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REVIEW

Richard J. Porter · Peter Gallagher · Stuart Watson · Allan H. Young

Corticosteroid-serotonin interactions in depression: a review of the human evidence

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Abstract *Rationale:* It has been suggested that corticosteroid-serotonin interactions are central to the pathophysiology of depression. These interactions have been investigated in healthy and depressed humans, primarily using neuroendocrine techniques. *Objectives:* To review the evidence regarding the nature of these interactions in healthy and depressed humans. *Methods:* Electronic searches were performed for relevant papers, employing MEDLINE and Web of Science. To focus the review, we selected only those articles involving (i) assessment of serotonergic function following experimental manipulation of the HPA axis in healthy volunteers; and (ii) assessment of both serotonergic and HPA axis function in clinically depressed subjects. *Results:* Pretreatment with hydrocortisone, both acutely and subacutely attenuates the GH response to GHRH in healthy subjects. This complicates the interpretation of 5-HT neuroendocrine studies employing GH output as a measure. In depression there is evidence that reduced availability of L-tryptophan impairs HPA axis feedback. There is also evidence that depressed and healthy subjects may adapt differently both to low tryptophan and hypercortisolaemic challenges. There is no consistent evidence of a simple relationship between HPA axis function and 5-HT function in depression. *Conclusions:* The putative reduction in central 5-HT function has not been shown to be a direct consequence of hypercortisolaemia. Rather, the 5-HT system and HPA axis have complex inter-relationships. Challenges to either system, such as stress or reduced dietary tryptophan, may perturb the other and subjects vulnerable to depression may fail to adapt to such challenges.

Keywords Serotonin · Corticosteroids · Depression · Drug interactions

R. J. Porter (✉)
Department of Psychological Medicine, Christchurch School of Medicine,
Christchurch, New Zealand
e-mail: richard.porter@chmeds.ac.nz
Tel.: +64-33720400
Fax: +64-3-3720407

P. Gallagher · S. Watson · A. H. Young
Stanley Research Centre, School of Neurology, Neurobiology and Psychiatry, University of Newcastle, Royal Victoria Infirmary,
Newcastle upon Tyne, NE1 4LP, UK

Introduction

Hypothalamic pituitary adrenal (HPA) axis abnormalities are well established in major depression (Steckler et al. 1999). Abnormalities of the serotonin (5-HT) system also appear to be important although evidence is less consistent (Cowen 1996). The most consistent neuroendocrine evidence in depression suggests a reduction in 5-HT_{1A} receptor function (Lesch et al. 1990; Power and Cowen 1992; Meltzer and Maes 1995; Riedel et al. 2002a; Shapira et al. 2000) and number (Drevets et al. 1999; Sargent et al. 2000). It has also been suggested that 5-HT_2 function is increased in depression. Studies investigating platelet 5-HT_2 binding suggest an upregulation of 5-HT_2 receptors as do some studies using putative 5-HT_2 challenge strategies (5-HTP, m-CPP) (Koyama and Meltzer 1986; Maes et al. 1987a; Riedel et al. 2002a). However, there are also negative studies (Heninger et al. 1990; Kahn et al. 1990).

It has been postulated, on the basis of this and extensive animal evidence (Chaouloff 1993, 2000), that the abnormalities of these two systems are linked and that this link is an important aetiological mechanism in depression (Dinan 1994; McAllister-Williams et al. 1998). In particular, it has been suggested that hypercortisolaemia reduces 5-HT_{1A} receptor function (McAllister-Williams et al. 1998) and increases 5-HT_2 receptor function or numbers (Maes and Meltzer 1995). Both of these changes may then act to dysregulate HPA axis function further. This article reviews the human evidence for interactions between corticosteroids and the 5-HT system, both in healthy volunteers and in subjects with major depression.

Search strategy

Electronic database searches were carried out for relevant papers, utilising MEDLINE and Web of Science. In the initial search, the terms: "serotonin" or "5-HT" and "HPA axis", "cortisol", "ACTH", "corticotropin" or "CRH" were used. To enable the inclusion of more recent articles, ScienceDirect was also searched using these keywords in the "abstract, title, keywords" field. To focus the review, we selected only those articles involving (i) assessment of serotonergic function following experimental manipulation of the HPA axis in healthy volunteers; and (ii) assessment of both serotonergic and HPA axis function in clinically depressed subjects. All were limited to English language publications and human subjects.

Methodologies

Two methods have commonly been used to investigate the relationship between HPA axis function and 5-HT function in humans, and in particular in depression. The first is to manipulate HPA axis or 5-HT function and observe the effects on the other system. The advantage of this is that if other factors are well controlled, causality can be attributed to the manipulation. However, neither the manipulation used nor the response to it may accurately reflect the situation in depression. The second method is to measure HPA axis function and 5-HT function and to examine correlations between the two in depressed patients. This method does not prove causality, but has the advantage of investigating the actual situation in depressed subjects.

Measurement of baseline HPA axis function

The methods used to examine 5-HT function are complex and discussed in the relevant sections. The method of measurement of HPA axis function also influences results. While it is beyond the scope of this review to examine in detail the validity of these methods, some preliminary points are as follows.

