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Serotonin-Corticosteroid Interaction in Affective Disorders

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Awareness, prescription, and research about mood regulating drugs has seen a considerable surge in recent decades, but affective disorders, or mood disorders, have been recognized as pathologies for close to a century. This broader category of disregulation includes two main subgroups: unipolar depression, in which patients exhibit depressive periods of low mood, lethargy, and a variety of physical symptoms; and bipolar depression, in which such depressive episodes are interspersed with contrasting manic periods of increased energy, irritability, and other arousal-type symptoms. Unipolar depression is further distinguished by either melancholic (anhedonic) or atypical (reactive and hypersensitive) features. While the exact biological mechanisms responsible for these disorders are not yet understood, many trends and correlations have been observed. Disruption in activity of the neurotransmitters serotonin (5-HT), dopamine, and norepinephrine have been shown to bring about depressive episodes; indeed, the efficacy of selective serotonin reuptake inhibitor (SSRI) treatments for depression confirms the importance of 5-HT in the disorder (Meltzer et al, 1984). Abnormal stress responses are also associated with affective disorders: depressed subjects show a decreased attenuation of cortisol levels in response to dexamethasone, which suppresses cortisol release in healthy patients (Meltzer et al, 1984). Additionally, current evidence suggests that depression is mediated by an increased sensitivity to stressful life events (Gotlib et al, 2008).

Despite the demonstrated involvement of 5-HT and HPA systems in depression, their interaction remains poorly understood. This paper will review a variety of attempts to elucidate the specific interactions between these two mood-modulating systems and will cover experiments probing their activity and mechanisms in subjects with affective disorders, healthy subjects whose responses provide insight into those of disordered patients, and lab animals.

Interactions in Affective Disorder Patients

In a seminal 1984 study, Meltzer et al found that oral administration of the serotonin precursor 5-HTP induced higher cortisol responses in patients with affective disorders. The authors compared the responses of both experimental and control groups' responses to 5-HTP and a placebo, and found that the higher responses observed in these patients were significant both in comparison to patients' responses to placebo and in comparison to control group's responses to 5-HTP: indeed, the control group's responses to 5-HTP and to a placebo were not significant (see fig. 1). These authors also examined the effects of dexamethasone on cortisol levels in comparison to the effects of 5-HTP, but found no significant differences between patients who demonstrated normal cortisol decrease in the presence of dexamethasone and patients with abnormally blunted responses. This absence suggests that the blunted cortisol decrease in the presence of dexamethasone, an effect characteristic of individuals with affective disorders (Maes et al, 1990), is "not mediated by an abnormality of 5-HT" (Meltzer et al, 1984). Indeed, these authors found elsewhere (Meltzer et al, 1983) that this blunted response is associated with higher 5-HT reuptake, which is more characteristic of non-disordered individuals.

The experimental group involved in this study represented a range of affective disorders: the group comprised 22 unipolar and 14 bipolar depressives, 8 schizoaffective depressives, and 21 manic patients. Patients ceased medication at least two weeks prior to the study, and no significant difference was observed based on length of time for which patients went unmedicated. The authors compared responses between patient subgroups, in addition to

between patients and controls, and while there were not significant differences between the responses of each subgroup there were trends toward slightly different behavior. Manic patients' increased cortisol levels tended to begin earlier and last longer (150 mins) than depressed patients' (120 mins). The overall similarity of all patients' responses, however, suggest a similar abnormality in the serotonergic pathologies characteristic of each group. The authors suggest that "an abnormality in 5-HT might be necessary but not sufficient for the development of both depression and mania," a hypothesis developed in a previous study (Prange et al, 1974) which is supported by the findings of Meltzer's group.

