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Serotonergic Dysfunction in Depression

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Various irregularities in serotonin (5-HT) function have been postulated as causes of affective disorders. Serotonin has been related to many of the major symptoms of depression, e.g. mood, appetite, sleep, activity, and cognitive dysfunction. Interference with 5-HT synthesis or storage has been shown to induce depression in vulnerable individuals. Decreased levels of 5-hydroxyindoleacetic acid (5-HIAA) in cerebrospinal fluid, decreased plasma tryptophan, low tryptophan neutral amino acid ratio, abnormalities in serotonergic function indicated by neuroendocrine challenge tests and various platelet measures, have been reported in depressed patients. Concentrations of 5-HIAA, the major metabolite of 5-HT in plasma, were found to be significantly negatively correlated with severity of depression as measured by the Hamilton Rating Scale for Depression score and specific depressive symptoms, despite the fact that plasma 5-HIAA is largely peripheral in origin. Blood platelets, which have been suggested as models for serotonergic nerve terminals, have a significantly decreased number of 5-HT uptake sites and ^{3}H-imipramine binding sites in depressed patients. Antidepressant drugs may act, in part, by enhancing serotonergic activity. The serotonergic deficit may occur at any of several levels: diminished availability of precursor, impaired activity of tryptophan hydroxylase, abnormalities in 5-HT release or uptake, 5-HT receptor abnormalities or interactions with other neurotransmitters.

Numerous neurotransmitters have been implicated in the biology of major depression, e.g. norepinephrine, acetylcholine, gamma-aminobutyric acid, dopamine, and serotonin (5-HT). There is evidence from biologic studies in depressed patients as well as inferential data from the mechanism of action of antidepressant drugs in laboratory animals and man to support some role for each of those neurotransmitters in the pathophysiology of depression. This paper will summarise briefly the evidence for the role of 5-HT in major depression. A more extensive discussion has appeared elsewhere (Meltzer & Lowy, 1987).

The 5-HT hypothesis of depression

The 5-HT hypothesis of affective disorders has been formulated in a variety of ways. One, proposed by Coppen (1967), Coppen *et al* (1972), and Lapin & Oxenkrug (1969) attributes increased vulnerability to either depression or mania, to decreased serotonergic activity. Deficiency of 5-HT has also been suggested as the proximate cause of depression (Koyama & Meltzer, 1986). On the other hand, Aprison *et al* (1977), among others, have postulated that increased serotonergic activity may cause depression. Most data favour the deficiency theory (Meltzer & Lowy, 1987; Coccaro *et al*, 1989).

Serotonergic abnormalities in depressed patients

Abnormalities in serotonergic function have been linked to many prominent symptoms of depression, e.g., appetite (Blundell, 1984), mood, sexual function, sleep dysfunction, and circadian rhythms (Meltzer & Lowy, 1987). A substantial body of evidence, in part to be reviewed here, reports serotonergic abnormalities in blood platelets, plasma, and cerebrospinal fluid (CSF) of depressed patients and post-mortem specimens from suicides, many of whom are presumed to have had a major depression or bipolar depression prior to suicide (Robins *et al*, 1959; Barraclough *et al*, 1974). Normal or decreased levels of 5-hydroxyindoleacetic acid (5-HIAA), the major metabolite of 5-HT in the cerebrospinal fluid of depressed patients or those who have made violent suicide attempts, further implicate diminished serotonergic activity in depression (Åsberg *et al*, 1984; Meltzer & Lowy 1987). A positive correlation between severity of depression and the cortisol response to 5-hydroxytryptophan (5-HTP) was observed (Meltzer *et al*, 1984*b*). This was attributed to an upregulation of 5-HT_2 receptors, possibly related to a deficiency in 5-HT.

Neuroendocrine challenge studies

Neuroendocrine challenge studies using serotonergic probes provide some measure of central serotonergic activity. We reported that the cortisol response to D,L-5-HTP, 200 mg was significantly greater in depressed patients than in normal controls (Meltzer *et al*, 1984*d*) (Fig. 1). Maes *et al* (1987) also found an enhanced cortisol response to L-5-HTP (200 mg, p.o.) in severely depressed females, compared with depressed males and in patients with minor depression (Fig. 2).

