treated with fluoxetine than in medicated patients ($F = 7.7$, df = 1/63, $p = .007$). There was a trend for lower HDRS score between unmedicated patients and those treated with typical antidepressants ($F = 3.1$, df = 1/63, $p = .08$). There was no difference in HDRS scores between fluoxetine- and tricyclic-treated depressed patients ($F = 0.5$, df = 1/18, $p = 0.5$).

L-5-HTP–induced Cortisol Responses in Medicated Versus Unmedicated Major Depressed Subjects

Table 2 shows AUC and peak L-5-HTP–induced cortisol responses in unmedicated, tricyclic-, and fluoxetine-treated major depressed subjects. Figure 1 shows the time by concentration curve of cortisol following pla-

Table 2. Measurements of T_0 and L-5-HTP-Induced AUC and Peak Cortisol Responses in Unmedicated and Medicated (fluoxetine and/or tricyclic antidepressants) Patients with Major Depression (MD) or OCD

	T_0 Cortisol		AUC Cortisol		Peak Cortisol	
Diagnosis Type of Medication	**Placebo Day**	**L-5-HTP Day**	**Placebo**	**L-5-HTP**	**Placebo**	**L-5-HTP**
MD						
1. No medication	10.3 (4.7)	10.3 (4.3)	64.6 (25.6)	89.9 (29.7)	12.0 (4.9)	17.4 (5.6)
2. Tricylic antidepressants	8.9 (3.0)	9.4 (3.5)	57.2 (18.7)	83.2 (27.5)	10.4 (3.2)	16.7 (6.3)
3. Fluoxetine	9.8 (3.7)	9.9 (3.1)	62.9 (27.6)	104.7 (36.0)	11.7 (5.0)	21.7 (7.4)
OCD						
4. No medication	10.3 (4.6)	10.1 (3.0)	61.3 (23.7)	82.3 (17.6)	10.9 (3.7)	16.4 (4.3)
5. Fluoxetine	10.8 (5.4)	10.0 (3.6)	72.0 (29.6)	112.0 (35.2)	13.2 (5.6)	22.1 (6.3)
Repeated-measures ANCOVAs with the three MD groups 1, 2, and 3 as factors						
L-5-HTP (df = 1/90)	—		$F = 78.4$ ($p < .0001$)		$F = 88.6$ ($p < .0001$)	
Medication (df = 2,90)	$F = .5$ ($p = 0.6$)		$F = 1.9$ ($p = .1$)		$F = 2.6$ ($p = .08$)	
L-5-HTP × medication (df = 2/90)	—		$F = 2.4$ ($p = .09$)		$F = 3.8$ ($p = .03$)	
T_0 cortisol (df = 1/90)	—		$F = 13.3$ ($p = .0005$)		$F = 3.1$ ($p = .08$)	
Repeated-measures ANCOVAs with MD versus OCD and no medication versus fluoxetine as factors (1, 3, 4, 5)						
L-5-HTP	—		$F = 101.4$ ($p < .0001$)		$F = 112.7$ ($p < .0001$)	
Fluoxetine	$F = 0.0$ ($p = .9$)		$F = 11.7$ ($p = .0009$)		$F = 11.9$ ($p = .0008$)	
Diagnosis	$F = 0.1$ ($p = .8$)		$F = 0.0$ ($p = .9$)		$F = 0.0$ ($p = .8$)	
L-5-HTP × Fluoxetine	—		$F = 8.1$ ($p = .005$)		$F = 8.3$ ($p = .005$)	
Diagnosis × Fluoxetine	$F = 0.1$ ($p = .7$)		$F = 1.9$ ($p = .2$)		$F = 0.9$ ($p = .3$)	
Diagnosis × L-5-HTP	—		$F = 0.0$ ($p = .9$)		$F = 0.0$ ($p = .9$)	
Diagnosis × Fluoxetine × L-5-HTP	—		$F = 0.2$ ($p = .7$)		$F = 0.1$ ($p = .8$)	
T_0 cortisol	—		$F = 25.2$ ($p = .0001$)		$F = 10.7$ ($p = .002$)	

All results are expressed as mean ± SD and in μg/dl.