To provide context for the increased cortisol response they found, the authors cite previous studies, including one (Krieger et al, 1975) that found that 5-HT antagonists blocked the increased CRH and cortisol levels characteristic of Cushing's disease, evidence which correlates with Meltzer et al's observation of 5-HT's stimulating effect on cortisol release. Others, however, have found conflicting results, as in the case of a paper describing inhibitory effects of 5-HT on the HPA axis (Scapagnini et al, 1971). The authors conclude with the speculation that 5-HT exerts a dual effect on cortisol secretion, perhaps through separate neural pathways. The remainder of this review will examine more recent studies whose findings support, refute, or extend the foundational hypotheses put forth by Meltzer et al.

Research conducted by Maes' group supports the trends found in the previous paper. A 1989 study (Maes et al, 1989) of the effects of serotonin precursors on glucocorticoid secretion found that patients with major depressive disorder had both decreased levels of L-tryptophan (L-TRP), an amino acid precursor to 5-HTP[1], and increased levels of cortisol in response to

[1] Referred to as L-5-HTP in their paper

dexamethasone. The same patients had significantly higher cortisol responses to 5-HTP. One possible explanation for this phenomenon is a hypothesized effect of L-TRP on negative feedback in the HPA axis. Patients with lower baseline L-TRP availability would thus fail to respond to high cortisol levels by ceasing its secretion, a mechanism which would account for the results found here. Traskman et al's 1980 study, which found a positive correlation between CRF and the serotonin metabolite 5-HIAA, was cited as evidence for this possibility.

Unlike the previous study, no non-disordered control subjects were tested; these results, rather, compare subjects with major depression, with and without melancholia, to those with minor depression. While the absence of such a control group prevents direct comparison between affective disorders and non-pathological states, the authors cite sufficient examples from previous literature--Meltzer's included--that give context for their study, which provides detail about intradisorder differences.

As in the previous study, Maes' group sought to examine correlations between dexamethasone suppression of cortisol (or lack thereof) and the cortisol and L-TRP responses studied. L-TRP was measured both by total amount present in the blood and as a ratio to the sum of other amino acids with which it competes (competing amino acids, or CAA) for uptake into the brain. Trends in these values were consistent in this study. They, too, found no evidence of correlation between cortisol levels induced by dexamethasone and 5-HTP, and they also found no evidence for correlation between the plasma availability of L-TRP and the cortisol response to its administration. The authors did, however, observe a significant correlation between a blunted cortisol decrease after dexamethasone administration and a low baseline L-TRP availability. The authors speculate that the mechanism underlying this phenomenon relies on glucocorticoid

up-regulation of hepatic L-TRP pyrolase, the "first enzyme of the major L-TRP degrading pathway" (Maes et al, 1989), decreasing the amount of available L-TRP. This disordered cortisol persistence was significant in patients who had major depression with melancholic features in comparison to patients with minor depression; while major depressives without melancholia showed a trend in the same direction, it was not significant in comparison with minor depressives.

A second study authored by Maes and others further investigated the interplay between L-TRP availability and cortisol (Maes, 1990). This study, however, looked at the effects of glucocorticoids on serotonin precursors--the inverse relationship of the previous experiment--and also at the variability of tyrosine, another amino acid and a precursor to catecholamines also implicated in HPA axis regulation. L-TRP and tyrosine availability were measured as described in the previous study, as total values and as ratios to competing amino acids. Unlike the previous study, this experiment included a control group in addition to the three types of depressives tested previously[2]; drug use varied between patients but no significant effects were found. The study found that plasma L-TRP and tyrosine levels decreased significantly in the presence of dexamethasone in all patients, with no significant group differences, and this finding provides direct evidence for the previous study's suggestion that higher glucocorticoid levels may lead to decreased available L-TRP in the blood. Significant differences were observed, however, in baseline values of L-TRP and L-TRP/CAA ratios, though not in baseline tyrosine measurements. Patients with major depressive disorder, with and without melancholia, have lower L-TRP availability than minor depressives and controls, and this difference was most pronounced in

[2] Those being minor depressives and major depressives with and without melancholia

melancholic patients.