What is the effect of treatment with tricyclic

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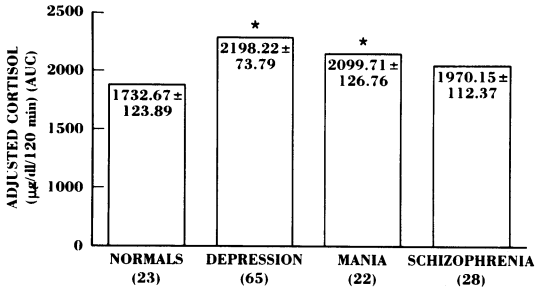


FIG. 1 5-HTP-induced increase in cortisol in normal controls and psychiatric patients.

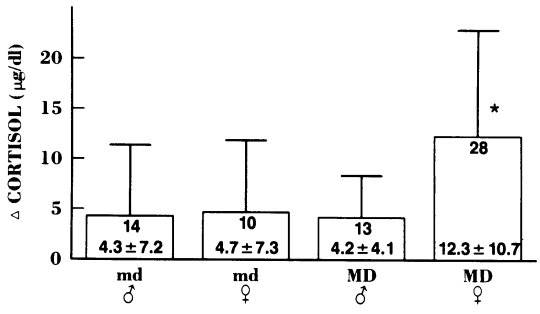


FIG. 2 Cortisol response after 5-HTP in controls and depressed patients (after Maes *et al*, 1987). md = minor depression; MD = major depression.

antidepressant drugs such as imipramine on 5-HTP-induced increases in cortisol? In our initial studies, which used half the dosage of 5-HTP in our currently used protocol, the tendency was toward a lesser — rather than greater — 5-HTP-induced increase in cortisol during treatment (Meltzer *et al*, 1984*b*). We have replicated that finding using L-5-HTP in a new series of depressed patients (Meltzer *et al*, unpublished data). Although it appears that blockade of 5-HT reuptake was achieved during treatment with the antidepressants, perhaps along with some alteration in 5-HT receptor sensitivity, no real enhancement of the response to 5-HT produced from the 5-HTP was seen. These results indicate that inhibition of uptake of 5-HT by such compounds may not be as marked as had been believed. On the other hand, there is stimulation of the 5-HTP-induced increase in serum cortisol with specific 5-HT uptake blockers such as sertraline and fluoxetine (Meltzer *et al*, unpublished). A significant negative relationship has been demonstrated between CSF 5-HIAA and the cortisol response to 5-HTP in major depression (Table I) that is consistent with the notion that decreased serotonergic activity is a factor responsible for enhanced response to 5-HTP in some depressed patients (Koyama *et al*, 1987). We suggested that this might be due to increased 5-HT_2 receptor sensitivity (Meltzer *et al*, 1984*b*), but this hypopthesis is not consistent with the normal cortisol responses observed following MK-212.

Plasma tryptophan

Some evidence has been presented that depressed patients may have lower plasma levels of tryptophan (Coppen & Wood, 1978; DeMyer *et al*, 1981) and, by implication, a decrease in 5-HT synthesis, because tryptophan concentration is believed to control the activity of tryptophan hydroxylase, the rate limiting enzyme in 5-HT synthesis. Cowen *et al* (1989) recently reported decreased plasma total tryptophan levels (primarily in female patients) in a small group of patients with depression. One study, however, showed no difference in plasma tryptophan levels in depressed patients (Møller, 1985). In our study, high-pressure liquid chromatography was employed to measure plasma tryptophan and 5-HIAA levels. No difference was found between the plasma tryptophan or 5-HIAA levels of 40 unmedicated patients diagnosed as having major

TABLE I
Spinal fluid metabolite correlations with 5-HTP-induced increase in serum cortisol

Metabolite	*n*	*CSF levels (ng/ml)* Mean	s.d.	*Correlation with 5-HTP-induced serum cortisol response (rho)*
5-HIAA	16	12.2	10.2	−0.65*
HVA	16	34.6	13.5	−0.46
DOPAC	16	2.7	2.1	0.21
MHPG	16	7.2	2.4	0.43

*P = 0.05.
Abbreviations: *n*, number of patients; s.d., standard deviation; 5-HIAA, 5-hydroxyindoleacetic acid; HVA, homovanillac acid; DOPAC, 3,4-dihydroxyphenylacetic acid; MHPG, 3-methoxy-4-hydroxyphenylglycol.

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TABLE II
Plasma tryptophan and 5-HIAA in unmedicated depressed patients and normal controls

Group	n	Tryptophan (μg/ml)	5-HIAA (ng/ml)
Normal controls	17	8.69 ± 2.26	5.52 ± 1.67
Depressed patients	40	8.07 ± 1.88	5.58 ± 2.02

No significant differences noted.

depression and 17 normal controls (Table II). However, significantly lower fasting plasma tryptophan levels were found in both depressed female patients and female control subjects, a possible contributory factor to why females are more vulnerable to depression.