Two distinct methods have been used to investigate HPA axis function in depression: (a) measurement of hormonal output and (b) measurement of feedback. Measures of cortisol output estimate the amount of cortisol to which 5-HT targets are exposed and, if repeated measures are made, the circadian pattern of this exposure. Measures of feedback estimate the function of glucocorticoid receptors, which may modulate 5-HT function. This may correlate with cortisol output. The commonly used measures of HPA axis feedback are the dexamethasone suppression test (DST) and combined dexamethasone/corticotrophin releasing hormone test (dex/CRH) (Heuser et al. 1994). The latter has not been used to investigate the relationship between the HPA axis and 5-HT system.

There is debate about the best measure of HPA axis function and in large clinical populations it is rarely possible to use more than one measure. Rubin et al. (1987) investigated the correlations between 24-h urinary cortisol before and after dexamethasone, and serum cortisol levels taken at various points both before and after dexamethasone administration. The study clearly demonstrated that average 24-h serum cortisol concentration correlated well with mean post-dexamethasone cortisol measures. The correlations among measures worsened as the measure taken became further removed from the average 24-h serum cortisol concentration, i.e. if a smaller segment of the 24-h serum profile was taken. The measure that correlated least well with results was a single plasma cortisol measure. Repeated basal cortisol measures therefore correlate with DST output and allow examination of diurnal rhythm. Twenty-four hour urinary free cortisol (UFC) does not measure diurnal rhythm and in the study of Rubin et al. (1987) did not correlate well with average 24-h serum cortisol. Saliva sampling, which was used in a number of the studies reviewed below allows repeated measurements of steroid hormones from large numbers of subjects and yields data on diurnal variation of secretion of these hormones. It is particularly useful when subjects are ambulant. Salivary levels of cortisol correlate well with serum levels and these correlate well with CSF levels (Guazzo et al. 1996). Only unbound cortisol is able to pass into the saliva and cross the blood-brain barrier. It has therefore been suggested that salivary cortisol is a better measure of brain exposure to cortisol than plasma cortisol (Vining et al. 1983).

Experimental manipulations of the HPA axis

Studies have investigated reduction of cortisol levels by administration of steroid synthesis inhibitors such as metyrapone or ketoconazole (which inhibit 11 β-hydroxylase, preventing the conversion of 11-deoxycortisol to cortisol). This has the disadvantage that these treatments interfere with other aspects of steroid hormone synthesis and cause accumulation of 11-deoxycortisol, which itself is psychoactive. In addition, producing hypocortisolaemia does not necessarily have the opposite effect to the hypercortisolaemia seen in depression.

More commonly, corticosteroids have been administered in an effort to mimic aspects of the hypercortisolaemia seen in depression. Most frequently used have been dexamethasone, a potent glucocorticoid receptor (GR) agonist, and hydrocortisone, which is essentially indistinguishable from cortisol (the corticosteroid present in highest concentrations in humans), which has high affinity for mineralocorticoid receptors (MRs) and considerably less affinity for GRs (Reul et al. 1990). These differences in receptor binding profile are important for their effects on 5-HT function, as is the marked difference in their ability to penetrate the brain. Dexamethasone is actively pumped out of the brain across the blood-brain barrier by the mdr1a p-glycoprotein (Meijer et al. 1998). It is difficult

therefore to predict the degree to which a particular dose of dexamethasone will enter the brain, making studies investigating pre-treatment with dexamethasone difficult to interpret.

Schedules of pre-treatment with hydrocortisone have generally involved either administration of a single dose the night before testing 5-HT function (acute) or a smaller dose taken twice a day (b.d.) for 4–10 days prior to testing (subacute). These schedules have generally been compared with pre-treatment with placebo, in a double-blind, counterbalanced design. Young et al. (1998) found, in healthy males, that a sub-chronic schedule of administration (20 mg b.d. for 10 days) elevated 24-h UFC into the range seen in depression. Newcomer et al. (1999) administered 100 mg at 7 a.m. and 60 mg at 7 p.m. to healthy males and found that 4 p.m. plasma levels were on average 700–800 nmol/l compared with 250 nmol/l in subjects treated with 25 mg at 7 a.m. and 15 mg at 7 p.m. and 120 nml/l in subjects who had taken placebo. This compares with 828–1104 nmol/l following major abdominal surgery (Chernow et al. 1987) and an average 1–4 pm plasma concentration for depressed DST non-suppressors of 310 nmol/l (Rubin et al. 1987). Equal doses morning and evening have been used in most studies on the basis of evidence that the diurnal variation in cortisol secretion is reduced in depression (Sachar et al. 1973; Deuschle et al. 1997). Recent animal work has suggested that a manipulation that does not alter corticosterone levels but does flatten circadian rhythm, does affect 5-HT_{1A} function in rats (Leitch et al. 2003). However, in healthy volunteers, twice-daily administration of hydrocortisone results in a sharp evening and morning peak of cortisol with a negative feedback induced lowering of cortisol levels in the middle of the day (Hearn et al. 2002). Therefore this schedule actually creates two peaks with an exaggerated decline in the hours following them. This manipulation therefore creates a situation that in terms of the pattern of cortisol secretion does not really mimic what is seen in depression.