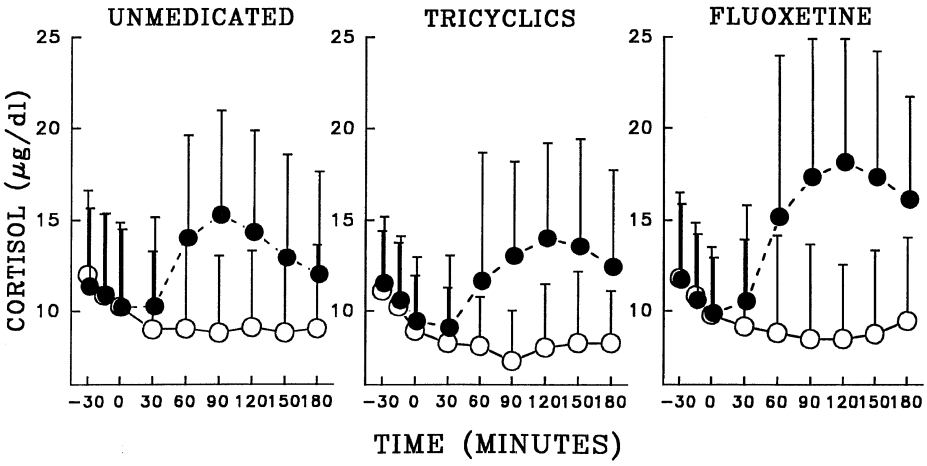

Figure 1. Effects of 200 mg L-5-HTP PO (administered at T_0) on plasma cortisol concentrations in unmedicated, tricyclic-, and fluoxetine-treated patients with MD. *Open circles*, placebo; *solid circles*, L-5-HTP. Results are shown as mean ± SD.

cebo and L-5-HTP administration. ANOVA showed a significant effect of L-5-HTP on AUC and peak cortisol secretion and a significant medication by L-5-HTP interaction for peak cortisol. There was a trend toward a significant medication by L-5-HTP interaction for AUC cortisol. L-5-HTP–induced AUC cortisol responses were significantly greater in fluoxetine-treated than in unmedicated ($p < .0001$) and tricyclic-antidepressant–treated ($p = .002$) major depressed subjects. L-5-HTP–induced AUC cortisol responses were not significantly different between unmedicated and tricyclic-treated major depressives ($p = .8$).

There were no significant relationships between the HDRS score and baseline-adjusted AUC cortisol in unmedicated ($r = .18$, p .1), fluoxetine-treated ($r = .05$, $p =$ .8), or antidepressant-treated ($r = .15$, $p = .6$) patients. Regression analyses pooled over the study groups of unmedicated, fluoxetine-, and tricyclic-antidepressant–treated depressed patients did not show a significant correlation between L-5-HTP–induced cortisol responses and the HDRS score. For example, for baseline-adjusted AUC cortisol ($r = .10$, $p = .3$).

In the unmedicated subjects, no significant relationships could be found between L-5-HTP–induced cortisol responses and the length of the drug-free period prior to these studies (e.g., for baseline-adjusted AUC cortisol, r = .20, and $p = .4$).

L-5-HTP–induced Cortisol Responses in Unmedicated versus Fluoxetine-Treated Patients with Major Depression versus OCD

Table 1 shows the effects of L-5-HTP on cortisol secretion in unmedicated and fluoxetine-treated major depressed or OCD patients. Figure 2 shows the time by concentration curves of cortisol secretion following placebo or L-5-HTP in both patient groups. There were no significant differences in L-5-HTP–induced AUC or peak cortisol responses between unmedicated major depressed and OCD patients. The interaction pattern between treatment (unmedicated versus fluoxetine) and L-5-HTP challenge was highly significant: the L-5-HTP–induced AUC cortisol responses were significantly higher in fluoxetine-treated major depressed ($p < .0001$) and OCD patients ($p = .0004$) than in unmedicated major depressed or OCD patients, respectively. There were no significant differences in L-5-HTP–induced AUC corti-

