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# Blunted Serotonergic Responsivity in Depressed Inpatients

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*We found a 38% lower maximal prolactin response to an oral challenge dose of 60 mg of dl-fenfluramine relative to placebo in younger (<30 years) depressed inpatients compared with the response in age-matched healthy controls ($p < .03$). Severity of depression did not correlate with prolactin response. Prolactin responses in older depressed patients (≥30 years) did not differ from older controls. Younger depressed patients differed from older depressed patients in terms of earlier age of onset of first lifetime episode of major depression, greater degree of suicidal intent during a recent suicide attempt, double the level of hopelessness on admission to hospital, and a higher rate of comorbid borderline personality disorder. A blunted prolactin response to fenfluramine may be interpreted as evidence for reduced serotonergic function in younger depressed patients and may underlie their observed greater suicidality and hopelessness.*
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There is evidence that serotonergic function is reduced in patients with major depression (Heninger et al. 1984) and that this effect may be greater in depressed patients with a history of suicide attempts (Mann and Stanley 1986; Mann et al. 1992). Part of this evidence comes from postmortem studies. Reduced levels of serotonin (5-HT) and/or its metabolite 5-hydroxyindoleacetic acid (5-HIAA) have been found in postmortem brainstem specimens from depressed patients and suicide victims (Shaw et al. 1967; Bourne et al. 1968; Pare et al. 1969; Lloyd et al. 1974; Moses and Robins 1975; Beskow et al. 1976; Crow et al. 1984; Korpi et al. 1986). Many but not all studies report reduced density ($B_{max}$) of presynaptic tritiated-imipramine binding sites on serotonergic nerve terminals (Stanley et al. 1982; Paul et al. 1984; Arató et al. 1987; Gross-Isseroff et al. 1989), which include the presynaptic 5-HT transporter binding site (Langer et al. 1987), and an increase in the number of postsynaptic 5-$HT_2$ receptors (Stanley and Mann 1983; Crow et al. 1984; Mann et al. 1986; Cheetham et al. 1988; Arango et al. 1990) in the prefrontal cortex of the brain of victims of violent suicide.

Further evidence of an association between reduced serotonergic function and depression comes from studies of depressed patients in vivo. Some but not all studies report that levels of 5-HIAA in the cerebrospinal fluid (CSF) of depressed patients as a group are lower compared with the levels in healthy controls (Åsberg et al. 1976a, b, 1981; Vestergaard et al. 1978; Ågren, 1980a; Gibbons and Davis 1986; Peabody et al. 1987; Nordin 1988; Westenberg and Verhoeven 1988). Most studies also report even lower levels of 5-HIAA in the CSF of those suicide attempters with a depressive disorder as compared with the 5-HIAA levels in depressed nonattempters (Åsberg et al. 1976b; Vestergaard et al. 1978; Ågren 1980b; Åsberg and Träskman 1981; Träskman et al. 1981; van Praag 1982; Palaniappan et al. 1983; Roy-Byrne et al. 1983; Lopez-Ibor et al. 1985; Ågren and Niklasson 1986; Edman et al. 1986; Roy et al. 1986; Secunda et al. 1986; Peabody et al. 1987; Nordin 1988; Westenberg and Verhoeven 1988; Jones

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et al. 1990). Several studies have reported a lower number of platelet tritiated-imipramine binding sites (Stanley et al. 1983) and decreased maximal platelet 5-HT uptake (Meltzer et al. 1981; Kaplan and Mann 1982; Carlsson and Carlsson 1988) in depressed patients compared with controls. A limitation of CSF and platelet studies is that they do not address the question of whether serotonergic net transmission in the brain is decreased. Actually the most convincing evidence for the role of the serotonergic system in depression is indirect, namely, the antidepressant efficacy of drugs that increase levels of serotonin at postsynaptic receptors by selective inhibition of 5-HT reuptake or by inhibition of catabolism by monoamine oxidase (Peroutka and Snyder 1980; Malone and Mann 1993). It has also been claimed that serotonin precursors are effective in treating depression (van Praag 1982). Depletion of serotonin by parachlorophenylalanine or a tryptophan-depleting diet has been reported to reverse the benefit of antidepressant drugs (Shopsin et al. 1975, 1976; Heninger et al. 1992).