We know of no studies which have followed cortisol levels through the night following acute pre-treatment with hydrocortisone and can therefore only speculate on the likely effects of the acute schedule. The half-life of hydrocortisone is approximately 90 min (Rang and Dale 1991) and Kasuya et al. (1995) demonstrated that 5 mg hydrocortisone increased levels to 55 nmol/l 30 min after administration (during the day). Extraolating from this, 100 mg would produce a peak of approximately 1100 nmol/l at 11:30 p.m. Since endogenous levels of cortisol at night are low, feedback inhibition of endogenous cortisol secretion is unlikely to have a significant impact on cortisol levels and we could therefore expect levels to decline at a rate in keeping with the biological half-life. Therefore at 4 a.m. (i.e. at 3 half lives or 4.5 h after peak) levels would have declined to be equivalent to having taken 12.5 mg hydrocortisone orally. Endgenous cortisol secretion at this time will be beginning to rise and may be restrained by the hydrocortisone present in the system. The following morning, cortisol levels appear to be significantly lower (Porter et al. 1998). Therefore, the effect of this manipulation is likely to be to increase cortisol levels dramatically at a time when they would normally have been low, during the nocturnal trough, with a compensatory reduction in the morning. Once again, it could be argued that this mimics to some extent the situation in depression, although it is likely that the concentrations reached using a dose of 100 mg (Porter et al. 1998) or even 50 mg (Bhagwagar et al. 2002a) are far higher than in most depressed patients at night. An important point is that MRs are largely occupied at all phases of the circadian cycle except at the nocturnal nadir. If they are occupied at this time (in depression or following pre-treatment with hydrocortisone), this is likely to affect their overall function since receptors which are permanently fully occupied are unlikely to function efficiently.

Other aspects of HPA axis dysregulation that may be present in people with depression or vulnerability to depression cannot be manipulated. It is possible, for instance, that the effects of increased cortisol are different in depression because of dysfunctional GRs (Holsboer et al. 1995) or MRs (although a recent study does not suggest impaired MR function in depression; Young et al. 2003). Furthermore, hydrocortisone administration in healthy volunteers is likely to inhibit CRH release, while in depressed subjects CRH release may be increased (Nemeroff 1996). CRH has important direct effects on GH release (Steiger and Holsboer 1997) and on the 5-HT system (Price et al. 1998b). Potentially, GR function could be manipulated using RU-486 and MR function using spironolactone. As far as we know the effects of such manipulations on 5-HT function have not been investigated.

Effects of corticosteroids on GH and PRL release

Studies investigating the 5-HT system have generally employed neuroendocrine techniques. Most of these measure pituitary hormone responses, primarily adrenocorticotropic hormone (ACTH), growth hormone (GH), prolactin (PRL) and (from the adrenal) cortisol, to a serotonergic probe. However, cortisol inhibits its own secretion and that of ACTH by negative feedback. There is also evidence that pituitary release of ACTH in response to CRH is reduced in depression (Gold et al. 1986) and that this correlates inversely with baseline cortisol levels (Holsboer et al. 1984). These measures are therefore unlikely to give a good indication of independent effects of HPA axis hormones on 5-HT function. HPA axis hormones may also directly affect GH and PRL release from the pituitary in a serotonin independent manner. The evidence regarding modulation of pituitary release of GH and PRL by HPA axis hormones is therefore reviewed below.

In vitro and animal studies suggest complex interactions between corticosteroids and the somatotrophic axis (see Thakore and Dinan 1994 for review). In humans,

Table 1 Studies investigating the effects of manipulation of steroid hormones on 5-HT function and L-TRP availability. HPA axis manipulations are all compared with placebo. Results are statistically significant unless stated otherwise

