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A neuroendocrine study of 5HT function in depression: evidence for biological mechanisms of endogenous and psychosocial causation

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Abstract. To investigate whether depression is a consequence of disturbed function in 5HT systems, neuroendocrine responses to infusions of the 5HT precursor L-tryptophan (LTP) were studied in patients and controls. After an overnight fast and 60 min bed rest, a solution of LTP (10 g/l) was infused intravenously to a dose of 100 mg/kg over 30 min. Circulating growth hormone (GH), prolactin (PRL), cortisol and tryptophan concentrations were followed from 60 min pre-infusion to 60 min post-infusion. GH responses were attenuated in 23 major depressives (DSM-III) compared with 22 controls and were almost absent in endogenous depressives (Newcastle criteria). PRL responses were normal in depressives who had lost more than 3 kg body weight but attenuated in those who had not. GH and PRL responses did not correlate with each other. Reduced basal tryptophan concentrations and more rapid tryptophan clearance were observed in the depressives, but there were no correlations with GH or PRL responses. However, basal cortisol concentrations, which were raised in depressives with chronic psychosocial difficulties, were strongly and inversely predictive of PRL responses in depressives and controls. Blunted GH and PRL responses to LTP appear to be distinct abnormalities in depression which may relate to two processes; (1), an endogenous mechanism indicated by reduced GH responses, and (2), an impairment in 5HT systems, indicated by blunted PRL responses and perhaps caused by raised circulating cortisol or reduced tryptophan concentrations.

Key words: 5HT – Prolactin – Growth hormone – Cortisol – Depression

Investigations of 5HT function in depression using biochemical measures have produced inconsistent or contradictory results. Measurement of CSF 5HIAA gives a global and indirect measure of presynaptic 5HT function in brain and many studies find reduced concentrations in depressives (Sjostrom and Roos 1972; Asberg et al. 1976). However, there are negative studies (Goodwin et al. 1973; Gjerris et al. 1987). Post-mortem brain studies allow the possibility of detecting localised changes in 5HT function but have their own problems of interpretation such as post-mortem neurochemical stability. There are some findings of reduced 5HT and 5HIAA concentrations in brains from depressives and suicides but there are a similar number of negative or opposite findings (Bourne et al. 1968; Cooper et al. 1986).

Assessment of post-synaptic 5HT receptor function in depression has, until recently, been confined to ligand binding studies in post-mortem brain. Some, but not all, of these studies report increases in 5HT2 receptor binding (Stanley and Mann 1983; Crow et al. 1984; Ferrier et al. 1986). This could be an adaptive response secondary to reduced presynaptic 5HT release in depression, but others have argued that 5HT receptor supersensitivity is the primary event in the pathogenesis of depression (Fuxe et al. 1977; Nagayama et al. 1981).

Neurochemical findings in depressives do not necessarily indicate that functional 5HT neurotransmission is altered; for example, pre- and post-synaptic changes could cancel out. In recent years, pituitary hormonal responses to 5HT agonist drugs have been used to investigate functional 5HT neurotransmission in depression. Charney et al. (1982) reported that infusions of the 5HT precursor L-tryptophan (LTP) caused increases in prolactin (PRL) secretion and that the response was reduced in depressives (Heninger et al. 1984). Cowen and Charig (1987) and Goodwin et al. (1987a, b) made the important observation that weight loss in depressives and in normal dieters increased PRL and also growth hormone (GH) responses to LTP. These effects were more marked in females (Goodwin et al. 1987b; Delgado et al. 1989). In depressives, attenuated PRL responses were seen only in those who had lost less than 10 lb in weight (Cowen

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and Charig 1987). The weight loss effect did not obscure a striking attenuation of GH responses to LTP. Cowen and Charig (1987) confirmed that blunted responses in depressives were not due to smaller increments in circulating tryptophan following the infusion. In contrast, Koyama and Meltzer (1986) found consistently reduced tryptophan concentrations in their depressives which could have caused the attenuation of PRL and GH responses. In view of these findings the present analysis investigates the influence of weight-loss, gender and tryptophan concentration on hormonal responses to LTP.