Whether net serotonergic transmission is decreased in patients with depression has been assessed by neuroendocrine responses using a variety of direct and indirect serotinin agonists and precursors. The serotonin precursor l-tryptophan has been reported to produce a blunted prolactin response in patients with a major depressive episode (MDE) (Heninger et al. 1984). The most commonly used serotonergic agent in neuroendocrine studies of depression is dl-fenfluramine. An anorectic agent structurally similar to amphetamine, dl-fenfluramine is an indirectly acting central serotonin agonist that causes serotonin release from presynaptic storage granules and inhibits reuptake (McBride et al. 1990). The major metabolite, norfenfluramine, may have a direct effect on postsynaptic receptors (Invernizzi et al. 1992). Acute oral fenfluramine administration increases serum prolactin levels in humans (McBride et al. 1990). This effect appears mediated via hypothalamic afferents from ascending fibers of raphe neurons, which result in release of prolactin from the anterior pituitary gland. Overall, dl-fenfluramine appears relatively selective in assessing the integrity of both the presynaptic and postsynaptic components of this serotonin-mediated response (Meyendorff et al. 1986; Fuller et al. 1988; Mann et al. 1992; Coccaro et al. 1993). Some but not all of these studies employing the fenfluramine challenge have found a blunted prolactin response in depressed patients (see Table 1 for a summary). It is unclear if the lack of agreement in these studies is due to the biochemical heterogeneity of major depression or if there is another explanation. For example, most of these studies did not address whether blunting of the prolactin response correlates with the presence of a major depression or is related to such other manifestations of psychopathology as a history of suicidal or aggressive behavior, a comorbid personality disorder, or a subtype of depressive disorder. Moreover, most studies (12 out of 15) did not provide data on fenfluramine and norfenfluramine blood levels, so pharmacokinetic and pharmacodynamic effects cannot be differentiated. A placebo control was used in only five of 15 studies, and only three of 15 studies had a placebo control and also assayed drug levels. A related issue is that gender and age have been shown to have significant effects on serotonin function, including the response to fenfluramine (McBride et al. 1990), and most studies have not addressed these effects.

We therefore studied the plasma prolactin response to oral dl-fenfluramine and placebo in order to evaluate the net responsiveness of the central serotonergic system in a group of drug-free hospitalized depressed patients and healthy controls, and to assess the relative contribution of depressive illness, personality disorder, suicidal behavior, sex, and age to central serotonergic responsivity. Blood levels of fenfluramine and its active metabolite norfenfluramine were assayed to assess pharmacokinetic effects.

## METHODS

dl-Fenfluramine, 60 mg, or an identical placebo, was administered orally to 26 unipolar depressed inpatients and 26 healthy controls in a single-blind protocol. All subjects were drug-free for a minimum of two weeks before testing. No patient had received fluoxetine or an oral neuroleptic for six weeks prior to study. None of the subjects had taken oral contraceptives for several months. To limit seasonal effects, we studied controls and patients recruited throughout the same time period. The groups (patients and healthy controls) were matched with respect to time of testing and phase of menstrual cycle. All subjects participated after giving written informed consent as required by the Institutional Review Board.

All patients (15 females, 11 males) satisfied the Research Diagnostic Criteria for major depressive disorder based on a Schedule for Affective Disorders and Schizophrenia structured clinical interview (Spitzer and Endicott 1978) and were hospitalized on the depression research unit after presenting for evaluation and treatment of depression. The minimum severity criterion was defined as Hamilton Depression Scale (Hamilton 1960) score of greater than 14 on the first 17 items. The Hamilton Depression group mean score was 27. Patients did not have other current comorbid Axis I psychiatric disorders such as anxiety disorders or substance abuse or dependence. All subjects were free of major medical illness based on a medical history screening, a physical examination, and routine laboratory and diagnostic tests. A major medical illness included any

**Table 1.** Published Studies Using a Fenfluramine Challenge Test with Depressed Patients

| Study | Population | Fenfluramine Dose | Drug Levels | Placebo | Finding |
|---|---|---|---|---|---|
| Mitchell and Smythe 1990 | 27 MDD, 14 controls | 60 mg, dl | No | No | PRL ↓ in mel vs. nonmel |
| Mitchell et al. 1991 | 26 MDD, 10 controls | 60 mg, dl | No | No | No difference after controlling for sex and age |
| O'Keane and Dinan 1991 | 23 MDD, 16 controls | 30 mg, dl | No | No | PRL ↓ vs. controls (no correlation with severity of depression but with anxiety) |
| Lopez-Ibor et al. 1990 | 17 suicidal patients, 17 controls | dl | No | No | PRL ↓ and cortisol ↓ vs. cont |
| Maes et al. 1989 | 40 MDD: compared for major and minor depression | 60 mg, dl | No | No | PRL ↑ in major vs. minor depression |
| Targum et al. 1990 | MDD + panic, $n$ = 12; $n$ = 17 MDD-panic, $n$ = 27 | Not available | No | Yes | PD + MDD and PD PRL ↑ |
| Kasper et al. 1990 | 31 MDD, no normal controls; effect of medication | 60 mg, dl | Yes | Yes | PRL correl before and after—no clear treatment effect |
| Weizman et al. 1988 | 8 MDD, 8 controls | 60 mg, dl | No | No | No difference |
| Lopez-Ibor et al. 1988 | 31 MDD | 60 mg, dl | No | No | No correlation with subtype of depression or suicidal behavior |
| Asnis et al. 1988 | 15 MDD and 10 healthy controls | 60 mg, dl | No | No | No difference |
| Siever et al. 1984 | 18 MDD, 10 controls | 60 mg, dl | No | Yes | Subset of MDD had PRL ↓ versus control |
| Mulbauer and Muller-Oerlinghausen 1985 | Bipolar: 11 on Li, 8 untreated euthymic, 11 controls | 60 mg, dl | No | No | Cortisol responses not altered in untreated depressed patients |
| Coccaro et al. 1989 | MDD vs. healthy controls | 60 mg, dl | Yes | Yes | PRL ↓ in MDD |
| Lichtenberg et al. 1992 | 24 MDD and 21 controls | 60 mg, dl | Yes | Yes | PRL ↓ in MDD |