Together, this study and the previous one authored by Maes present evidence for a self-perpetuating sensitization of the 5-HT system in depressed patients. In this study, depressed patients' available plasma L-TRP levels and L-TRP/CAA ratios decreased in response to dexamethasone; previously, cortisol increased in response to 5-HTP in these same patients. The authors suggest that the increased cortisol levels lead to decreased serotonin precursors and thus to decreased serotonin synthesis. When serotonin precursors are introduced pharmocologically--here, by 5-HTP administration--the level of available serotonin is uncharacteristically high, and thus induces a significantly higher response in the HPA axis it mediates. The latter study suggests a similar phenomenon in the interaction of catecholamines and the HPA axis, as tyrosine also decreased in response to dexamethasone, and the norepinephrine and dopamine into which tyrosine is synthesized have also been observed to modulate the HPA axis (Lal et al, 1980; Gagnon et al, 1984).

Bhagwagar et al also investigated depressed' patients glucocorticoid response to changes in the serotonergic system (Bhagwagar et al, 2002). In contrast to previous studies discussed here, this group used the selective serotonin reuptake inhibitor (SSRI) citalopram (sold under the brand name Celexa) to increase circulating serotonin in the brain, and measured the changes in cortisol and prolactin that followed administration of 10mg citalopram. This experiment studied the differences between healthy controls, patients with major depression, and patients who had recovered from at least two major depressive episodes in the past. No differences in basal levels of cortisol or prolactin were observed between groups in samples taken at noon (to avoid morning peaks in their circadian rhythms), but the groups' responses to citalopram differed

significantly. Acutely depressed patients showed decreased cortisol and prolactin responses compared with controls, and recovered patients had a nearly equal decrease prolactin--but not cortisol--levels. These findings are inconsistent with previous work showing that higher 5-HT availability increases cortisol response in depressive patients, but they are in keeping with Meltzer et al's hypothesis that 5-HT exerts a dual effect on the HPA axis. This paper cites the role of 5-HT_{1A} receptors in the pathology of depression--a theory which will be discussed later in this review--and the consistency of these findings with previous studies examining the role of these receptors (Sargent et al, 2000; Yatham et al, 2000). They also note that the pathology of the 5-HT system that mediates cortisol response is not well understood, and call for further examination of this interaction.

Interactions in Asymptomatic and Healthy Experimental Groups

Thus far, this review has focused on depressive disorders' correlation with irregular 5-HT and glucocorticoid regulation, with the exception of Melter's more inclusive study. Nurnberger et al conducted a similar investigation of the effects HPA responses to L-TRP activity, but they examined differences between healthy controls and euthymic[3] bipolar patients (Nurnberger, 1990). In response to oral L-TRP administration, control subjects showed a significant elevation in cortisol levels in comparison both to their baseline levels and to control subjects given a placebo. A trend toward increased levels of ACTH was also observed. In euthymic bipolar patients, on the other hand, there was no significant difference in cortisol or ACTH responses between the group given L-TRP and the placebo group. The euthymic group also had higher

[3] That is, subjects diagnosed as bipolar who were not exhibiting symptoms of either depressive or hypomanic episodes at the time

baseline plasma tryptophan levels.

These finding presents a third trend in contrast to those observed by Meltzer et al and Maes et al, who saw increased cortisol responses to the serotonin precursor 5-HT and low baseline L-TRP levels, and by Bhagwagar et al, who saw decreased responses to SSRIs in recovered depressives (similar to euthymic patients in their lack of symptoms). Taken together, these trends constitute substantial evidence for a complex effect, if not specifically the dual effect Meltzer et al hypothesized, of 5-HT on the HPA axis. Nurnberger et al cite Meltzer's paper specifically, and suggest that the divergent findings may imply separate mechanisms of cortisol stimulation. These authors also discuss at length the lack of precision inherent in using 5-HTP to increase serotonin production. In high doses, 5-HTP--and, to a lesser extent, L-TRP--will affect other monoamine systems, including those which regulate the HPA axis (van Praag et al, 1987). This imprecision, the authors suggest, may also play a role in the conflicting reports of serotonergic regulation of cortisol release. Another possibility, is that bipolar depression involves biological differences in the interaction of 5-HT systems and the HPA axis. This theory is mentioned only briefly, though, and is less substantial in light of the similarities Meltzer et al observed between the cortisol responses of bipolar and unipolar depressives.