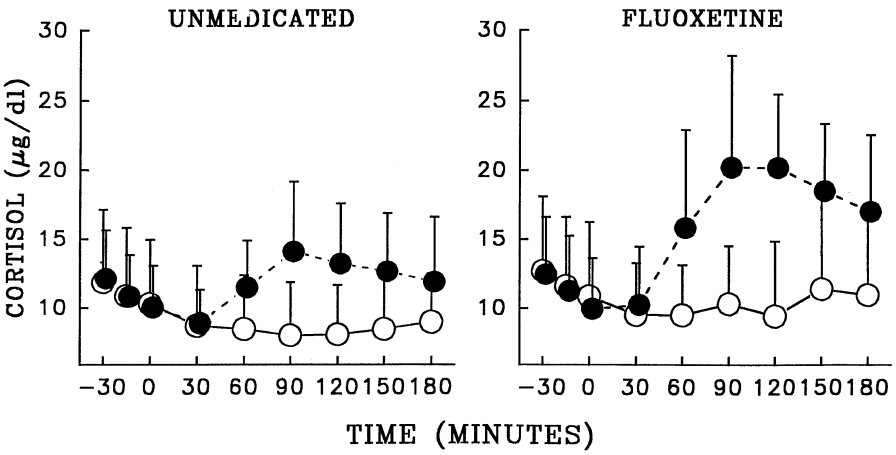

Figure 2. Effects of 200 mg L-5-HTP PO (administered at T_0) on plasma cortisol concentrations in unmedicated and fluoxetine-treated patients with OCD. *Open circles*, placebo; *solid circles*, l-5-HTP. Results are shown as mean ± SD.

Table 3. Measurements of T_0 and L-5-HTP-Induced AUC and Peak PRL Responses in Unmedicated and Medicated (fluoxetine and/or tricyclic antidepressants) Patients with Major Depression (MD) or OCD

Diagnosis Type of Medication	T_0 PRL		AUC PRL		Peak PRL	
	Placebo Day	L-5-HTP Day	Placebo	L-5-HTP	Placebo	L-5-HTP
MD						
1. No medication	4.7 (2.4)	4.9 (3.0)	30.7 (13.5)	34.8 (22.3)	5.6 (2.6)	7.4 (5.2)
2. Tricylic antidepressants	5.5 (2.0)	5.8 (3.2)	36.3 (15.1)	36.9 (17.7)	6.6 (2.8)	7.7 (4.6)
3. Fluoxetine	5.9 (1.3)	7.5 (4.0)	38.8 (7.2)	69.5 (28.6)	6.8 (1.1)	19.4 (14.4)
OCD						
4. No medication	5.6 (2.5)	6.0 (2.9)	36.3 (16.9)	39.5 (15.8)	6.7 (2.8)	7.7 (3.3)
5. Fluoxetine	6.8 (5.4)	7.7 (6.7)	53.3 (53.0)	67.6 (38.4)	9.7 (9.0)	13.9 (6.7)
Repeated-measures ANCOVAs with MD groups 1, 2, and 3 as factors						
L-5-HTP (df = 1/59)	—		$F = 11.3$ ($p = .001$)		$F = 18.3$ ($p < .0001$)	
Medication (df = 2/59)	$F = 2.6$ ($p = .8$)		$F = 7.1$ ($p = .002$)		$F = 7.8$ ($p < .0001$)	
L-5-HTP × medication (df = 2/59)	—		$F = 6.8$ ($p = .002$)		$F = 8.7$ ($p < .0001$)	
T_0 PRL (df = 1/59)	—		$F = 13.0$ ($p = .0006$)		$F = 1.0$ ($p = .03$)	
Repeated-measures ANCOVAs with MD versus OCD and no medication versus fluoxetine as factors (all df = 1/78)						
L-5-HTP	—		$F = 16.5$ ($p < .0001$)		$F = 22.9$ ($p < .0001$)	
Fluoxetine	$F = 4.5$ ($p = .04$)		$F = 26.5$ ($p < .0001$)		$F = 21.3$ ($p < .0001$)	
Diagnosis	$F = 1.0$ ($p = .8$)		$F = 1.3$ ($p = .2$)		$F = 0.2$ ($p = .6$)	
L-5-HTP × Fluoxetine	—		$F = 9.3$ ($p = .003$)		$F = 13.1$ ($p = .0005$)	
Diagnosis × Fluoxetine	$F = 0.1$ ($p = .8$)		$F = 0.2$ ($p = .7$)		$F = 1.0$ ($p = .3$)	
Diagnosis × L-5-HTP	—		$F = 2.2$ ($p = .1$)		$F = 5.5$ ($p = .02$)	
Diagnosis × Fluoxetine × L-5-HTP	—		$F = 1.5$ ($p = .2$)		$F = 3.9$ ($p = .052$)	
T_0 cortisol	—		$F = 13.0$ ($p = .0005$)		$F = 0.6$ ($p = .5$)	

All results are expressed as mean ± SD and in ng/dl.

sol responses between fluoxetine-treated major depressed and OCD patients ($p = .9$).