Abbreviations: MDD = major depressive disorder; PRL = prolactin; mel = melancholia; nonmel = nonmelancholia; ↑ = greater; ↓ = less or blunted; cont = control; dep = depression; PD = personality disorder, Li = lithium.

neurological disorder, cardiac failure, carcinoma, autoimmune disorder, renal failure, anemia or blood dyscrasias, migraine, carcinoid disease, and obstructive airways disease. Consecutive admissions meeting these criteria were included in this study. Controls were screened by a research psychiatrist to exclude those with a lifetime history of a psychiatric Axis I or Axis II cluster B disorder, or a medical illness. A family history of an Axis I psychiatric disorder in a first-degree relative was also an exclusion criterion. The healthy, drug-free controls (10 females, 16 males) were studied as outpatients.

Further clinical assessment at the time of the fenfluramine challenge testing included the Global Assessment Scale (Endicott et al. 1976) and Beck Hopelessness Scale (Beck et el. 1974). The Suicide Intent Scale (Beck et al. 1974, 1976) was used to characterize suicide attempts made during the current depressive episode. A checklist was used to diagnose cases with comorbid borderline personality disorder or antisocial personality disorder according to the DSM-III-R criteria. Lifetime history of aggression was assessed by the Brown-Goodwin Scale (Brown et al. 1979, 1982a, b).

Fenfluramine was administered in the second challenge session so as to avoid possible carryover effects on the placebo challenge, and to enhance the effectiveness of the single-blind design during the placebo challenge. Subjects fasted except for water from midnight the night before testing. An intravenous solution of 5% dextrose in 0.45% sodium chloride was administered via a forearm vein throughout the challenge period, commencing at approximately 8:00 A.M. and ending at about 2:00 P.M. Approximately 200 ml/hour of intravenous solution was administered over the six-hour span to prevent dehydration and offset the hypoglycemic effect of fenfluramine. Subjects fasted and remained at rest until completion of the challenge test protocol. Blood samples were drawn from a port in the intravenous tubing 15 minutes prior to and immediately before drug or placebo administration, and then hourly for 5 hours. Samples were kept on ice until centrifugation, and plasma samples were stored at −70°C. Plasma

prolactin levels were measured by immunoradiometric assay kits purchased from Hybritech Incorporated (San Diego, CA). The lower limit of sensitivity of the assay was 0.3 ng/ml of prolactin, and the interassay coefficient of variance was 4%. Plasma fenfluramine and norfenfluramine levels were assayed in samples obtained at 0, 3, and 5 hours using gas-liquid chromatography (Krebs et al. 1984). The minimum detectable levels of fenfluramine and norfenfluramine were 2.0 ng/ml at 5.0 ng/ml, respectively. The coefficients of variation were 3.4% for fenfluramine and 6.8% for norfenfluramine.

The fenfluramine stimulated prolactin response for each subject was calculated by subtracting plasma prolactin concentrations at each time point on the placebo day from the level at the corresponding time point on the fenfluramine day. Peak fenfluramine-stimulated prolactin response was determined as the maximum prolactin increase on fenfluramine after subtracting the placebo day prolactin concentration at that same time point. Comparisons between two sets of data were made using *t*-tests; for more than two sets of variables, an analysis of variance for repeated measures was carried out. All significance levels reported are two-tailed. Correlations were calculated using the Pearson correlation coefficient method. Data are reported as mean ± SD, unless indicated otherwise.

## RESULTS

### Prolactin Responses to Fenfluramine Relative to Placebo

In both the 26 controls and the 26 depressed inpatients, fenfluramine elicited a robust increase in plasma prolactin over time compared to placebo ($F = 34.4$, $df = 6,300$, $p < .0001$). The peak prolactin response occurred between hours 3 and 5 in younger subjects (Figure 1). Older subjects appeared to experience a delay in the peak level to between 4 and 5 hours (Figure 2), although the difference in time to peak level was not statistically significant.

### Effect of Sex and Age on Fenfluramine-Induced Prolactin Response in Healthy Controls

We reported elsewhere, in a study of healthy control subjects that included all of the controls in this study (McBride et al. 1990), that the prolactin response to fenfluramine challenge is significantly greater in females and declines with age. Statistically significant negative correlations were found between age and prolactin increases over placebo levels at 3 hours post drug ($r = -0.45$, $p < .02$), 4 hours ($r = -0.51$, $p < .008$), and peak increase in prolactin ($r = -0.52$, $p < .007$) when the entire control group was considered. Examination of the distribution of peak prolactin increase with age in healthy controls suggested lower fenfluramine-stimulated prolactin response in subjects from age 30 onward. When the control group was divided into subjects younger than 30 years of age and those 30 years of age and older, 3-, 4-, and 5-hour and peak prolactin responses no longer correlated significantly with age within either age group. Based on our observation of a marked decline in fenfluramine-induced prolactin response in control subjects around 30 years of age, we compared members of the depressed patient group who were younger than 30 years of age with those aged 30 years and older. The age and gender effects on the prolactin response to fenfluramine were independent of basal prolactin levels.