Subjects investigated	HPA axis manipulation	5-HT measure	Results	Notes	Reference
Healthy volunteers (16), depressed patients (50)	Dexamethasone 1 mg 9 h before assay	L-TRP, tyrosine, L-TRP/LNAA ratio, TYR/LNAA ratio	Reduction in all measures but no difference between groups	Baseline measures at different points between groups (see text)	(Maes et al. 1990a)
Depressed subjects (26)	Dexamethasone 1 mg 9 h before assay	L-TRP, tyrosine, L-TRP/LNAA ratio, TYR/LNAA ratio	Reduction in all measures but no difference between groups	–	(Maes et al. 1990b)
Healthy male volunteers (11)	Hydrocortisone 20 mg b.d. for 10 days	PRL response to D-FEN	No effect	–	(Young et al. 1998)
Healthy male volunteers (5)	Metyrapone for 24 h	PRL response to D-FEN	Increased response	–	(Dinan and Scott 1996)
Healthy male volunteers (6)	Hydrocortisone 10 mg t.i.d. for 24 h	PRL response to D-FEN	Reduced response	PRL response to TRH also attenuated	(Dinan and Scott 1996)
Healthy male volunteers (11)	Hydrocortisone 20 mg b.d. for 1 week	Hormonal and hypothermic responses to buspirone	No effect on hormonal responses. Decreased hypothermic response	Also found reduced REM sleep	(Young et al. 1994)
Unipolar depressed subjects (15), healthy controls (12)	Ketoconazole (1000 mg)	Hormonal and hypothermic responses to ipsapirone	No effect on non HPA axis responses	Altered HPA axis responses as expected	(Price et al. 1997a)
Healthy male volunteers (6)	Dexamethasone 1 mg 10 h before testing	Hormonal responses to L-TRP	Enhanced PRL response	No effect on TRP	(Traskman-Bendz et al. 1986)
Healthy male volunteers (16)	Dexamethasone 5 mg 11 h before testing	Hormonal responses to L-TRP	Reduced PRL response	No effect on TRP	(Porter et al. 1999)
Healthy male volunteers (15)	Hydrocortisone 100 mg 11 h before testing	Hormonal responses to L-TRP	Reduced GH response	No effect on TRP	(Porter et al. 1998)
Healthy male volunteers (14)	Hydrocortisone 20 mg b.d. for 1 week	Hormonal responses to L-TRP	Reduced GH response	No effect on TRP	(Porter et al. 2002a)
Healthy controls (20), recovered depressed (11)	Hydrocortisone 50 mg 10.5 h before testing	Hormonal response to L-TRP	Reduced GH response in recovered depressed (non-significant) and increased response in controls	Hydrocortisone reduced plasma TRP in both groups and post infusion TRP lower in patient group	(Bhagwagar et al. 2002a)
Healthy male volunteers (9)	Hydrocortisone 100 mg 11.5 h before testing	5-HT_{1A} binding (PET scanning)	No effect	–	(Montgomery et al. 2001)
Patients requiring steroid treatment	>7.5 mg prednisolone for 6 months	5-HT_{1A} binding (PET scanning)	No effect	1 subject had untreated Cushing's disease and not pre-treatment with prednisolone	(Montgomery et al. 2001)

naturalistic studies have shown that long-term hypercortisolaemia, as seen in Cushing's disease, is associated with reduced growth and GH levels (Wajchenberg et al. 1996). Dexamethasone has been used in a number of studies examining this effect. The time lag between administration of the corticosteroid and measurement of GH is of significance; dexamethasone has an initial stimulatory and a later inhibitory effect on GHRH induced GH release (Casanueva et al. 1988). Using pre-treatment with the physiological corticosteroid hydrocortisone, Frantz and Rabkin (1964) demonstrated a reduced GH response to insulin-induced hypoglycaemia. GHRH induced GH release is reduced in a dose dependant manner by acute pre-treatment with cortisone acetate (Giustina et al. 1990) while stimulated (insulin and arginine) GH release is enhanced in states of chronic hypocortisolaemia and reversed by corticosteroid replacement (Giustina et al. 1989). Studies using metyrapone to reduce cortisol levels in healthy volunteers have shown both an enhanced response (Dinan et al. 1994) and no significant effect (Burguera et al. 1990).

We investigated the effects of two different schedules of administration of hydrocortisone on GHRH mediated GH release (Watson et al. 2000). The GH response to GHRH was significantly reduced by pre-treatment with both the chronic (20 mg b.d. for 7 days) and acute (100 mg, 11 h before testing) schedules. Baseline levels of GH were unaffected by either schedule.

The GHRH test has been extensively investigated in depression and in other conditions (see Skare et al. 1994 for review). Studies divide roughly equally into those which show blunting, enhancement and no difference in GH response to GHRH in depressed compared with control subjects. Lesch (1989a) investigated the relationship between the GH response to GHRH and the ACTH and cortisol responses to CRH in depression. There was no correlation. Data regarding the correlation between baseline cortisol secretion and GH response was not reported. Birmaher (2000) investigated adolescents at high risk of major depressive disorder according to family history, but with no past or current history of depression. There was a significantly lower GH response to GHRH in these subjects compared with controls and no correlation between various measures of cortisol secretion and the GH response to GHRH (Birmaher et al. 2002).

Data on GH response to various 5-HT agents is reviewed below, but studies have also investigated the correlation between GH response to other agents and HPA axis measures. Dolan (1986) found a significant negative correlation between the GH response to clonidine and urinary free cortisol levels in 14 depressed patients. Matussek (1980) and Amsterdam (1990) have also found a negative correlation between basal measures of plasma or urinary cortisol and GH release in response to clonidine. Mokrani (1997) found that DST non-suppressors had a significantly lower GH response to clonidine than suppressors. Therefore, there is reasonably consistent evidence that increased cortisol secretion and/or impaired feedback reduces the GH response to clonidine. Whether this is mediated at the pituitary level or not is unclear at present.

In vitro, there is evidence that sub-chronic hydrocortisone reduces pituitary synthesis of PRL (Dannies and Tashjian 1973). In healthy humans, acute (24 h) reduction of cortisol levels by metyrapone increased the PRL response to TRH (in six healthy subjects) and the PRL response to D-fenfluramine (n=5) and enhanced the nocturnal surge of PRL secretion (Dinan and Scott 1996). Treatment for 24 h with hydrocortisone (n=6) abolished the nocturnal rise in PRL secretion and reduced the PRL response to D-fenfluramine (see Table 1). Although there was no data regarding the effects of hydrocortisone on PRL response to TRH the authors interpreted the latter finding as likely to be secondary to direct suppression at the pituitary.