L-5-HTP–induced PRL Responses in Medicated versus Unmedicated Major Depressed Subjects

Table 3 shows T_0 PRL and L-5-HTP–induced AUC and peak PRL responses in unmedicated, tricyclic-, and fluoxetine-treated major depressed subjects. Figure 3 shows the time by concentration curve of PRL following placebo and L-5-HTP in the three study groups. ANOVA showed a significant effect of L-5-HTP on PRL section; there was a significant medication by L-5-HTP interaction pattern. The L-5-HTP–induced AUC PRL responses, for example, were significantly greater in fluoxetine-treated than in unmedicated ($p < .0001$) and tricyclic-antidepressant–treated ($p = .002$) major depressed subjects. The L-5-HTP–induced PRL responses were not significantly different between unmedicated and tricyclic-treated major depressives ($p = .8$).

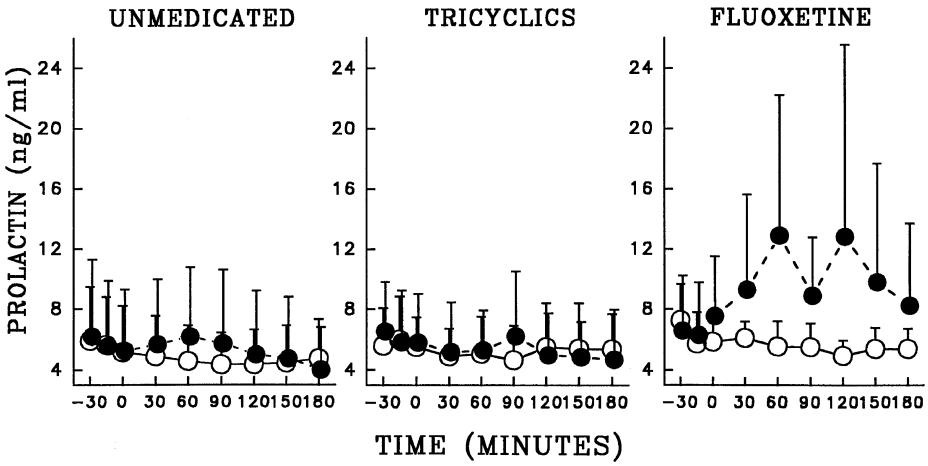

Figure 3. Effects of 200 mg L-5-HTP PO (administered at T_0) on plasma PRL concentrations in unmedicated, tricyclic-, and fluoxetine-treated patients with major depression. *Open circles*, placebo; *solid circles*, L-5-HTP. Results are shown as mean ± SD.

Regression analyses pooled over the unmedicated, fluoxetine-treated, and tricyclic antidepressant–treated study groups showed that there were no significant relationships between L-5-HTP–induced PRL responses and the HDRS score (e.g., for baseline-adjusted AUC PRL, $r = .10$ and $p = .5$). In the unmedicated patients, no significant relationships could be detected between L-5-HTP–induced PRL responses and the length of the drug-free period before these tests were carried out ($r = .20$, $p = .4$).

L-5-HTP–induced PRL Responses in Unmedicated versus Fluoxetine-Treated Patients with Major Depression versus OCD

Table 3 shows the effects of L-5-HTP on PRL secretion in unmedicated or fluoxetine-treated major depressed or OCD patients. Figure 4 shows the time by concentration curves of PRL secretion following placebo or L-5-HTP in both major depressed and OCD patients. There were no significant differences in L-5-HTP–induced PRL responses between unmedicated major depressed and OCD patients. The interaction pattern between treatment (unmedicated versus fluoxetine) and L-5-HTP was highly significant: the L-5-HTP–induced PRL responses were significantly higher in fluoxetine-treated major depressives ($p < .0001$) and OCD patients ($p = .0002$) than in unmedicated major depressives or OCD subjects, respectively. There were no significant differences in L-5-HTP–induced PRL responses between fluoxetine-treated major depressed and OCD patients ($p = .7$).