It has been reported that in women the prolactin response to d-fenfluramine is greater premenstrually (O'Keane et al. 1991), however no significant difference in time since the last menstrual period was reported by patients (13.4 ± 11.2 days for patients receiving fenfluramine) as compared with the controls (19.4 ± 10.8 days).

### Demographic Characteristics and Pharmacokinetic Data in Younger and Older Control and Depressed Groups

Table 2 lists the characteristics of control and depressed subjects after division by sex and age (younger versus age 30 and older). Within each age group, the mean ages of the control and depressed subjects were well matched. Gender ratios did not differ significantly (<30 years: $\chi^2 = 0.10$, $p < .75$; ≥30 years: $\chi^2 = 1.0$, $p < .31$). There were no significant differences in mean 3- and 5-hour serum fenfluramine and norfenfluramine levels between the control and depressed subjects in either age group.

### Age-Related Differences in Prolactin Response in Control versus Depressed Subjects

The maximum prolactin response after fenfluramine administration was significantly blunted in the younger depressed patients compared to controls (14.0 ± 6.6 versus 22.7 ± 9.5 ng/ml; $t = 2.37$, $p < .03$) (see Figure 1). This blunting was statistically significant among younger depressed females compared to control females (16.7 ± 6.3 versus 27.2 ± 9.9 ng/ml; $t = -2.2$, $p < .05$), and there was a trend toward blunting in younger depressed males versus control males (8.5 ± 2.8 versus 18.3 ± 7.4 ng/ml; $t = -2.15$, $p < .07$).

There was a statistically significant difference in the pattern of age effects on prolactin responses in patients compared to controls when the effects of gender were controlled. Controls exhibited a steeper decline after 30 years of age compared to the depressed subjects

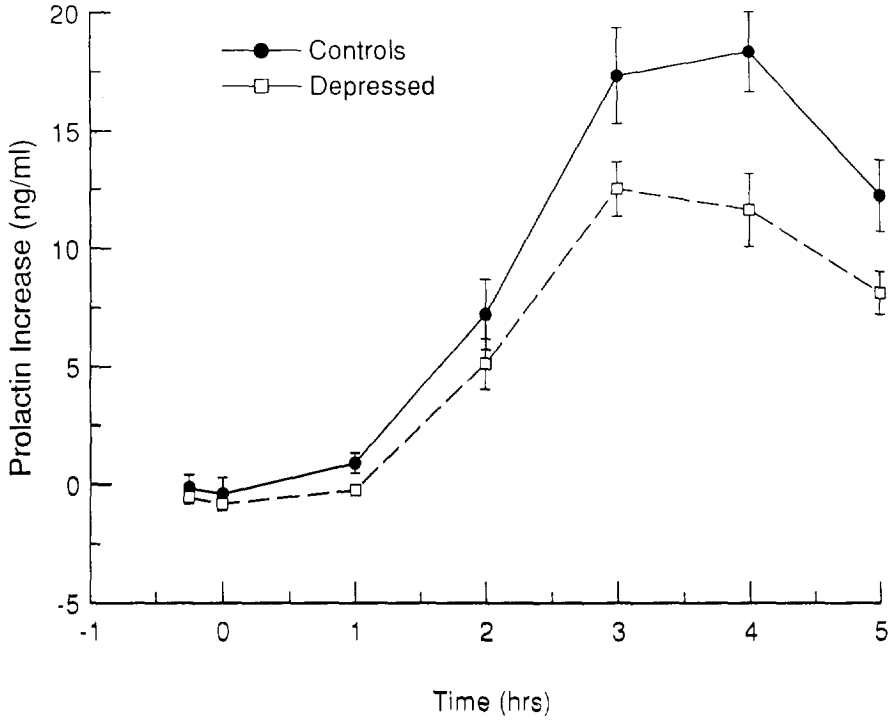


**Figure 1.** Fenfluramine-induced prolactin response in controls and depressed subjects younger than 30 years of age.

(repeated measures ANOVA $F = 8.4$, $df = 1,48$, $p < .006$, patient × age group interaction). This difference remained statistically significant when males were analyzed separately ($F = 10.6$, $df = 1,23$, $p < .003$), although the difference among female groups was significant only at a trend level ($F = 3.7$, $df = 1,21$, $p < .07$). Controls also exhibited a significantly greater age-related decline in peak prolactin response compared to depressed subjects ($F = 11.6$, $df = 1,23$, $p < .001$, patient × age group interaction). This interaction was statistically significant for both males ($F = 7.5$, $df = 1,23$, $p < 0.01$) and females ($F = 5.2$, $df = 1,21$, $p < .03$). A three-way ANOVA where age group, diagnostic group, and sex are independent variables and prolactin is the dependent variable proved less informative due to the limited sample size.