In another study involving a symptom-free experimental group, Sobczak et al examined the interaction between cortisol and L-TRP in first-degree relatives of bipolar patients (both Type I and Type II) (Sobczak et al, 2002). Rather than give subjects L-TRP supplements, these authors induced acute tryptophan depletion (ATD) by administering an oral solution of 75g of all amino acids except L-TRP, which lowerered the L-TRP/CAA ratio (discussed in Maes, et al 1989) and thus decreased 5-HT synthesis. Previous studies have shown that ATD induces

depressive symptoms in recovered depressed patients (Smith et al, 1997). Following administration of the amino acid drink participants were given a stress-inducing speech test (SIST), and plasma cortisol was measured. Relatives of bipolar patients exhibited a significant decrease in cortisol after ATD compared to the control group and compared to relatives given a placebo. Control subjects under ATD exhibited an increase in cortisol compared to those given a placebo. These effects are consistent with those described in the Meltzer et al and Maes et al papers: the experimental group shows a direct correlation between the level of available serotonin precursors and the level of cortisol secreted. This study, however, found no differences in the baseline levels of L-TRP before ATD.

While the studies reviewed previously (Meltzer et al, 1984; Maes et al, 1989; Nurnberger et al, 1990) have investigated changes in mood during their experiments, none provided evidence of any significant changes in mood. In this study, however, moods varied significantly between groups after ATD. Relatives of patients with bipolar type II reported an elevated mood in response to ATD, while relatives of type I bipolar patients and controls both reported slightly lower moods.

These results imply an underlying genetic vulnerability to affective disorders. Although the baseline L-TRP levels in the relatives observed here were normal, their response to decreased levels of this 5-HT precursor was more characteristic of patients experiencing symptoms of disorders. Their responses also stand in contrast to those that Bhagwagar et al observed in similarly asymptomatic recovered patients, though the difference in methods of 5-HT modulation (precursor volume manipulation and SSRI administration) may partially account for this discrepancy. In the context of the self-perpetuating 5-HT sensitization discussed earlier, these

findings suggest--however ambiguously--the possibility of a cortisolemic initiation of affective disorder symptoms, given the normal baseline levels of L-TRP. Without further evidence of a purely genetic predisposition to affective disorders, though, this claim remains tenuous, as only a genetic similarity connects this experimental group with patients from previous studies.

Young et al also studied interaction between glucocorticoids and 5-HT in asymptomatic subjects (Young et al, 1994). These authors administered hydrocortisone to healthy subjects over one week in amounts which mimicked the hypercortisolemia exhibited by patients with affective disorders, as judged by cortisol concentration in urine. Rather than measuring bioavailable 5-HT precursors, however, these researchers assessed 5-HT_{1A} receptor function by measuring hypothermic and HPA responses to a receptor agonist, busiprone, previously shown to induce hypothermia and ACTH release in normal subjects, with similar but blunted responses in depressed patients (Lesch et al, 1990). They found that the group which had taken hydrocortisone had significantly decreased hypothermic and cortisol responses to busiprone (see fig. 2) when compared to controls taking placebo instead of hydrocortisone. The authors discuss the study's limitations resulting from possible direct effects of hydrocortisone on body temperature and cortisol levels: hydrocortisone itself may alter a subject's temperature in unknown ways. To control for hydrocortisone's modulation of cortisol secretion via negative HPA axis feedback, the experimenters gave a group of experimental subjects pindolol, a 5-HT_{1A} partial agonist, which decreased the cortisol response. Barring confounding effects of hydrocortisone, however, the authors conclude that hydrocortisone confounds normal 5-HT_{1A} receptor functioning, leading to a decreased effect of agonists at those receptors.