In normal volunteers, pretreatment with the 5HT reuptake blocker clomipramine potentiated PRL and GH responses to LTP, suggesting the involvement of 5HT synapses (Anderson and Cowen 1986). However, only the PRL response was blocked by the mixed 5HT1/5HT2 receptor antagonist metergoline and this raises doubts about the involvement of 5HT receptors in the GH response (Deakin and Pennell 1986; McCance et al. 1988). The PRL response is not antagonised by the 5HT2 receptor antagonist ritanserin, which suggests it is mediated by 5HT1 receptors (Charig et al. 1987). Clearly, an abnormality of 5HT1 receptors themselves in depression cannot be inferred from blunted PRL responses to LTP – this would be one of many possible explanations. However, blunted PRL responses in depression do indicate an impairment somewhere in a system which influences PRL secretion and which involves 5HT1 receptors. The impairment could be at any step before, at or beyond the 5HT1 receptor.

Whether reduced function in 5HT1 receptor systems is of aetiological significance in depression is not clear. It has seemed at odds with animal experiments which have implicated 5HT systems in mechanisms of aversion (Wise et al. 1970; Tye et al. 1977; Deakin 1983). Such 5HT punishment theories have associated excessive 5HT function with anxiety and depression. One idea is that different 5HT projections and receptor subtypes mediate different adaptive responses to aversive events (Deakin 1989). Anxiety/avoidance is an immediate protective response and may involve 5HT2 receptors (Ceuleman et al. 1985). If the aversive event is not terminated or prevented then longer term adaptive responses maintain resilience or persistence and this may be a function of 5HT1 receptor mechanisms. When this system fails, learned helplessness and depression result (Deakin 1989). If abnormal 5HT function is part of such a causal pathway in depression, abnormal hormonal responses to LTP should relate to clinical aspects of aetiology such as the occurrence of aversive events, and this possibility is investigated below.

Materials and methods

Subjects and assessments. Patients were in-patients or out-patients of the Department of Psychiatry at the University of Manchester. Controls were hospital staff members with no previous psychiatric history. This paper reports on every subject tested. Interviews were based on the Present State Examination and diagnoses were made according to DSM-III criteria. Patients were rated on the Hamilton scale (mean for major depressives = 23.3; range 17–34) and the Newcastle scale for endogenous depression. Weight loss was defined as a score of 2 (more than 3 kg lost) on the Hamilton weight item. Table 1 shows details of age, sex and diagnosis. For simplicity, data from patients with recurrent self-harm (3), hypomania (3), obsessional neurosis (2) and a euthymic bipolar are not presented. Patients were tested, where possible, after at least 3 weeks free of antidepressants and neuroleptics. Twenty-one of the 23 major depressives had been drug free for more than 1 month and 17 for more than 6. One was tested 3 days after inadvertantly receiving 3 days of antidepressant treatment and another 3 days after intermittant prochlorperazine 5 mg. One of the bipolar depressives had taken a neuroleptic until 7 days before the test. Small doses of benzodiazepines were permitted. One control and four major depressives were post-menopausal.

Six months after completion of tryptophan testing, case notes of the major depressives were scrutinised and a checklist of six

Table 1. Subject characteristics and group means of GH and PRL responses. Minor depressives met criteria for dysthymic disorder but had illnesses of less than 2 years duration

	Control	Anxiety	Major depression	Bipolar depression	Minor depression
N	22	5	23	5	3
Females *n*	9	1	16	2	3
Endogenous *n*	0	0	11	2	0
Weight loss *n*	0	0	8	1	1
Age $\bar{x}$ (range)	34.4 (22–57)	32.0 (26–35)	42.7 (21–65)	26.8 (22–29)	28.3 (26–47)
Log GHD $\bar{x}$ (SEM) (detransformed)	1.20 (0.09) (15.9)	1.12 (0.18) (13.2)	0.88* (0.11) (7.6)	0.84 (0.34) (6.9)	0.70 (5.0)
Log PRLD $\bar{x}$ (SEM) (detransformed)	2.30 (0.10) (200)	2.28 (0.17) (191)	2.12 (0.12) (132)	2.48 (1.10) (302)	2.65 (447)