Six (four females, two males) of the nine younger

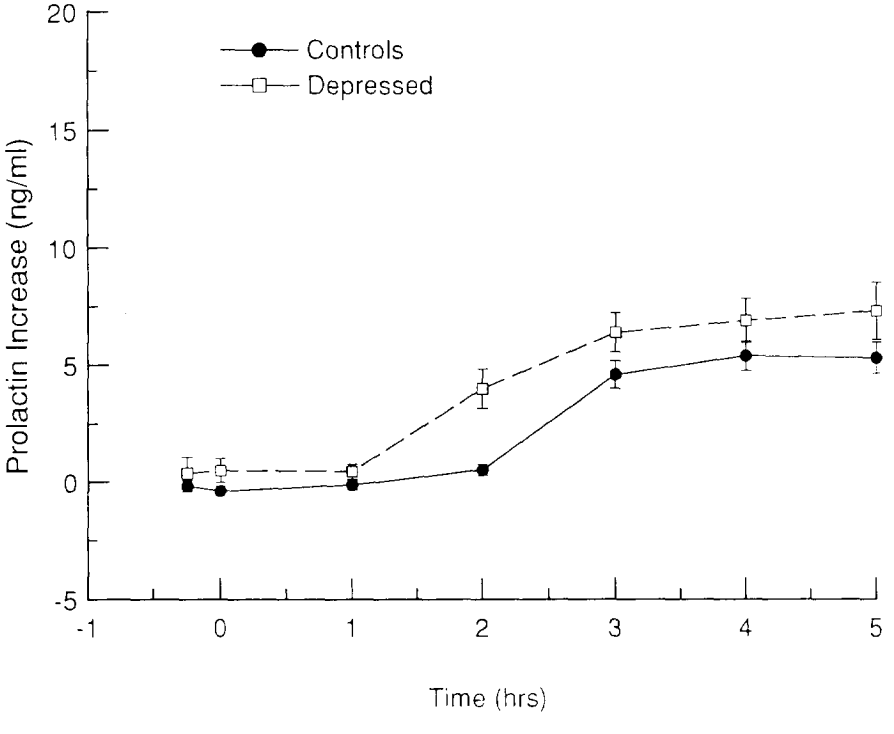


**Figure 2.** Fenfluramine-induced prolactin response in controls and depressed subjects at or older than 30 years of age.

**Table 2.** Demographic Characteristics of and Drug Levels in Younger and Older Control and Depressed Groups

| | <30 Years of Age | | ≥30 Years of Age | |
|---|---|---|---|---|
| | **Controls** | **Depressed** | **Controls** | **Depressed** |
| Demographics | | | | |
| Number of subjects | 12 | 9 | 14 | 17 |
| Male:female ratio | 1:1 | 1:2 | 5:2 | 8:9 |
| Age (years) | 24.5 ± 2.6 | 24.7 ± 3.2 | 46.5 ± 15.3 | 46.9 ± 11.4 |
| Fenfluramine + norfen fluramine levels(ng/ml) at 3 hours and 5 hours | | | | |
| Male (3 hr) | 57.5 ± 16 | 64.0 ± 9.8 | 58.4 ± 14.5 | 64.0 ± 17.5 |
| Female (3 hr) | 67.9 ± 16.2 | 85.7 ± 40 | 73.5 ± 10.6 | 67.8 ± 10.7 |
| Male (5 hr) | 60.3 ± 10.7 | 51.0 ± 6.1 | 55.6 ± 18.9 | 58.7 ± 10.3 |
| Female (5 hr) | 65.7 ± 11.9 | 74.5 ± 22.1 | 72.3 ± 19.3 | 54.3 ± 13.8 |

depressives had made suicide attempts during the current depressive episode. There were no significant differences between attempters and nonattempters in the peak prolactin response (13.7 ± 7.1 versus 14.3 ± 6.8 ng/ml; $t = 0.14$, $p > 0.8$). Among the older subjects, there were no significant differences in prolactin responses between depressed patients and controls at hour 3 (6.4 ± 4.3 versus 4.6 ± 3.0 ng/ml; $t = 1.43$, $p < .16$), hour 4 (6.9 ± 4.8 versus 5.4 ± 3.2 ng/ml; $t = 1.07$, $p < .3$), and hour 5 (7.3 ± 6.2 versus 5.3 ± 3.4 ng/ml; $t = 1.07$, $p < .3$) (see Fig. 2). The mean maximal prolactin increases in the older depressed patients also did not differ significantly from that in the older controls (9.4 ± 6.2 versus 6.8 ± 3.5 ng/ml; $t = 1.37$, $p < .18$).