These authors also investigated the effects of hydrocortisone treatment on sleep

characteristics, and found that subjects taking hydrocortisone had significantly decreased amounts of REM sleep. In this respect, hydrocortisone did not mimic the biology of an affective disorder, as depression is characterized by greater REM sleep, and SSRI administration is often accompanied by a decrease in REM sleep. In this respect, hydrocortisone mimicked antidepressant drugs more closely than depressive biology.

Interactions in Non-Human Experimental Groups

Experiments involving human subjects are necessarily limited to an indirect examination of underlying mechanisms at work. Leitch et al examined the effects of abnormal cortisol levels on the function of 5-HT_{1A} receptors in rats, using a model similar to Young et al's, but updated to reflect a recently improved understanding in cortisol pathology in affective disorders (Leitch et al, 2002). Depressed patients show flatter circadian fluctuations in cortisol levels, in addition to generally elevated plasma cortisol (Deuschle et al, 1997). In this study, rats were implanted with controlled-release corticosterone pellets to mimic the flat cortisol profile of depressed patients, and both this group and a sham group were given the 5-HT_{1A} receptor agonist 8-OH-DPAT[4]. This agonist binds to 5-HT_{1A} autoreceptors, resulting in a decreased secretion of 5-HT in affected neurons, and thus a lower level of 5-HT in the presence of 8-OH-DPAT indicates an increased sensitivity of these 5-HT_{1A} autoreceptors. The authors examined, through microdialysis, the levels of 5-HT in the ventral hippocampus, an area in which chronic stress has been shown to modulate the activity at 5-HT_{1A} receptors (Beck et al, 1994; Karten et al, 1999). Importantly, fluoxetine, an SSRI, was included in the fluid used in microdialysis, so that increases in 5-HT secretion would be reflected in the total amount of 5-HT observed.

[4]8-hydroxy-2-(di-*n*-propylamino)tetraline

The authors observed that all rats exhibited dose-dependent reductions in hippocampal 5-HT in response to 8-OH-DPAT. THe mechanism of action in this observed effect is though to result from autoreceptors at the dorsal and median raphe nuclei, which have high concentrations of 5-HT_{1A} receptors and which innervate the ventral hippocampus where decreased 5-HT was observed. Rats with corticosterone implants had blunted (by roughly 50%) decrease in 5-HT levels in comparison to sham controls, though there was no significant difference in basal levels of 5-HT between groups. This blunted effect of 8-OH-DPAT in experimental animals "suggests a functional desensitization of these somatodendritic autoreceptors" (Leitch et al, 2002). Other studies, however, suggest that 8-OH-DPAT has an antidepressant-like effect on rats (Martin et al, 1990), which current pharmacological therapies would suggest indicate an increase in 5-HT. The exact mechanism through which 8-OH-DPAT modulates 5-HT pathways remains unclear. The experimenters note that experimental rats' cortisol levels never exceeded the normal circadian peak. The normal basal levels of 5-HT indicate that corticosterone flattening did not affect 5-HT release from intrahippocampal terminals (as opposed to terminals in the raphe nuclei). These results provide a more detailed biological context for the findings of Young et al: taken together, these studies suggest that the effects of 5-HT_{1A} receptor agonists such as 8-OH-DPAT and busiprone are due to a modulation of 5-HT release via autoreceptor binding. The findings in this study also suggest a second mechanism, in addition to decreasing available 5-HT precursors, through which glucocorticoids modulate 5-HT pathways.