Effects of Age, Gender, and BMI

In unmedicated, fluoxetine-, and tricyclic-treated major depressed subjects and in the unmedicated and fluoxetine-treated OCD patients, no significant correlations were found between L-5-HTP–induced baseline-adjusted AUC cortisol or PRL responses and either age or gender (even without Bonferroni's p correction for multiple testing). In the three study groups, no significant relationships could be found between L-5-HTP–induced, baseline-adjusted cortisol and PRL responses and BMI, except in the unmedicated OCD patients ($r = .57$, $p = .03$; without p correction for multiple testing).

DISCUSSION

A major finding of this study is that (sub)chronic treatment with fluoxetine, but not tricyclic antidepressants, significantly enhanced L-5-HTP–induced cortisol and PRL responses in major depression as well as in OCD. In major depressed subjects, fluoxetine treatment resulted in a significantly greater L-5-HTP–induced cortisol and PRL response than in unmedicated patients or depressed subjects treated with tricyclic antidepressants. No difference between the L-5-HTP–induced increases in cortisol in unmedicated and tricyclic antidepressant-treated depressed patients was found in the present study. Therefore, we did not replicate our previous findings of a decreased cortisol response to L-5-HTP in tricyclic antidepressant-treated depressed patients (Meltzer et al 1984). On the other hand, no evidence for any potentiation was noted, which supports our previous suggestion of a lack of potentiation of the 5-HT–mediated cortisol response by tricyclic antidepressants.

Results of 5-HTP–induced cortisol, PRL, and behavioral responses following treatment with SSRIs in rodents also indicate that fluoxetine stimulates central serotonergic activity, whereas the effects of tricyclic antidepressants are more variable. Thus, the cortisol responses to 5-HTP in rodents are significantly enhanced by chronic treatment with fluoxetine, suggesting that fluoxetine is a potentiator of central 5-HT activity (Lahti and Barsuhn 1980). The lack of significant enhancement by tricyclic antidepressants, such as imipramine, amitriptyline, desipramine, or nortriptyline, on the L-5-HTP–

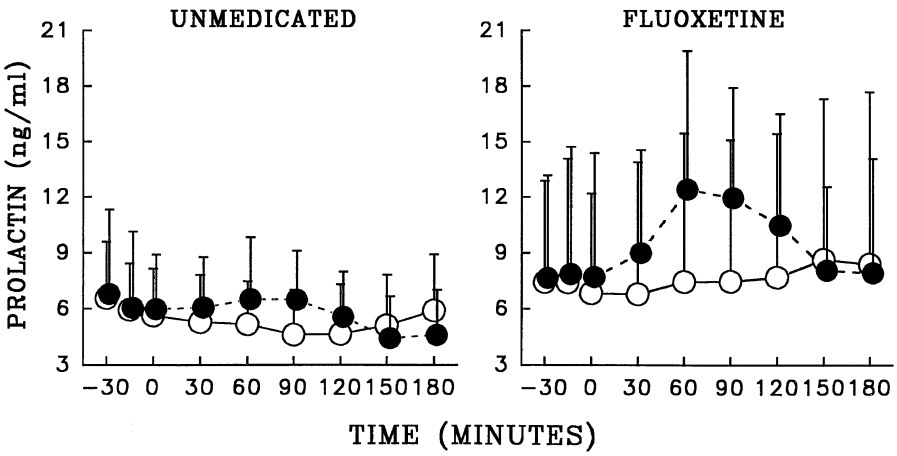

Figure 4. Effects of 200 mg L-5-HTP PO (administered at T_0) on plasma PRL concentrations in unmedicated and fluoxetine-treated patients with OCD. *Open circles*, placebo; *solid circles*, L-5-HTP. Results are shown as mean ± SD.