Six (four females, two males) of the 17 older depressed patients had made suicide attempts during their current illness. Three other patients had a past history of suicide attempts but no history of a current attempt. There were no significant differences in the mean peak prolactin increase between current attempters and those who had never made a suicide attempt (9.7 ± 6.6 ng/ml versus 9.4 ± 6.5 ng/ml; $t = 0.14$, $p < .9$).

### Correlations of Psychopathology with Prolactin Response in Younger and Older Depressed Groups

Table 3 compares psychopathology at the time of fenfluramine challenge testing in the younger and older depressed groups. Severity of depression as measured by the Hamilton Depression Scale and Global Assessment Scale did not differ between the two groups. The age of onset of the affective disorder was significantly earlier in the younger depressed subjects. However, both groups had suffered a comparable number of episodes of major depression and had been ill for a similar period of time. On admission to hospital, the younger depressives rated themselves as more hopeless than did those in the older group. Also, 78% (seven) of the nine depressed subjects under age 30 years had a comorbid borderline personality disorder, compared to 29% (five of 17) of the depressed patients over 30 years of age (Fisher Exact Test, $p = .0375$).

Six of the nine depressed subjects under age 30 years and six of 17 older depressives had made a suicide attempt during the current major depressive episode. Suicide attempts in 11 out of 12 were nonviolent (drug or substance overdose, $n = 11$), and one patient cut his or her wrist. The younger attempters were rated as having greater suicide intent at the time of their attempt compared to the older suicide attempters.

Peak prolactin increase after fenfluramine did not correlate significantly with total Hamilton Depression Scale ($r = 0.09$, $r = 0.28$), Global Assessment Scale ($r = 0.004$, $r = -0.27$), or the Beck Hopelessness Scale ($r = 0.15$, $r = 0.24$) scores in either the younger or the older age groups of depressed subjects, respectively. Among suicide attempters in both groups, Suicide Intent Scale scores ($r = -0.14$, $r = -0.23$) did not correlate significantly with prolactin responses. The correlations remained nonsignificant when age and sex were controlled in a multiple regression analysis.

## DISCUSSION

The significantly blunted peak prolactin response to fenfluramine challenge in depressed patients under age 30 years compared to age-matched controls is consistent with the hypothesis of reduced central serotonergic function in depression.

We found 14 published studies of the effects of fenfluramine challenges on prolactin or cortisol in depressed and personality-disordered patients (see Table 1) (Siever et al. 1984; Muhlbauer and Muller-Oerlinghausen 1985; Asnis et al. 1988; Lopez-Ibor et

**Table 3.** Psychopathology Ratings in Younger and Older Depressed Groups

| | <30 Years of Age | ≥30 Years of Age | *p* |
|---|---|---|---|
| Hamilton Depression Scale score | 26.5 ± 8.3 | 27.8 ± 6.0 | NS |
| Global Assessment Scale score | 43.4 ± 4.1 | 44.8 ± 7.4 | NS |
| Age at first episode of depression | 18.0 ± 4.7 | 38.8 ± 15.2 | .0001 |
| Number of previous major depressive episodes | 3.9 ± 2.8 | 4.3 ± 4.0 | NS |
| Beck Hopelessness Scale score | 14.1 ± 3.4 | 7.0 ± 6.4 | .007 |
| Ratio of attempters to nonattempters | 6/9 | 6/17 | NS |
| Suicide Intent Scale total score | 20.9 ± 5.4 | 12.8 ± 3.4 | .01 |

al. 1988; Weizman et al. 1988; Coccaro et al. 1989; Maes et al. 1989; Kasper et al. 1990; Lopez-Ibor et al. 1990; Mitchell and Smythe 1990; Mitchell et al. 1990; Targum 1990; O'Keane and Dinan 1991; Lichtenberg et al. 1992). The results are not in apparent agreement, perhaps in part because most studies (10 out of 14) lack a placebo control. A placebo challenge can determine whether differential stress responses distinguish the groups, a significant point given that depressed patients may be stress sensitive. The placebo condition can determine if a depression is associated with an abnormal response to the stress of the procedure or if prolactin responses or levels are influenced by the hypothesized reduction in dopaminergic activity, hypothesized to be present in major depression (Kapur and Mann 1992). Another concern is drug levels. Most studies (12 out of 15) did not check blood levels of the drug and therefore were unable to detect potential pharmacokinetic effects. Other potential reasons for apparently divergent results include heterogeneity of patient populations, methodology of the challenge, and effects of residual drugs. A blunted prolactin response was reported by four studies (Siever et al. 1984; Coccaro et al. 1989; Mitchell and Smythe 1990; O'Keane and Dinan 1991). However, one of these studies also reported no difference in prolactin response in patients experiencing nonmelancholic major depression (Mitchell and Smythe 1990). Because most studies did not separately report data on melancholic and nonmelancholic subgroups, we cannot determine the importance of this distinction in explaining differences in reported results. Other studies found no change in patients with major depression versus the controls (Weizman et al. 1988; Targum 1990).