* $2P < 0.05$, *t*-test

aetiological items was completed; (1) duration of symptoms in months; (2) chronic psychosocial difficulties (yes/no); (3) acute precipitant (yes/no); (4) pre-morbid neurotic traits (yes/no); (5) other impairment of pre-morbid personality (yes/no); (6) response to treatment graded 1 – chronic persisting symptoms at 6 months, 2 – improvement but original symptoms persist at 6 months, 3 – significant resolution by 3 months and eventual near total recovery, 4 – complete and rapid resolution of symptoms by 2–3 months. Items 1–5 record the opinion of the treating team as stated in the University case notes: the items are not ratings. Item 5 was intended to identify hysterical, antisocial personalities but there was only one positive rating and the item was dropped from analysis. All rated subjects received reuptake blocking drugs in therapeutic doses and five received ECT. Response could not be rated in three subjects due to treatment refusal, rapid remission and loss to follow-up.

Neuroendocrine testing. L-Tryptophan was dissolved in a solution containing sodium chloride (0.72%) and sodium sulphite (0.05%) to a concentration of 10 g/l. The pH was adjusted to 7.5 and the solution autoclaved. Subjects were tested at 8.30 a.m. after an overnight fast. Subjects remained supine and awake. After insertion of an intravenous cannula, baseline samples were taken immediately and after 60 min rest. LTP (100 mg/kg) was infused over 30 min. Further blood samples were taken at 30, 40, 50, 60, 70 and 90 min after the start of the infusion.

Hormone and tryptophan assays. Serum hormone concentrations were determined by standard radioimmunoassay in the Regional Radioimmunoassay Laboratory. Within and between assay coefficients of variation were, respectively, less than 4.2% and 11.6% for both GH and PRL. The laboratory is a member of the National Quality Assurance Scheme. Cortisol, oestradiol, progesterone and tryptophan concentrations were determined in a subset of the major depressives and controls. Tryptophan was estimated by HPLC. Hormonal responses were calculated as the difference between peak post-infusion concentration and immediate pre-infusion baseline (GHD, PRLD).

Statistics. Analysis of variance and covariance was used to test for significant differences in hormonal parameters between groups. Hormonal data were log transformed to produce normal distributions and equal variances between groups. However, untransformed and individual data are presented for clearer evaluation. Table 1 shows that the major depressives are significantly older and include more females than the controls. Therefore, in all analyses of variance, checks were made for covariation with age and for main effects of sex and its interactions. *t*-Tests were used in simple group comparisons. Spearman's non-parametric correlation coefficients were used to investigate hormonal and clinical associations.

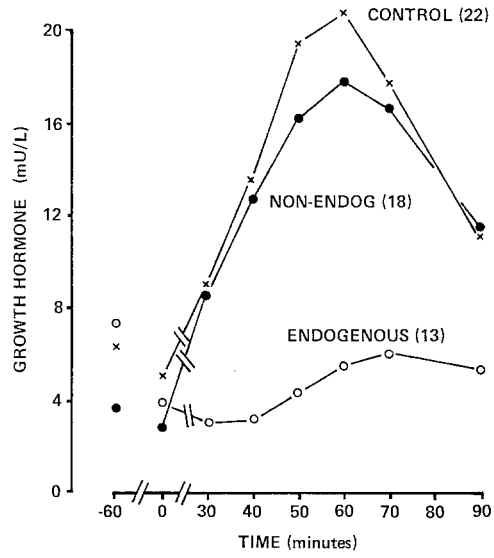

Fig. 1. Serum GH concentrations in controls, endogenous depressives (11 major depressives and 2 bipolars), and nonendogenous depressives (12 major, 3 minor and 3 bipolar depressives)