induced cortisol response in the major depressed subjects noted here is in agreement with animal experiments showing that these compounds exhibit only weak or no significant stimulating effects on 5-HTP–induced corticosterone secretion (Lahti and Barsuhn 1980). We have previously reported that acute administration of fluoxetine had a significant stimulatory effect on 5-HTP–induced PRL secretion in the rodent; chronic treatment with imipramine significantly increased L-5-HTP–induced PRL secretion, antitriptyline significantly reduced those responses, and desipramine had no significant effect (Meltzer et al 1981). Subchronic treatment with fluoxetine may augment the 5-HTP–induced 5-HT syndrome (stereotypic behaviors, piloerection hyperthermia, tremor) in rats (Hwang and VanWoert 1980; Hwang et al. 1980). This syndrome probably reflects postsynaptic 5-HT receptor activation (Wilkinson and Dourish 1991), and changes in expression of this syndrome following fluoxetine treatment reflect an increase in net serotonergic transmission (Beasley et al 1992). The results of the present study also are in accordance with the findings that L-TRP– or D,L-fenfluramine–induced PRL secretion in patients with major depression are significantly enhanced by chronic treatment with SSRIs, such as fluoxetine (O'Keane et al 1992), clomipramine (Anderson and Cowen 1986; Shapira et al. 1992), and fluvoxamine (Price et al 1989). Finally, the different responses to TRP depletion reported by the Yale group in SSRI- (worsening of depression) and tricyclic- (no effects) treated depressed subjects support the different activities of SSRIs versus typical antidepressants on brain 5-HT- turnover (Delgado et al 1990). Thus the results of the present study and the literature suggest that chronic treatment with fluoxetine (or other SSRIs) stimulates central serotonergic activity in patients with major depression as well as OCD.

Fluoxetine is an SSRI with little or no affinity for 5-HT receptor subtypes, such as 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, and 5-HT_3 receptors (Peroutka and Snyder 1980; Hall et al. 1984; Wong et al. 1991). The effects of chronic or subchronic exposure to fluoxetine and other SSRIs on central 5-HT neurotransmission have been investigated in the rodent through electrophysiological studies (Blier et al. 1988, 1990; Chaput et al. 1991). These studies suggested that subchronic treatment with fluoxetine enhances 5-HT release per impulse because of the desensitization of different feedback systems that normally restrain 5-HT turnover (Briley and Moret 1993). Thus (sub)chronic treatment with fluoxetine (1) downregulates the number of 5-HT_1 receptors (Wong and Bymaster 1981; Dumbrille-Ross and Tang 1983; Wong et al. 1985; Wamsley et al. 1987; Yen et al. 1987), particularly, of the somatodendritic 5-HT_{1A} inhibitory autoreceptor in the dorsal raphe (Welner et al. 1989); (2) desensitizes the terminal autoreceptor (probably the 5-HT_{1B} in rodents or the 5-HT_{1D} in humans) (Blier et al. 1988, 1990; Chaput et al. 1991); and (3) may induce TRP hydroxylase activity (Briley and Moret 1993). However, given chronically, fluoxetine intensifies the mCPP-induced hypothermia in the mice, suggesting that fluoxetine increases the sensitivity of 5-HT_{1B} receptors (Maj and Moryl 1993).

Brain microdialysis studies have shown that acute administration of SSRIs, such as fluoxetine, causes a 3- to 5-fold increase in 5-HT in the synaptic cleft, but at the same time may decrease the activity of the 5-HT neuron itself through activation of the presynaptic, inhibitor 5HT-$_{1A}$ autoreceptors (Fuller 1994). Chronic administration of SSRIs causes larger increases in extracellular 5-HT because SSRIs may desensitize there 5-HT_{1A} autoreceptors, thus decreasing the release-controlling serotonergic feedback signals (Chaput et al. 1991; Briley and Moret 1993; Fuller 1994). Recent findings show that (1) 5-HT_{1A} receptor antagonists can augment the increase of extracellular 5-HT elicited by chronic treatment with SSRIs in the rodent (Arborelius et al. 1995; Hjorth 1992); and (2) pindolol, a 5-HT_{1A} receptor antagonist at central 5-HT receptors (Hjorth and Carlsson 1986; Meltzer and Maes 1994) may shorten the latency of onset of SSRIs in the treatment of depression (Artigas et al. 1994) or may augment the efficacity of a subtherapeutical dosage of an SRI in the treatment of major depression (Maes et al. 1996).