Dexamethasone has been shown to blunt the PRL response to TRH (Sowers et al. 1977). In Cushing's disease, PRL secretory dynamics are altered but there is no difference in the PRL response to TRH (Caufriez et al. 1981). Furthermore, pre-treatment with a chronic schedule of hydrocortisone (see Table 1) had no effect on the PRL response to TRH in healhy volunteers (Porter et al. 2002a).

Two studies have investigated both the PRL response to TRH and the PRL response to a 5-HT challenge in depression (Golden et al. 1990; Anderson et al. 1992). Both showed reduced PRL response to clomipramine but no difference in PRL response to TRH, in depressed subjects compared with healthy controls. In the study of Golden et al. (1990), the two challenges were carried out in the same group of patients. The data suggest that the response to TRH is unimpaired in depression therefore the blunting of PRL responses to 5-HT challenges are not mediated by dysfunction in PRL production or release from lactotrophs.

Serotonergic control of HPA axis function

Serotonin precursors

In humans, the 5-HT precursors 5-HTP and L-TRP stimulate ACTH and cortisol release, as does the 5-HT releasing agent fenfluramine and the 5-HT_{1A} agonists ipsapirone and buspirone (Fuller 1992). However, this does not mean that serotonergic activation is physiologically necessary for cortisol secretion, either basally or during stress.

Human studies have investigated the effects of manipulation of the 5-HT system on HPA axis feedback. Maes et al. (1991a) demonstrated that in DSM-III "major depressives" but not "minor depressives" 5-HTP either augmented existing dexamethasone non-suppression or caused escape from suppression in previous non-suppressors. In a further study, this was confirmed (Maes et al. 1995), with the further finding that 5-HTP stimulated escape from suppression not only of cortisol but also of ACTH. The authors suggest that upregulation of 5-HT_2 receptors in depression may mediate this effect. However, neuroendo-

crine challenges with large doses of 5-HTP are unphysiological and do not necessarily add evidence regarding the likely effects of more subtle fluctuations in 5-HT function. Furthermore 5-HTP may have significant catecholaminergic effects (van Praag et al. 1987).

Longer-term administration at lower doses (3.5–7 g per day for 1–2 weeks) of L-TRP in 20 depressed patients (Nuller and Ostroumova 1980) increased dexamethasone suppression of cortisol. The likely mechanism in this case is unclear. A related issue is that there is some evidence that L-TRP has antidepressant properties at least as an augmentation agent (Barker et al. 1987).

Antidepressants

In healthy volunteers and depressed subjects, acute 5-HT stimulation by various antidepressants, as with 5-HT precursors (see above), leads to an acute stimulation of ACTH and cortisol release (Laakmann 1990; Bhagwagar et al. 2002b).

Studies of both serotonergic and noradrenergic antidepressants suggest that successful treatment normalises the DST, dex/CRH and other measures of HPA axis function in depressed subjects (Greden et al. 1983; Holsboer-Trachsler et al. 1991; Inder et al. 2001). It has been suggested that this is central to their antidepressant activity (Barden et al. 1995; Holsboer and Barden 1996), something that is supported by studies suggesting that relapse is likely if HPA axis activity is not normalised (Zobel et al. 2001). Whether they do this primarily by acting on the 5-HT system or by a common activity on a cellular level is unclear (Duman et al. 1997).

Whether antidepressants with 5-HT activity affect HPA axis function in healthy subjects is not as clear although there is abundant evidence that they do this in animals (Holsboer and Barden 1996). Heuser et al. (1996) found no effect of amitriptyline on basal cortisol/ACTH or the dex/CRH test in healthy elderly subjects and Kathol et al. (1991) failed to find an effect of imipramine on HPA axis responses to insulin induced hypoglycaemia after 10 days (n=6). In contrast, Michelson et al. (1997) found that while 6 weeks treatment with imipramine did not affect basal hormones, responses to ovine CRH and arginine vasopressin (AVP) were reduced in healthy volunteers (n=14). A recent study investigated activated HPA axis function by measuring the increase in salivary cortisol that occurs in the hour following waking. While neither reboxetine nor citalopram influenced basal salivary cortisol in healthy volunteers, 6 days of treatment with citalopram significantly enhanced the increase in cortisol produced by waking while reboxetine had no effect. This argues against the hypothesis that the effect of all antidepressants is mediated via the HPA axis, suggesting that this is selective to serotonergic antidepressants (Harmer et al. 2003).

Acute tryptophan depletion

Studies using the technique of acute tryptophan depletion (ATD) have investigated the effects of reduced 5-HT transmission on HPA axis function. ATD induced an increase in cortisol levels in patients with seasonal affective disorder, which was associated with depressive relapse (Hesselmann et al. 1997). In currently depressed patients, ATD induced no change in cortisol levels (Price et al. 1997b, 1998a). Porter et al. (2002b) investigated the effects of ATD on salivary and plasma cortisol in patients with Alzheimer's disease and healthy elderly subjects. This study also used a battery of cognitive tests that gave rise to a small rise in cortisol levels presumably secondary to the stress of testing. However, there was no effect of ATD on cortisol at any point. Miller et al. (2000) investigated the effects of ATD on cortisol in patients with panic disorder and healthy controls and found no effect of ATD on cortisol even when patients had panic attacks induced by CO_2 inhalation. This procedure, however, did not raise cortisol. Sobczak et al. (2002) investigated the effects of ATD on stress induced cortisol release in 1st degree relatives of patients both with bipolar I and bipolar II disorder and in healthy volunteers. The stressor was a stress inducing speech task, which induced a robust increase in cortisol greater than that seen in the study of Porter et al. (2002b). This was attenuated by ATD in the subjects with a family history but not in control subjects. However, a report of a larger number of control subjects did suggest a reduction of stress induced cortisol secretion by ATD (Riedel et al. 2002b).