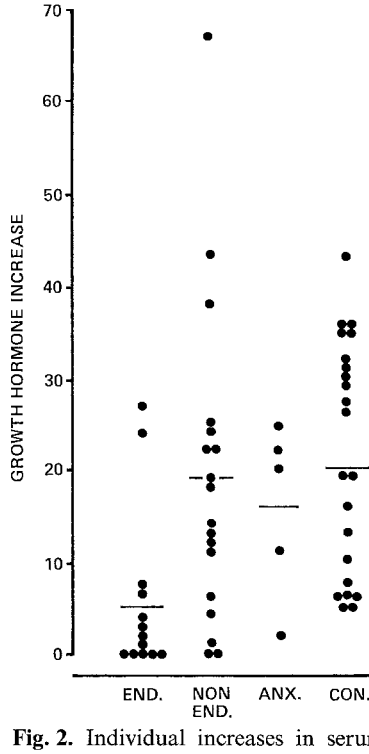

Fig. 2. Individual increases in serum GH concentration (mU/l; Peak-baseline concentration) by clinical group. *END*, endogenous depressives; *NON END*, non-endogenous depressives; *ANX*, anxiety diagnoses; *CON*, controls

Results

Growth hormone

One control subject had an abnormally raised pre-infusion GH concentration (51 mU/l) and was excluded from the analysis. Depressives tended to have reduced basal GH concentrations compared to controls but the difference was not significant.

Patients with major depression had smaller increments in GH secretion (GHD) following LTP than controls (Table 1). There were non-significant reductions in GHD in the other depressive groups (bipolars and mild), while the anxiety diagnoses had a normal mean log GHD. Reductions in GH responses to LTP were especially marked in depressed patients who met the Newcastle criteria for endogenous depression (Figs. 1 and 2).

In the analysis of covariance of log GHD, the clinical grouping factor was significant ($F=4.71$; 2,46; $P<$

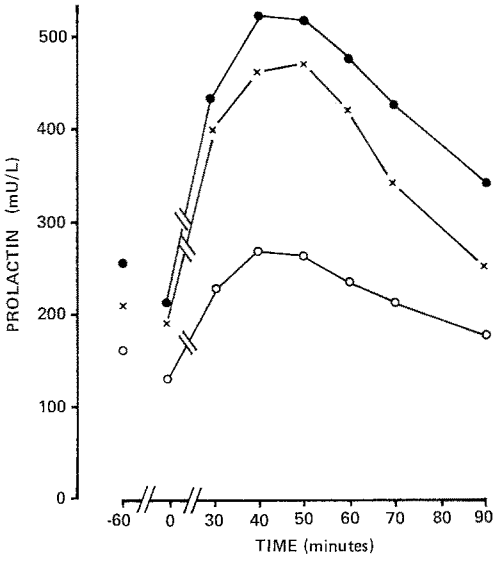

Fig. 3. Serum PRL concentrations in controls and major depressives with Hamilton weight-loss ratings of 2 (>3 kg) and with ratings of less than 2. ●—● Major depression (weight loss, n = 8); x—x control (22); o—o major depression (no weight loss, n = 15)

0.02); endogenous depressives had significantly lower GH responses to LTP than non-endogenous or controls (see Fig. 2). Neither age nor basal GH emerged as significant covariates ($F = 0.0$ and 0.34, respectively; 1,46; $P > 0.1$). There was no main effect of sex ($F = 0.12$, 1,46; $P > 0.1$). The sex by group interaction was not significant.

Depressives with a history of recent weight loss of more than 3 kg (Hamilton rating) had slightly greater basal GH concentrations and responses to LTP than those without, but the differences did not approach statistical significance.

Prolactin

One subject in the anxious group with a basal PRL concentration of 1067 mU/l was excluded.

Table 1 shows that there were no differences between the groups in mean PRL responses to LTP. However, recent weight loss had a powerful influence on PRL concentrations; depressives with recent weight loss (more than 3 kg) had significantly increased PRL concentrations before and after LTP compared to those with less or no weight loss (2 $P < 0.05$, t-tests each time-point; Fig. 3). To remove the confounding effects of weight loss on the clinical correlates of PRL responses, patients with Hamilton weight loss scores of 2 were excluded from further analysis.