In another rodent study, Li et al investigated the interaction of 5-HT_{1A} receptor activity and glucocorticoids using mice lacking the serotonin transporter (5-HTT) gene (Li et al, 1999). 5-HTT regulates the extracellular concentration of 5-HT by recycling 5-HT in the synapse and is

the target of SSRI medications which modulate these concentrations. Control mice, knockout mice, and mice that were heterozygous for the 5-HTT gene were given 8-OH-DPAT, and body temperature and hormonal responses were measured. In control and heterozygous rats, 8-OH-DPAT produced dose-dependent hypothermia and increased concentrations of oxytocin and corticosterone. In knockout mice, however, no hypothermic or corticosterone response was observed, while oxytocin responses were not significantly different. These results indicate that a lack of 5-HTT is associated with the desensitization of 5-HT_{1A} receptors, a fact which offers a possible explanation for the interaction of pathological corticosterone patterns and 5-HT observed in the last study. While Leitch et al's experimental mice exhibited a smaller decrease of 5-HT release in response to 8-OH-DPAT, it is possible that the disturbed glucocorticoid rhythms disrupted the activity of 5-HTT and that this accounts for the higher 5-HT levels observed.

ACTH levels in heterozygous and in knockout mice was increased in response to 8-OH-DPAT, a result which seems inconsistent with the variation in corticosterone levels. The authors suggest two possibilities for the discrepancy between ACTH and corticosterone levels. First, it is possible that adrenal sensitivity to ACTH was influenced by the lack of 5-HTT receptors, given the presence of 5-HTT binding sites that previous studies have shown to be present in the adrenal gland. An absence of or decrease in 5-HTT could, then, prevent ACTH from stimulating corticosterone release. Another possibility lies in the effects of a decrease in 5-HTT on fearful behavior: administration of 8-OH-DPAT necessitated handling of rats, and the ACTH response may have been higher if rats without 5-HTT have a tendency towards fearful behavior. Indeed, if 5-HTT irregularities are implicated in human affective disorders, this fearful behavior hypothesis could explain the higher stress responsiveness in depressed patients.

Genetic Conditions Mediating Interactions

The role of the 5-HTT gene in interactions between 5-HT and the HPA axis was investigated in humans by Gotlib et al in a 2008 study of a polymorphism in the gene which codes for 5-HTT (5-HTTLPR). The genetic polymorphism observed in 5-HTTLPR comprises a long (*l*) and a short (*s*) allele and affects transcription rates of 5-HTT, with the *s* allele causing decreased transcription. Previous studies have shown that subjects who have at least one copy of the *s* allele exhibit higher rates of affective disorders as a function of increasing stressful life events than *l*-homozygous individuals.

This experiment compared the family history of depression and the genetic polymorphisms of 9- to 14-year-old girls to their cortisol responses to a stressful interview situation. Results were controlled for a number of confounding factors which might influence the stress reactivity of these subjects, including mothers' marital status, age, scores on a verbal intelligence test, and a questionnaire to assess depressive tendencies. With these controls in place, subjects who were homozygous for the *s* allele exhibited higher cortisol levels during and after the stressful interview. In contrast to previous findings, homozygous subjects were not more stress-reactive than *l*-homozygous individuals; the authors speculate this may be a result of an insufficiently stressful interview paradigm. Contrary to expectation, no significant correlation was found between genotype and risk for depression based on family history; experimenters thus combined groups defined by risk for depression in analysis of genotype and cortisol correlations.

The higher stress-reactivity of *s*-homozygous individuals suggests a mechanism through which stressful life events increase the risk of depression, a well-known correlation. This result

also suggests a similarity in the pathologies exhibited by these human subjects and the mice examined by Li et al. In the mice, an unexpectedly higher ACTH response was explained as a possibly heightened stress reaction somehow engendered by the lack of 5-HTT. In humans, decreased presence of 5-HTT is again shown to increase hormonal responses to stress, though here only cortisol levels were measured. While the exact mechanism through which 5-HTT influences HPA activity and stress reaction remains unclear, there is clear evidence of an interaction.