Lopez-Ibor et al. (1990) and Cocarro et al. (1989) found a blunted prolactin response in patients with a personality disorder characterized by suicidal acts but who were experiencing major depression, as compared with the response in patients with a similar disorder but no history of suicide attempts. These results are consistent with our findings in that 78% of the younger depression cases had comorbid borderline personality disorders, compared to only 29% of the older group ($p = .0375$). O'Keane et al. (1992b) found blunted prolactin responses compared to placebo in patients with antisocial personality disorder. In contrast, Targum et al. (1990) found increased prolactin responses in patients with major depression and panic attacks or comorbid panic disorder, as compared with responses in patients experiencing major depression without panic attacks and with responses in healthy controls. In a study that raised questions about the diagnostic specificity of these findings, Lerer et al. (1988) reported a blunted prolactin response in schizophrenics compared with the response in controls. Lerer et al. did not provide data on the presence or absence of a history of depression or suicide attempts in their population. Thus, the subtype of depression, the presence of a personality disorder (particularly from cluster B), comorbid panic disorder, or the presence of panic attacks, and a history of suicide attempts, are potential correlates of an altered prolactin response to fenfluramine. A number of other studies have reported altered serotonergically mediated neuroendocrine responses using other agents that also support the indoleamine deficiency hypothesis of depression. Heninger et al. (1984) found a diminished prolactin response to intravenous tryptophan in depressed patients compared to matched controls. This finding has been replicated by others (Koyama et al. 1987; Cowen et al. 1990; Deakin et al. 1990; Price et al. 1991). Domipramine administered intravenously has been found to generate a blunted prolactin response in depressed patients (Anderson et al. 1992; Golden et al. 1992). Increased cortisol responses to 5-hydroxytryptophan in depressed and manic patients have been attributed to increased serotonin receptor sensitivity (Meltzer et al. 1984). Studies of the 5-$HT_{1A}$ receptor have generated conflicting results. Cowen et al. (1994) reported an attenuated hypothermic response in male but not female depressed patients (an effect attributed to the 5-$HT_{1A}$ autoreceptor). Lesch et al. (1991) also found an attenuated hypothermic response in depressed patients to the 5-$HT_{1A}$ agonist ipsapirone. In contrast, growth hormone (Cowen et al. 1994), adrenocorticotropic hormone (Cowen et al. 1994), cortisol (Meltzer and Maes 1994), and prolactin (Meltzer and Maes 1994) responses to buspirone, which are indices of postsynaptic 5-$HT_{1A}$ mediated effects, have been found normal in depressed patients. However, a blunted growth hor-

mone and adrenocorticotropic hormone response was reported by Lesch (1991) to ipsapirone in depression. Thus, although other general serotonergic neuroendocrine responses appear blunted in depression, it remains to be seen if this effect involves the post-synaptic 5-$HT_{1A}$ receptor. Furthermore, the prolactin response to m-chlorophenylpiperazine (mCPP) in depressed patients is normal (Kahn et al. 1990; Anand et al. 1994). As mCPP is 5-$HT_{2C}$ and 5-$HT_{1A}$ agonist, a mixed agonist/antagonist at the 5-$HT_{2A}$ receptor, and a 5-$HT_3$ antagonist, this result also suggests that serotonin receptor responses are not altered.

Fenfluramine-stimulated increase in prolactin levels appears primarily mediated by serotonin rather than other neurotransmitter systems (Fuller et al. 1988). Prolactin responses to the serotonin selective isomer d-fenfluramine correlate closely with responses to dl-fenfluramine (Coccaro et al. 1993). We have reported elsewhere that a positive correlation exists between CSF 5-HIAA levels and prolactin responses to fenfluramine in patients (Mann et al. 1992). Norepinephrine appears to play no significant role in prolactin secretion (Fuller et al. 1988). In a number of studies, dopaminergic effects have not been observed in humans after comparable or higher doses of fenfluramine. Meyendorff et al. (1986) gave fenfluramine (60 mg/day) to suicidal patients for four weeks and found significant reductions in peripheral and central indices of 5-HT function but no changes in CSF homovanillic acid levels. However, differential levels of endogenous dopaminergic activity may potentially modulate prolactin responses to fenfluramine. Because decreased dopaminergic activity has been associated with depression (Kapur and Mann 1992), such a change may be associated with elevated prolactin levels. We found no evidence of elevated prolactin levels during the placebo day in the depressed patients, suggesting that endogenous dopaminergic tonic regulation of prolactin release in depressed patients did not differ from that of the healthy controls.