Major depressives without weight loss had lower basal PRL concentrations than controls and diminished responses to LTP (Fig. 3). There were significant main effects of group (depressed, control; $F = 6.67$; 1,33; $P < 0.02$) and of sex ($F = 7.44$; 1,33; $P = 0.01$). Group and sex effects remained significant when adjusted for the covariation with basal PRL which was also significant ($F = 5.59$; 1,36; $P = 0.02$; $r = 0.44$, $P < 0.02$). Age was not a significant covariate. There was no significant interaction between group and sex. Figure 4 illustrates the main effects. Females have greater PRL responses than males (main effect of sex) and depressives smaller responses than controls (main effect of group).

PRL and GH responses were not significantly correlated in controls or depressives, or in any subsample defined by sex and/or weight loss.

Cortisol

Basal cortisol concentrations were increased in depressives ($n = 18$) compared to controls ($n = 11$; detransformed means, respectively, 347 versus 263 ng/ml; $t = 1.7$; 2 $P < 0.1$).

Increased basal cortisol concentrations were strongly associated with reduced PRL responses to LTP in the total sample ($r = -0.52$, $n = 29$, $P = 0.002$), in the depressives ($r = -0.66$, $n = 18$, $P = 0.001$), in female depressives ($r = -0.75$, $n = 12$, $P = 0.002$) and in female depressives without weight-loss ($r = 0.77$, $n = 6$, $P = 0.04$). Correlations between basal cortisol and basal PRL concentrations in any grouping were less than 0.15 and not significant.

Neither weight-loss nor sex influenced basal cortisol concentrations.

There were no consistent changes in cortisol secretion following LTP in any group and these data are not considered further.

Tryptophan

Basal tryptophan concentrations were lower in major depressives than controls (Table 2). Peak serum tryptophan did not differ between the groups but depressives showed an accelreated decline by 90 min after initiation of the LTP infusion (Table 2). Increases in serum tryptophan did not correlate with increases in GH or PRL in any subgrouping defined by sex, diagnosis or weight-loss.

Course of illness and hormonal variables

There were only three significant intercorrelations between the five features of the depressive illnesses recorded from the case notes; precipitated illnesses, long duration and chronic difficulties were significantly associated with poor outcome ($r > 0.4$, $n > 20$, $P < 0.05$).

Figure 5 shows that lack of a precipitant and non-neurotic personality were associated with blunted GH responses to almost the same extent as the endogenous syndrome. Absence of chronic difficulties was not associated with blunted GH responses and there were no correlations between GH responses and duration of illness (months) or grade of therapeutic response (1–4).