Møller *et al* (1980) have pointed out that a relative elevation of the concentration of large neutral amino acids may also contribute to a deficiency of brain 5-HT in depression, because plasma tryptophan must compete with those amino acids for entry into the brain. Determination of plasma free tryptophan and the concentration of neutral amino acids may be more revealing than the measure of tryptophan reported. Cowen *et al* (1989) also found a significantly lower ratio of plasma tryptophan to neutral amino acids in depressed patients.

Koyama & Meltzer (1986) attempted to replicate the findings of Charney *et al* (1984) and those of Heninger *et al* (1984), who reported a blunted plasma prolactin response to an intravenous tryptophan load (100 mg/kg over 20 min) in unmedicated depressed patients. We also measured the increase in plasma tryptophan levels and found them lower in depressed patients. Although the findings of a low prolactin response were replicated, when the difference in plasma tryptophan levels was covaried, no blunting of the prolactin response was found. However, the study did show a striking inhibition of the growth hormone response that persisted even after adjustment for differences in tryptophan levels. This finding further suggests inadequate 5-HT production in depressed patients or perhaps diminished responsiveness of the 5-HT receptor subtype that mediates the growth hormone response.

In the study that showed markedly smaller increases in plasma tryptophan in depressed patients, plasma 5-HTP and 5-HIAA levels were also measured following the tryptophan infusion (Koyama & Meltzer, 1986). A non-significant trend toward lower 5-HTP levels was observed, whereas a markedly decreased level of 5-HIAA was found. Those results are consistent with the possibility that tryptophan might be metabolised via other pathways or perhaps be incorporated into proteins. Either way, these results suggest inadequate conversion of tryptophan to 5-HT in some depressed patients.

TABLE III
Univariate correlations between plasma 5-HIAA and psychopathology in major depression

Variable	n	Spearman rho	P
Hamilton-DEP (Total)	25	−0.42	0.04
Guilt	25	−0.46	0.02
Suicide	25	−0.38	0.06
Insomnia, late	25	−0.51	0.009
Hopelessness	25	−0.53	0.007
Worthlessness	25	−0.46	0.02

Plasma 5-hydroxyindoleacetic acid

Plasma 5-HIAA levels in unmedicated depressed patients were significantly negatively correlated with severity of depression as measured by the total Hamilton Rating Scale for Depression (Hamilton, 1960) and with the following items: guilt, suicide, insomnia, hopelessness, and worthlessness (Table III). These results suggest that plasma 5-HIAA concentration could be an indicator of brain serotonergic activity. This rather surprising finding needs to be replicated in an independent sample because numerous peripheral factors, such as metabolism of 5-HT in the gut affect plasma 5-HIAA levels.

The blood platelet as a model for brain 5-HT neurons

The blood platelet has been often suggested as a model for serotonergic nerve terminals, and it has, therefore, been used to study various aspects of 5-HT chemistry in man as well as the effect of antidepressant drugs on the 5-HT system. Coppen *et al* (1978), Meltzer *et al* (1981), and Healy *et al* (1986) found a decreased number of 5-HT uptake sites in the platelets of depressed patients. Our research has shown this decrease to be most marked in bipolar and psychotically depressed patients (Table IV). A marked decrease in platelet ^{3}H-impramine binding sites was also found in these patients (Meltzer *et al*, 1984*a*).

We have studied children, aged 6 to 18 years, who were suffering from major depressive disorder or were in recovery from major depressive disorder for less than 2 months (Ambrosini *et al*, unpublished). The control group consisted of normal subjects and non-depressed psychiatric patients. Significantly decreased numbers of ^{3}H-imipramine binding sites (B_{max}) were found in the depressed children. No difference in the number of platelet 5-HT uptake sites was detected, however. In a separate group of recovered depressed children, we

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TABLE IV
Platelet 5-HT uptake in psychiatric disorders