A few significant trends emerge from this body of literature. There is clear evidence for reciprocal modulations of 5-HT and HPA systems, and there are clear trends toward 5-HT sensitization in depressed patients. This sensitization was shared by healthy subjects--both human and rodent--with glucocorticoid or genetic similarities to disordered individuals. The evidence also suggests a sensitization of stress response as a result of 5-HT pathology in both humans and rodents. While some specific chemical mechanisms remain unclear, the increasing depth of experimental investigations and the increasing efficacy of the treatments they inform suggest continued clinical advancement in spite of this incomplete understanding.

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Figures

Fig. 1

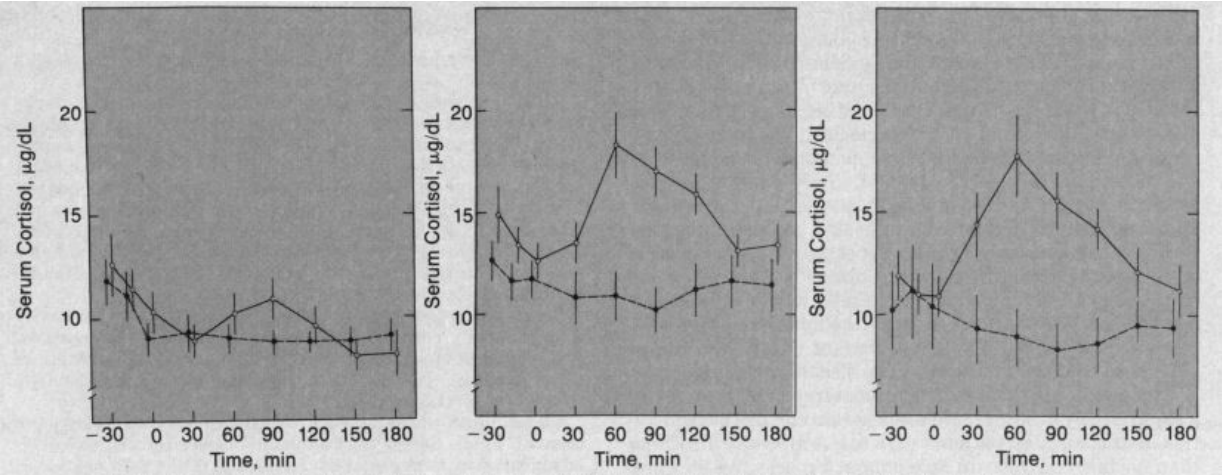

Fig 1.—Effect of placebo (black circles) or 5-hydroxytryptophan (white circles), 200 mg orally, in normal controls (left), depressed patients (center), and manic patients (right). Each point represents mean ± SE.

Fig. 2

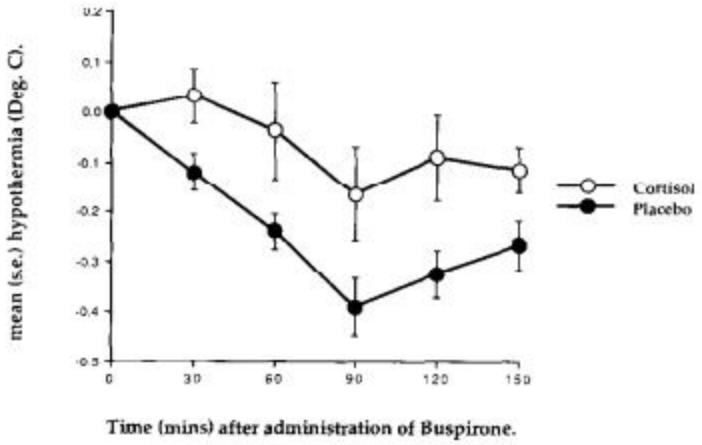

Fig. 1. Mean hypothermic response (change from baseline) to Buspirone (0.5 mg/kg, orally) following 7 day treatment with hydrocortisone (20 mg) or placebo twice daily. The hypothermic response is significantly attenuated on the occasion following hydrocortisone when analysed by two-way, repeated measures ANOVA ($P < 0.05$, see text) and by comparison of the AUC ($P < 0.05$, Wilcoxon signed rank test).