Thus stress induced cortisol release may be dependent on 5-HT transmission in humans as in animals (Joseph and Kennett 1983). This may be exaggerated by 5-HT vulnerability in subjects suffering from or with a family history of affective disorder.

Summary of effects of the 5-HT system on HPA axis function

There is some evidence that reduced L-TRP availability impairs the cortisol response to stress. This may be exaggerated in subjects with an underlying vulnerability to affective disorder. Basal secretion of cortisol appears unaffected by ATD in healthy subjects and patient groups including currently depressed subjects. No studies have specifically investigated the effects of experimental reduction of 5-HT function on HPA axis feedback rather than output. Antidepressants and administration of L-TRP may normalise HPA axis feedback in depressed subjects. Whether this is by a direct 5-HT effect is unknown.

HPA axis effects on 5-HT function

Studies using experimental HPA axis manipulations

Tryptophan availability

The synthesis of 5-HT is directly dependent on the amount of L-TRP in the brain. In animals, the main metabolising enzyme of L-TRP, TRP 2,3-dioxygenase is induced by hydrocortisone (Badawy et al. 1995). This may mediate a reduction in L-TRP availability in response to hypercortisolaemia. There is no direct evidence regarding the effects of steroids on TRP 2,3-dioxygenase in man. Central L-TRP availability is mediated by entry of L-TRP into the brain which occurs via a transport mechanism in competition with five other large neutral amino acids (LNAAs) (Wurtman 1982). Glucocorticoid treatment induces hepatic and brain tyrosine aminotransferase which is the major tyrosine degrading enzyme (Hirota et al. 1985) therefore tyrosine levels may also be altered by changes in glucocorticoid levels. Tyrosine is one of the competing LNAAs and is important in the synthesis of noradrenaline and dopamine; therefore, it is useful to measure the ratio and not only L-TRP levels.

Maes (1990a) examined TRP and TYR availability after administration of 1 mg dexamethasone to patients with major depression (n=50) and controls (n=16). TRP and TYR were measured at 8:00 a.m. after administration of the dexamethasone the night before. In healthy controls, baseline amino acid levels were measured before dexamethasone testing while in depressed subjects they were measured 3 days later when residual effects on HPA axis regulation were possible. Patients with melancholia and/or psychotic features had significantly lower baseline values of L-TRP and L-TRP/LNAA compared with controls and other depressed subjects. Dexamethasone significantly reduced L-TRP and TRP/LNAA ratio and TYR and TYR/LNAA ratio. However, there was no group by treatment interaction, i.e. no differential effect in any group. In a further study, in 26 depressed patients, administration of dexamethasone also reduced availability of both TRP and TYR (Maes 1990b) (see Table 1). In contrast, two studies (Traskman-Bendz et al. 1986; Porter et al. 1999) showed no effect of dexamethasone on L-TRP levels in healthy controls. However, these studies were smaller and did not measure other LNAA levels. One study (Bhagwagar et al. 2002a) suggests an effect of administration of hydrocortisone on L-TRP levels both in healthy controls and recovered depressed subjects but our own studies do not (Porter et al. 1998, 2002a).

Responses to D-fenfluramine

D-Fenfluramine (D-FEN) causes acute release of 5-HT from presynaptic terminals and also blocks 5-HT reuptake into presynaptic terminals (Newman et al. 1998). There is further evidence that the PRL response to fenfluramine reflects release of a "functional" pool of newly synthesised 5-HT (Coccaro et al. 1998). The PRL response to D-FEN is seen as an indicator of the responsiveness of postsynaptic 5-$HT_{2A/2C}$ subtype receptors (Goodall et al. 1993; Coccaro et al. 1996a, 1996b) and of the general integrity of the 5-HT system. Challenge with the racemic mixture DL-fenfluramine may be contaminated by significant catecholaminergic effects (Smythe and Mitchell 1992) because L-fenfluramine releases dopamine and noradrenalin (Invernizzi et al. 1986).

Young et al. (1998) found no attenuation in D-fenfluramine induced PRL release following hydrocortisone pre-treatment for 10 days (20 mg b.d.) compared with placebo. In contrast, following acute pre-treatment with hydrocortisone (10 mg t.i.d. over 24 h), Dinan (1996) found the PRL response to be attenuated, while pre-treatment with metyrapone enhanced the response. However, metyrapone also enhanced the response to TRH, suggesting a direct effect at the pituitary level (see above).