Group	n	K_m (μm)	V_{max} (pmol/10^7 platelets per min)
Normal controls	140	0.47 ± 0.13	12.5 ± 2.9
Major depression	100	0.43 ± 0.13	9.7 ± 2.9*
unipolar	63	0.43 ± 0.13	10.4 ± 2.9*
bipolar	37	0.43 ± 0.12	8.5 ± 2.9*
psychotic	52	0.43 ± 0.13	9.1 ± 3.2*
non-psychotic	48	0.44 ± 0.12	10.4 ± 2.6*
Unipolar psychotic	23	0.43 ± 0.12	10.1 ± 2.9
Unipolar non-psychotic	40	0.44 ± 0.13	10.6 ± 2.8
Bipolar psychotic	29	0.43 ± 0.13	8.4 ± 2.9*
Bipolar non-psychotic	8	0.44 ± 0.13	9.0 ± 3.0*
Schizoaffective depressed			
mainly affective	10	0.44 ± 0.14	8.4 ± 2.8*
mainly schizophrenic	13	0.48 ± 0.15	11.1 ± 5.4
Manic	38	0.45 ± 0.13	9.8 ± 2.1*
Schizophrenic	84	0.45 ± 0.13	10.9 ± 3.3

*Significantly less than normal controls.

found that the number of ^{3}H-imipramine binding sites was also within normal limits.

Suranyi-Cadotte *et al* (1985) and others have reported decreased ^{3}H-imipramine binding in the frontal cortex of suicides. We have been unable to replicate the finding of decreased ^{3}H-imipramine binding in the frontal cortex of suicide victims (Arora & Meltzer, in press). Gross-Isseroff *et al* (1989) also found no difference in ^{3}H-imipramine binding in the pre-frontal cortex of suicide victims, but did find increases in the hippocampus and decreases in the post-central cortical gyrus, insular cortex, and claustrum. These results as well as those of others (Demeter *et al*, 1986) imply that abnormalities in the serotonergic system of depressives and suicides may be region-specific.

A 5-HT_2-like receptor in platelets has been described that has features comparable to those of brain 5-HT_2 receptors (Geany *et al*, 1984). Two studies have now found that depressed patients have higher numbers of 5-HT_2 receptors in platelets. Biegon *et al* (1987) reported increased numbers of 5-HT_2 sites in blood platelets of unmedicated depressed patients. We have also found an increase in the number of 5-HT_2 binding sites using ^{3}H-lysergic acid diethylamide as a ligand (Arora & Meltzer, 1989*b*). Biegon *et al* (1987) using ketanserin reported that the number of sites was normalised after 4 weeks of antidepressant therapy. These studies are of interest in light of the reports of increased numbers of 5-HT_2 binding sites in the frontal cortex of suicides (Mann *et al*, 1986; Arora & Meltzer, 1989*a*).

Serotonergic basis of effective treatment of depression

A considerable body of evidence from both pre-clinical and clinical studies shows that chronic administration of the following can enhance serotonergic activity: tricyclic antidepressants, specific 5-HT uptake inhibitors, MAO inhibitors, precursors of 5-HT, electroconvulsive therapy, and lithium (Meltzer & Lowy, 1987). These modalities may act as antidepressants by correcting or compensating for an underlying deficit in the serotonergic system.

We are studying the effects that specific serotonergic blockers, such as fluoxetine, have on the 5-HTP-induced increase in serum cortisol in unmedicated depressed or obsessive–compulsive patients. Treatment with the 5-HT uptake blockers produce an enhancement in the cortisol response not evident with non-specific tricyclic agents, such as desipramine, nortriptyline, and amitriptyline (Meltzer *et al*, unpublished). This enhancement may reflect the specific 5-HT uptake inhibitor's ability to more effectively block 5-HT uptake in the brain, although the tricyclics are effective inhibitors of 5-HT uptake in platelets. However, the effect of the direct acting 5-HT agonist, MK-212 on cortisol secretion is also enhanced by 4 to 6 weeks of treatment with fluoxetine, but not by commonly used tricyclic antidepressants (Meltzer *et al*, unpublished). These results suggest that if the MK-212 response is indeed a 5-HT-mediated effect, then an upregulation of 5-HT receptors with the specific 5-HT uptake blockers

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TABLE V
Multivariate prediction of SADS-C Depression Scale score from CSF metabolites in major depression

Variable	*Standard estimate*	*P*
HVA	−0.55	0.06
5-HIAA	0.44	0.13

$F = 1.981$; d.f. = 2, 22; $P = 0.16$.

(e.g. fluoxetine) can be achieved that is not evident with common tricyclic agents. Such an effect may well be 5-HT receptor selective. If a serotonergic deficiency is present in depression, upregulation of 5-HT_2 receptors might occur to compensate for diminished serotonergic activity. These findings may explain why drugs such as fluoxetine are more effective in treating obsessive–compulsive disorder. One would expect them also to be more effective as antidepressants if enhancement of serotonergic activity is so critical for the treatment of depression but this does not appear to be the case. This apparent inconsistency with the 5-HT hypothesis of depression must be explained, or current hypotheses of the role of 5-HT as a specific cause of depression will have to be modified.