We found that the blunted prolactin response was evident in younger but not older depressed patients. A diminished prolactin response was not observed in depressed patients age 30 years and older compared with the response of controls in our sample. Older controls had one-third the peak elevation in plasma prolactin after fenfluramine compared with the elevation in controls younger than age 30 years. In contrast, depressed patients did not exhibit an age-related decline in prolactin responses but had a lower response in the younger age range. The age-related decline in fenfluramine-induced responsivity in controls was not due to differences in fenfluramine or norfenfluramine levels between the older and younger groups (see Table 1). Therefore, this finding may reflect age-related differences in the following: uptake of fenfluramine by presynaptic serotonin receptors, stores of presynaptic serotonin available for release, or responsivity or number of serotonin postsynaptic receptors mediating prolactin release. It may also reflect an age-related change in dopaminergic control of prolactin release or a direct age effect at the level of the pituitary lactotroph. However, the absence of such effects on placebo-associated prolactin levels suggests our results cannot be attributed to altered dopaminergic function. The significance of the age-related change may be further elucidated by serotonin receptor binding studies in the hypothalamus and direct serotonin and dopamine agonist neuroendocrine challenge studies. The absence of a detectable difference between patients and controls over the age of 30 years may also be due to the reduced range of serotonin responsivity in older subjects, although our data do not even hint at a blunting in older depressed patients.

Previous studies (Table 1) have not evaluated older and younger depressed patients separately or controlled for age of onset of major depressive disorder. Our study results are not due to our subjects' duration of illness or number of episodes, which do not differ in the two groups. But the two groups do differ in terms of age of onset of the first episode of major depression and their levels of hopelessness and suicide intent (both were higher in the younger group). Thus the younger group may have a different form of depressive illness that has biological correlates. Another possible difference between the younger and older depression cases is suggested by the possibility of a higher rate of comorbid borderline personality disorder in the younger cases. Our results are consistent with Cocarro et al. (1989), suggesting that Axis II psychopathology may be more closely related to a blunted prolactin response than major depression.

Most studies have not addressed the question of sex differences in prolactin responses to a serotonergic challenge (see Table 1). It appears that the prolactin response is more robust in females, independent of basal prolactin levels (McBride et al. 1990). Our study and two other studies of depression (O'Keane and Dinan 1991; O'Keane et al. 1992a) also found that female depressed patients have higher prolactin responses to fenfluramine than do depressed males. One study did not find a gender difference (Lichtenberg et al. 1992). Thus overall, most studies find a gender difference that appears present in both patients and controls.

The response of prolactin to tryptophan releasing hormone provides an index of lactotroph function. No difference in prolactin responses to tryptophan releasing hormone have been found in depressed patients (Anderson et al. 1992; Golden et al. 1992; Kjellman et al. 1983), indicating that lactotroph function is not compromised in depression and does not explain the blunted prolactin response to fenfluramine.

We found no differences in the fenfluramine-stim-

ulated prolactin response between suicide attempters and nonattempters in our depressed patient sample. A correlation between serotonin and suicidal behavior is suggested by findings of reduced postmortem brain levels of 5-HT and 5-HIAA (Shaw et al. 1967; Bourne et al. 1968; Pare et al. 1969; Lloyd et al. 1974; Moses and Robins 1975; Beskow et al. 1976; Crow et al. 1984; Korpi et al. 1986), decreased brain tritiated-imipramine binding sites (Stanley et al. 1982; Paul et al. 1984; Arató et al. 1987; Gross-Isseroff et al. 1989), and increased 5-$HT_2$ brain receptors in suicide victims (Stanley and Mann 1983; Crow et al. 1984; Mann et al. 1986b; Cheetham et al. 1988; Arango et al. 1990), and by lower levels of CSF 5-HIAA (Åsberg et al. 1976a; Ågren 1980a; Träskman et al. 1981; Brunello et al. 1982; van Praag 1982; Banki and Arató 1983; Banki et al. 1984; Lopez-Ibor et al. 1985; Roy et al. 1986) in suicide attempters. Moreover, CSF 5-HIAA appeared reduced in suicide attempters who had made more highly planned suicide attempts in contrast to those whose attempts had been impulsive (Mann et al. 1992). It is conceivable that in this study population, the severity of the suicidal behavior was insufficient to have a detectable relationship to fenfluramine-stimulated prolactin responses. Alternatively, the sample size may have been too small when divided into attempters and nonattempters to detect an effect. However, the younger patients, who had the blunted prolactin response, were also characterized by greater hopelessness, shown by Beck et al. (1985) to correlate with risk for future suicide and suicidal acts. Moreover, the same younger group had higher suicide intent scores. Thus, the blunting of prolactin responses to fenfluramine in younger depressives may be correlated with the predisposition to suicidal behavior and the degree of intent.

Fenfluramine, by inducing presynaptic release of 5-HT and blocking reuptake, increases intrasynaptic levels of 5-HT, which then stimulate postsynaptic receptors (Fuller et al. 1988). Thus it assesses net central serotonergic responsivity. Fenfluramine challenge cannot discriminate between alterations in available presynaptic 5-HT or alterations in postsynaptic 5-HT receptor responsivity. Nor can fenfluramine distinguish effects on specific serotonin receptor subtypes. Future studies are indicated involving neuroendocrine challenges that employ direct 5-HT receptor agonists and give valuable additional information regarding the functional status of the postsynaptic 5-HT receptor subtypes in depressed patients which can extend the findings reported with fenfluramine.

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