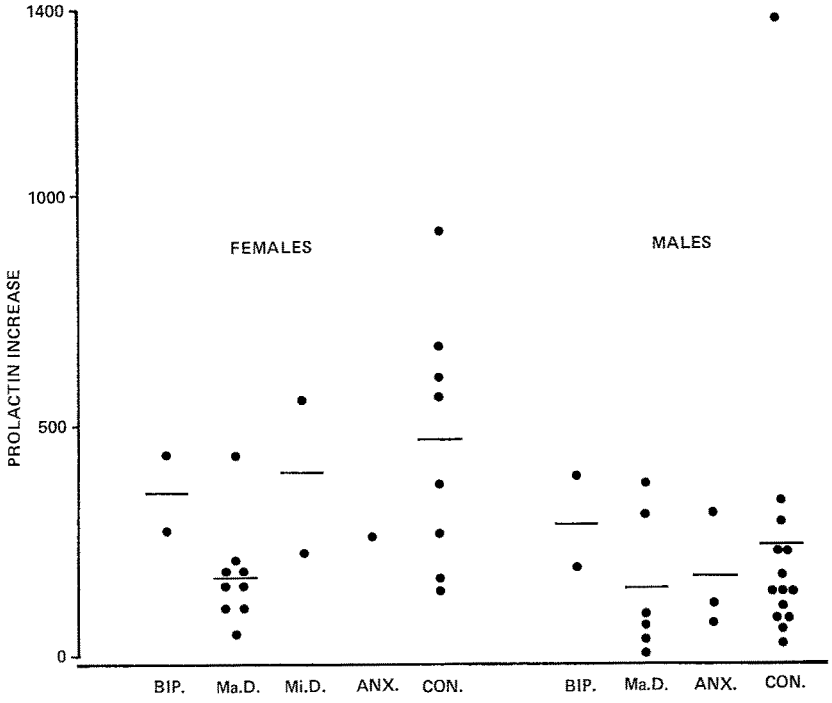

Fig. 4. Individual increases in serum PRL concentrations (mU/l; peak – baseline) by diagnostic group. *BIP*, bipolars; *Ma.D*, major depressives; Mi.D., minor depressives; *ANX*, anxiety diagnoses, *CON*, controls. Patients with Hamilton weight loss ratings of 2 excluded

Table 2. Serum tryptophan concentrations μg/ml before and after LTP infusion

	Baseline	30 min	40 min	90 min
Control (12)	12.9	231.9	209.7	191.0
±SE	1.9	6.6	7.8	8.0
Depressives (15)	9.8*	240.5	201.2	159.1**
±SE	0.51	7.6	8.2	4.2

* $2P<0.1$; ** $2P<0.005$, *t*-test

No relationships were seen between the five illness variables and PRL responses in the depressed sample nor in the subgroup of nine females without weight loss.

Basal cortisol concentrations were uninfluenced by endogeneity, precipitation or neurotic personality (Fig. 5). However, in patients with chronic psychosocial difficulties, basal cortisol was 45% greater than in those without ($F=8.2$; 1,16; $P=0.01$) irrespective of sex. Months of illness correlated with cortisol in the females ($r=0.59$, $P=0.020$) and females with illnesses longer than 2 years had increased cortisol concentrations (Fig. 5). This could not be assessed in males because the six with cortisol data had short illnesses. Increased basal cortisol predicted a poor response to treatment in females (Fig. 5) but not males (response × sex interaction $F=9.9$; 1,13; $P=0.01$) and the correlation between cortisol and the four grades of response was −0.8 in females.

Increases in LTP were not associated with the illness markers but low basal LTP concentrations predicted a good response to treatment ($r=0.61$, $n=14$, $P=0.01$), especially in females ($r=0.77$, $n=11$, $P=0.005$).

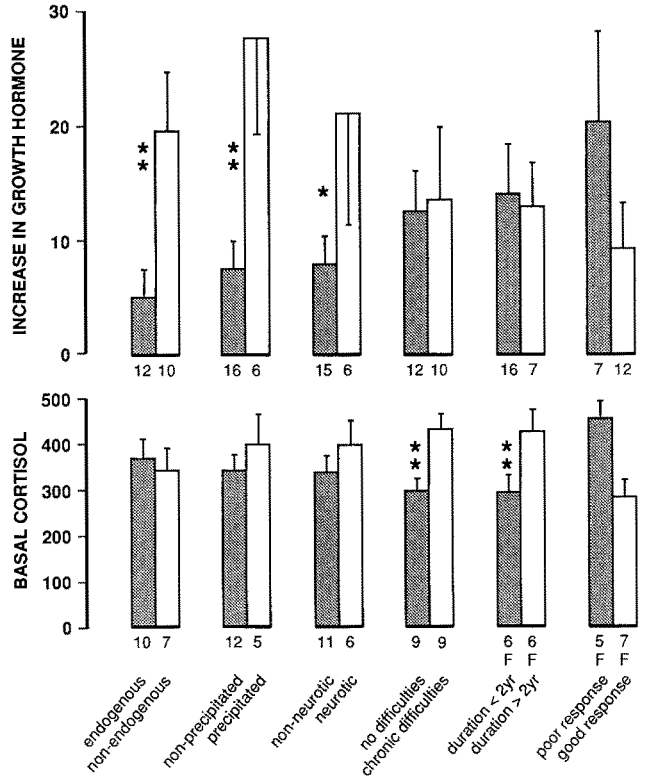

Fig. 5. GH responses and basal cortisol concentrations (nmol/l) in major depressives divided into two groups (shaded versus open columns) according to clinical features. *F*=females