On the other hand, no significant effects of (sub)chronic treatment with SSRIs at postsynaptic 5-HT_{1A} receptors could be found in the rat hippocampus, although tricyclic antidepressants and electroconvulsive shock increase the responsivity of this receptor (Chaput et al. 1986). Maj and Moryl (1993) could not detect significant effects of acute or chronic fluoxetine administration on the 8-OH-DPAT–induced behavioral syndrome, which is mediated by postsynaptic 5-HT-$_{1A}$ receptors. Li et al. (1993), on the other hand, reported that chronic exposure to fluoxetine decreases 5-HT_{1A} receptor function (e.g., signal transduction) in the rodent, as assessed by means of 8-OH-DPAT–induced HPA axis hormonal and PRL responses.

No consistent downregulation of 5-HT_2 receptors upon chronic fluoxetine treatment has been found, whereas typical antidepressants caused downregulation of 5-HT_2 receptors (review: Wong et al. 1995). Other authors, however, reported that subchronic treatment with fluoxetine may downregulate postsynaptic 5-HT_{2A} receptors (Stolz et al. 1983; Wamsley et al. 1987) and diminishes 5-HT_2 receptor–mediated behavioral responses to various serotonergic agonists (Maj and Moryl 1993).

By inference, the increased L-5-HTP–induced cortisol and PRL secretion following chronic treatment with fluoxetine in both major depression and OCD found in the present study may be due to an increase in serotonergic transmission related to various presynaptic phe-

nomena, such as decreased responsiveness or downregulation of the inhibitory terminal and somatodendritic autoreceptors, increased TRP hydroxylase activity, and inhibition of 5-HT reuptake.

The findings of the present study, however, are at variance with the reports that L-TRP– or D,L-fenfluramine–induced PRL responses in major depression are significantly increased by various tricyclic antidepressants, such as amitriptyline or desipramine (Charney et al. 1984), tricyclics and lithium (Cowen et al. 1989), imipramine (Shapira et al. 1989), and amitriptyline (O'Keane et al. 1992). Charney et al. (1984) suggested that this effect of tricyclic antidepressants was likely to be due to increased sensitivity of postsynaptic receptors rather than by making more 5-HT available or increasing L:-TRP availability. However, the inability of tricyclic antidepressants to potentiate the effect of L-5-HTP on either cortisol or PRL secretion in the present study suggests that no increase in 5-HT_{1A} or 5-HT_{2A} receptor sensitivity occurred or that there might be offsetting effects to counteract such an effect. It is possible that the effect of tricyclics to potentiate the PRL responses to L-TRP or fenfluramine could be due to increased L-TRP or TRP hydroxylase activity or fenfluramine levels or ability of fenfluramine to increase 5-HT release or even possibly to a decrease in the dopamine-induced inhibition of PRL secretion.

Some limitations in the design of the study should be considered for correct interpretation of the data. First, fluoxetine-treated major depressed patients were less severely depressed than the unmedicated subjects. Therefore, differences in severity of depression explain the differences in hormonal responses between these study groups. However, no significant relationships were observed between L-5-HTP–induced cortisol or PRL responses and severity of illness in either unmedicated or fluoxetine-treated subjects. Moreover, as there were no significant differences in severity of depression between fluoxetine- and tricyclic-antidepressant–treated subjects, the differences in L-5-HTP–induced hormonal responses between these study groups may not be related to differences in severity of illness. Second, there is some evidence from other studies that 5-HT agonist–induced cortisol and PRL responses of females are greater than those of males (for review see Maes and Meltzer 1995). A potential limitation with regard to the lack of PRL response to L-5-HTP in the tricyclic-treated group is the unbalanced gender distribution compared to the other groups. However, in the present study we were unable to detect a significant association between gender and the L-5-HTP–induced hormonal responses. There also are possible differences within females in 5-HT-agonist/precursor–induced PRL responses according to the phase of the menstrual cycle or pre- or postmenopausal state (Maes et al. 1989a; O'Keane et al. 1991). In the present study we were unable to detect a significant association between age and the L-5-HTP–induced hormonal responses.

In conclusion, this study showed that L-5-HTP–induced cortisol and PRL responses were significantly higher in fluoxetine-treated patients with major depression or OCD than in unmedicated patients. These results may indicate that fluoxetine increases central 5-HT activity. The efficacy of fluoxetine in both major depression and OCD may be related to increased 5-HT activity that compensates for serotonergic deficiencies in major depression and OCD.

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