Response to buspirone

Buspirone is a direct 5-HT_{1A} receptor agonist, administration of which gives rise to a hypothermic response and GH and PRL responses. There is debate regarding whether pre or postsynaptic 5-HT_{1A} receptors mediate the hypothermic response to buspirone. 5-HT_{1A} mediated hypothermia is generally thought to be mediated by presynaptic receptors in animals. However, in humans, the technique of acute tryptophan depletion does not attenuate the hypothermic response (Blier et al. 2002), suggesting a direct post-synaptic action. Other problems in interpretation of neuroendocrine responses to buspirone are that it also acts as a dopamine-D_2 receptor antagonist (Gregory et al. 1990; Meltzer et al. 1992), has a pharmacologically active metabolite 1-pyrimidinylpiperazine (1-PP) (Mahmood and Sahajwalla 1999), and may have 5-HT_{1A} partial agonist properties. Furthermore, the neuroendocrine findings in depressed patients with this drug have been inconsistent (Power and Cowen 1992).

Young (1994) investigated the effects on responses to buspirone of treatment with hydrocortisone, 20 mg twice a day for 1 week, in 11 healthy volunteers. There was no blunting of GH or PRL responses following hydrocortisone compared with placebo. However, there was blunting of the hypothermic response. A possible explanation is that hormonal responses are mediated by post-synaptic 5-HT_{1A} receptors while hypothermia is mediated by presynaptic receptors and that the function of these is attenuated by sub-acute hydrocortisone. As discussed above, the origin of the hypothermic response is still unclear.

Responses to ipsapirone

Ipsapirone is a partial 5-HT_{1A} agonist. It appears to have negligible affinity for the 5-HT_{1D}, 5-HT_2 or 5-HT_3 subtypes (Peroutka 1988). At doses of 0.3 mg/kg it

induces a hypothermic response that is blocked by pindolol (a 5-HT_{1A} antagonist and β-adreno receptor antagonist). There is also an ACTH, cortisol and GH response in normal human subjects but not a reliable PRL response (Lesch et al. 1989b). The origin of the hypothermic response (whether pre- or post-synaptic) is not entirely clear.

Price et al. (1997a) investigated the effects of administration of the cortisol synthesis-inhibitor, ketoconazole (1000 mg over 24 h prior to neuroendocrine testing with ipsapirone, in a double-blind, placebo controlled study) to healthy controls and depressed subjects. In neither group were the non-HPA responses enhanced. As expected, the cortisol response was inhibited while the ACTH response was enhanced (presumably a result of reduced negative feedback).

Responses to L-TRP

In humans, intravenous infusion of 7 g L-TRP over 20 min causes a robust increase in GH and PRL (Charney and Heninger 1982). The GH response has been shown to be particularly sensitive to blockade by the 5-HT_{1A} antagonist, pindolol (Smith et al. 1991) and hence is likely to be mediated by the 5-HT_{1A} receptor. The PRL response is less blunted by pindolol, suggesting an additional component. It is, however, abolished by metergoline (McCance et al. 1987). This may suggest that a receptor other than the 5-HT_{1A} receptor plays a role in the response. Since L-TRP competes with tyrosine for transport across the blood-brain barrier (Wurtman 1982) infusion may reduce dopamine synthesis by reducing brain tyrosine. Evidence suggests that loading with LNAAs other than tyrosine selectively reduces dopamine rather than noradrenalin function (McTavish et al. 2001). That this occurs during IV infusion of L-TRP is supported by evidence that an infusion of 5 g L-TRP causes a reduction in post-probenecid cerebrospinal fluid (CSF) concentrations of the dopamine metabolite homovanillic acid (HVA) (van Praag et al. 1987). The PRL response to L-TRP may therefore be mediated, in part, by a reduction in dopamine synthesis, which releases PRL secretion from tonic inhibition by dopamine.

In healthy volunteers, pre-treatment 10 h before infusion with dexamethasone (1 mg) compared with placebo, resulted in a significantly greater PRL response, but no effect on GH response (Traskman-Bendz et al. 1986). In contrast, 5 mg dexamethasone in healthy volunteers (11 h before infusion) reduced the PRL response even when an increased baseline PRL was taken into account (Porter et al. 1999). The degree of entry of dexamethasone into the brain at different doses is not known. A possible interpretation of the difference in these studies is that 5 mg is sufficient to enter the brain and bind to GRs to a significant extent, while 1 mg is not.

We found a reduction in GH but not PRL response to L-TRP in healthy volunteers following pre-treatment with hydrocortisone (100 mg) 11 h before infusion (Porter et al. 1998). A similar result was found with the sub-chronic schedule (20 mg b.d. for 1 week) (Porter et al. 2002a). Both can be interpreted as an effect at the pituitary level, given the finding of a similar effect of the same pre-treatments on GHRH mediated GH release (Watson et al. 2000).

Bhagwagar (2002a) used a similar acute pre-treatment schedule to investigate subjects who had recovered from depression and had a history of at least two episodes, compared with healthy controls. Hydrocortisone (50 mg orally) compared with placebo 10.5 h before IV L-TRP, reduced GH release in the recovered depressives, but not significantly, and significantly increased GH release in controls.