Discussion

Growth hormone

GH responses to LTP were clearly highly attenuated in major depressives compared to controls. This appears to be a robust neuroendocrine abnormality in depres-

sion, since it is large and unequivocal in three independent studies (Deakin and Pennell 1986; Koyama and Meltzer 1986; Cowen and Charig 1987). In the present study, blunted GH responses to LTP in depressives could not be explained by differences from controls in age, sex or basal GH concentrations. Depression often involves loss of weight but this has been associated with increased rather than blunted GH responses to LTP in depressives and in normal dieters (see Introduction). In the present study, the slight trend to greater GH responses in depressives with weight-loss than in those without did not approach significance.

Prolactin

Several factors influenced the magnitude of PRL responses to LTP. In agreement with other studies, PRL responses to LTP were considerably increased in depressives who had lost weight compared to those who had not (Goodwin et al. 1987a, b; Delgado et al. 1989). It was suggested that receptor supersensitivity develops due to reduced 5HT function due to reduced dietary LTP. However, basal tryptophan concentrations were not reduced in patients with weight-loss as defined by the Hamilton rating and there were no relationships between tryptophan variables and PRL responses.

Females had substantially greater PRL responses than males and this confirms two other reports (Goodwin et al. 1987b; Delgado et al. 1989). Gender differences in human 5HT function may explain differences in clinical and psychophysiological responses to drugs with actions on 5HT systems (MRC 1965; Deakin and Wang 1989; Guimaraes et al. 1990). There is evidence of sex differences in 5HT function in animals and evidence for influences of ovarian steroids on 5HT function (e.g. Wilson and Hunter 1985). Serum oestradiol and progesterone were determined in basal samples from 12 of the 16 female major depressives but no relationships with PRL variables could be discerned and four menopausal subjects had unremarkable PRL data. Thus, in agreement with Cowen and Charig (1987), menstrual status did not appear to influence PRL responses. This does not rule out the possibility that ovarian steroids are responsible for the gender effect on PRL.

Patients with major depression who had not lost weight had reduced PRL responses to LTP. Basal PRL concentrations were also reduced and were correlated with reduced increments in PRL. However, when the influence of basal PRL was covaried, significant differences between depressives and controls remained. These results are closely similar to those of Cowen and Charig (1987).

Mechanism of reduced PRL response in depression

It is possible that reduced PRL responses to LTP in depressives are due to changes in peripheral tryptophan metabolism. Reduced basal concentrations of tryptophan were found in the depressives and tryptophan cleared more rapidly from their circulation (Table 2). Possible explanations of these findings include enhanced tryptophan metabolism by liver pyrrolase and enhanced uptake to the brain or other organs due to reduced concentrations of amino acids which compete for tryptophan transporter (Joseph et al. 1976). While such mechanisms could result in reduced PRL responses in depression, the rise in tryptophan concentrations which followed the direct intravenous infusion of LTP was extremely large and identical in depressives and controls at the time of maximal PRL response (40 min, Fig. 3). Furthermore, in agreement with other studies (Cowen et al. 1987, 1989), indications of altered peripheral tryptophan metabolism in depressives (reduced basal concentrations and more rapid clearance) did not correlate with PRL responses.

Basal cortisol concentrations were strongly and inversely predictive of the magnitude of PRL responses to LTP but not of basal PRL concentrations. This suggests the possibility that cortisol reduces PRL responsivity to LTP and that cortisol hypersecretion in depression is a possible mechanism of attenuated PRL responses. Increased cortisol secretion could attenuate PRL responses by an effect on peripheral metabolism as described in animals (Joseph et al. 1976) but there were no relationships between cortisol and tryptophan variables in this study. Lopez-Ibor et al. (1988) and Mitchell and Smythe (1989) have reported that greater basal cortisol concentrations predict reduced PRL responses to fenfluramine and this suggests that cortisol may reduce LTP effects by a central rather than a peripheral mechanism.