Induction of depression

The induction of depressed mood or depression by decreasing 5-HT synthesis presents more compelling evidence for the relationship between 5-HT and depression. Interfering with 5-HT synthesis or storage by administering parachlorphenylalanine (PCPA) (Shopsin *et al*, 1976) or reserpine (Goodwin and Bunney, 1971) has induced depression in vulnerable individuals. Recent studies suggest that a reduction of dietary tryptophan, coupled with an increase in neutral amino acids, can bring about depressive symptoms even in normal subjects (Young *et al*, 1986; Smith *et al*, 1987). Similar results have now been reported in major depressives (Heninger *et al*, 1989). These findings strongly suggest the need for a tonic serotonergic effect to maintain normal mood.

Relationship to other neurotransmitters

Our group has measured CSF 5-HIAA and homovanillic acid (HVA), the major metabolite of dopamine, in 30 patients with major depression and 18 schizophrenic patients who had undergone at least a one-week washout period. The CSF data were log-transformed for normalisation. There were significantly lower CSF 5-HIAA levels in the depressed patients (105.2 ± 33.2 nmol/litre v. 128.2 ± 35.0 nmol/litre ($P = 0.03$); CSF HVA levels were also significantly lower in the depressed patients (167.6 ± 65.0 nmol/litre versus 213.8 ± 82.7 nmol/litre) than in the schizophrenic patients. The concentrations of CSF HVA were not significantly correlated with the Depression Subscale of the Schedule for Affective Disorders and Schizophrenia (SADS-C; Endicott & Spitzer, 1978). There was also no relationship between suicide ratings and CSF 5-HIAA or HVA levels. We found a highly significant correlation between CSF 5-HIAA and HVA in depressed patients (rho = 0.62, $n = 30$, $P = 0.0001$). A recent summary by Potter *et al* (1987) of the studies of CSF levels of 5-HIAA and HVA in depression concluded that the most consistent finding was a decrease in HVA, not a decrease in 5-HIAA concentrations.

Because of the high correlation between CSF HIAA and HVA levels, a multivariate analysis to predict severity of depression from both variables was carried out. There was a nearly significant negative relationship between CSF HVA and SADS-C depression ratings after adjusting for 5-HIAA levels (Table V). This suggests low dopaminergic activity may be a predictor of severity of depression.

Causes of 5-HT deficit

Several causes for the postulated 5-HT deficit in depression have been discussed. Diminished availability of 5-HT may be caused by limited precursor, by changes in activity of tryptophan hydroxylase, or by abnormalities in release or reuptake of 5-HT at the synapse. A functional deficit of 5-HT relative to other neurotransmitters of neuromodulators may occur. 5-HT receptors may show abnormalities, with a subsensitivity of one or more subtypes, or an abnormal interaction may occur between 5-HT receptor subtypes.

Second messenger systems linked to 5-HT receptors may be abnormal in depression. Further inquiry is necessary into the possibility that function of either adenylate cyclase, which is the second messenger for the 5-HT_2 receptor, may be anomalous.

We found no evidence in our studies that 5-HT receptor subsensitivity was a primary causal factor in depression. Our examination of 5-HT binding in those who had committed suicide revealed an upregulation of both the 5-HT_1 and 5-HT_2 sites in some subtypes rather than a decrease (Matsubara & Meltzer, unpublished; Arora & Meltzer, 1989*a*,*b*).

Various behaviours influenced by 5-HT may depend on an interaction between 5-HT receptor subtypes (Pericic & Manev, 1988). The possibility exists that such an interaction between two subtypes (both of which

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might be upregulated) leads to a net decrease in 5-HT-regulated behaviour.

Summary

A variety of evidence implicates 5-HT in depression. Current genetic data indicate that heterogeneity is present in bipolar depression, suggesting the probable involvement of various neurotransmitters. Similar abnormalities need not necessarily occur in all patients with major depression. Therefore, variance between subjects could make detection of specific abnormalities difficult. The evidence reviewed here suggests that diminished availability of 5-HT is one of the crucial factors in depression. Low plasma tryptophan levels, a low tryptophan-neutral amino acid ratio, and the difference in achieved levels of tryptophan following a tryptophan load are consistent with this. Decreased ^{3}H-imipramine binding and decreased uptake changes in platelet are difficult to interpret. Future studies must investigate the issue of inactivation of 5-HT in depression at the CNS level.

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