There is evidence that corticosteroids modulate 5HT1 receptor function and that 5HT1 receptors mediate the PRL response to LTP. Chronic corticosteroid treatment reduced rats' behavioural responses to 5HTP (Nausieda et al. 1982) and the small subgroup that reportedly became supersensitive may be an artefact of post-hoc selection. More specifically, components of the rat 5HT syndrome thought to be mediated by 5HT1 receptors were reduced following chronic corticosteroid treatment (Dickinson et al. 1985), including when the behaviours were evoked by the 5HT1 receptor agonist 5-methoxy-N,N-dimethyltryptamine. The latter finding suggests steroid effects at or beyond the 5HT1 receptor. In radioligand binding studies, adrenalectomy increased 5HT1 receptor binding in the rat forebrain and this was reversed by corticosteroid administration (Biegon et al. 1985; De Kloet et al. 1986). These findings suggest that raised cortisol secretion in depression could decrease 5HT1 receptor function and thus attenuate PRL responses to LTP as in this study and to fenfluramine as in others (Lopez-Ibor et al. 1988; Mitchell and Smythe 1989).

Implications for the psychobiology of depression

Cortisol-induced impairment of 5HT1 neurotransmission may be an important mechanism in the psychoso-

cial origins of depression. Studies in animals suggest that 5HT1 receptors may be concerned with adaptation to aversive events. Kennet et al. (1985, 1987) showed that male rats became tolerant to the effects of repeated immobilisation stress on open field behaviour and that this was associated with enhanced function in 5HT1 receptor systems. Corticosterone release appears to retard the development of behavioural adaptation and to reduce 5HT1 receptor function (Dickinson et al. 1985). The authors thus propose an animal model in which depression is due to a failure of adaptive responses to repeated stress, mediated by impaired 5HT1 receptor mechanisms. Chronic hypercortisolaemia – as in chronic stress – predisposes to depression by interfering with 5HT1 stress-adaptation systems. In the present study as in others, depression, especially in those with chronic psychosocial difficulties and chronicity of symptoms, was associated with raised cortisol secretion (Fig. 5; Dolan et al. 1985). This may have compromised 5HT1 receptor function (as suggested by the negative correlation with PRL responses) in systems concerned with adaptation to chronic aversive stimuli, resulting in loss of normal psychosocial functioning and the development of helpless and other depressive behaviours (Deakin 1989).

Depressives with lower LTP concentrations had a better response to treatment as reported by Moller et al. (1986). This would be compatible with the idea that the ability of chronic antidepressant treatments to enhance 5HT function causes their antidepressant action (De Montigny and Aghajanian 1984; Kennett et al. 1987; Deakin 1989). While blunted PRL responses, putatively indicative of impaired 5HT neurotransmission, did not predict outcome, the influence of gender and weight-loss might well have obscured such a relationship in a study of this size. Raised cortisol predicted a poorer outcome but this is likely to be due to the association of chronic symptoms with raised cortisol and poor outcome.

Conclusion

Reduced GH and PRL responses to LTP in depression appear to be independent abnormalities and this suggests the existence of two processes. The first is the endogenous mechanism, of uncertain neurochemistry, which is indicated by blunted GH responses. The second process involves impairment of function in systems incorporating 5HT1 receptors. Increased cortisol secretion and abnormal peripheral tryptophan metabolism in depression may contribute to the impairment of neurotransmission in 5HT1 receptor systems. This results in attenuated PRL responses to LTP and, speculatively, in reduced behavioural resilience to psychosocial adversity. Antidepressant therapies may work by restoring 5HT1 neurotransmission (DeMontigny and Aghajanian 1984) thereby promoting adaptation to adversity (Deakin 1989).

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