There was a reduction of peripheral tryptophan in both groups following treatment with hydrocortisone. Plasma TRP after infusion was significantly lower in the depressed patients than the control subjects. This is surprising given the very large and equal amounts of IV L-TRP given to both groups. Baseline measures of cortisol were taken only immediately prior to the infusion and there were no differences between groups following either placebo or hydrocortisone. A possible interpretation of the findings of the increased GH responses after pre-treatment with hydrocortisone in controls but not recovered depressives is that healthy control subjects were able to up-regulate 5-HT_{1A} function in response to hydrocortisone, while recovered depressed subjects were unable to mount such a response. It could also be that the results reflect a failure of adaptation of pituitary mediated GH release in response to hydrocortisone pre-treatment in depressed subjects. A further interpretation is that the treatment altered cortisol rhythms in a different way in recovered depressed subjects compared with control subjects and that this is the origin of the difference in response to L-TRP rather than there being a different adaptive response to an equal change in cortisol levels.

5-HT_{1A} receptor binding

Animal studies suggest that both function and numbers of post synaptic 5-HT_{1A} receptors are affected by alterations in HPA axis function. For example, postsynaptic 5-HT_{1A} receptor binding is increased following adrenalectomy, an effect that is reversed by administration of corticosterone (de Kloet et al. 1986; Martire et al. 1989; Mendelson and McEwen 1992a; Kuroda et al. 1994). Chronic administration of corticosterone causes a reduction in the expression of post-synaptic 5-HT_{1A} receptor mRNA (Meijer and de Kloet 1994) and binding to 5-HT_{1A} receptors (Mendelson and McEwen 1992b).

In humans, Montgomery et al. (2001), using PET scanning techniques, showed no reduction in 5-HT_{1A} binding following pre-treatment with hydrocortisone (100 mg taken 11.5 h before testing) compared with placebo (the study was specifically designed to be analogous to Porter et al. 1998). In addition, a small group of patients on chronic prednisone therapy and a

single patient with Cushing's disease were tested and found to have no difference in 5-HT_{1A} binding compared with age matched controls.

EEG measures of 5-HT function

McAllister-Williams and Massey have demonstrated that buspirone and pindolol administration to healthy subjects engenders a shift in the EEG frequency spectrum and suggest that this may reflect somatodendritic 5-HT_{1A} receptor function (McAllister-Williams and Massey 2003). This group has recently demonstrated that this effect is significantly attenuated by pre-treatment with a sub-acute schedule of hydrocortisone for 7 days (Fairchild et al. 2003).

Studies in depression correlating HPA axis measures with 5-HT function

Tryptophan availability

In three separate studies, Maes et al. (1987b, 1988, 1990c) investigated the relationship between post-dexamethasone cortisol and TRP/LNAA ratio in depression. Cortisol responses to dexamethasone were significantly and negatively associated with availability of L-TRP in all three studies (Table 2). However, in Maes et al. (1990c) there was no correlation between TRP/LNAA ratio and basal plasma cortisol (8:00 a.m.) and three further studies have failed to find a correlation between TRP/LNAA ratio and measures of basal cortisol output. Maes et al. (1990b), in a relatively small study (26 patients), found no correlation with 24-h urinary cortisol and Mulder et al. (2003) in 100 depressed subjects found no correlation between baseline plasma cortisol (average of three morning measures) and TRP/LNAA ratio (data regarding this correlation not reported in the original report: but see Table 2). Strickland et al. (2002) found no correlation between salivary cortisol throughout the day and L-TRP availability in depressed and healthy women (P. Strickland, personal communication). In a group of carers of patients with dementia, Da Roza Davis and Cowen (2001) did demonstrate raised cortisol secretion as measured by midday and 10:00 p.m. salivary cortisol and reduced total plasma tryptophan but there was no correlation between the two measures. Several other studies have measured tryptophan levels or availability and HPA axis function in depression but not reported on correlations between the two that may therefore be lacking (Cowen and Charig 1987; Price et al. 1991).

In summary, there appears to be a degree of consistency of a finding of a negative correlation between HPA axis activity and L-TRP availability when measures of HPA axis feedback rather than cortisol output are used. A possible interpretation of this is that rather than high cortisol levels reducing L-TRP availability, low L-TRP availability leads to impaired glucocorticoid mediated inhibitory feedback on the HPA axis and therefore resistance to dexamethasone suppression. Based on animal evidence (Budziszewska et al. 1995), it has been suggested that reduced activation of 5-HT_{1A} receptors in the hippocampus may be responsible for impaired feedback at this level which in turn leads to activation of the HPA axis (McAllister-Williams et al. 1998).

Response to 5-HTP

Evidence suggests that the PRL response to 5-HTP is mediated by 5-HT_{1A} receptors, while the cortisol response is not (Meltzer and Maes 1994). Interpretation of responses to 5-HTP may be complicated by a lack of 5-HT specificity. 5-HT is taken up by catecholaminergic as well as 5-HT neurones (Fuxe et al. 1971) and may thus release dopamine and noradrenalin by displacement. There is evidence that at the doses used in challenge tests there are significant catecholaminergic effects in humans (van Praag et al. 1987).

Maes (1990c), in 64 depressed females, showed that the cortisol response to 5-HTP was not related to L-TRP availability or to post-dexamethasone cortisol. They do not report on the relationship with the PRL response. Meltzer et al. (1984) also failed to find a relationship between cortisol response to 5-HTP and post-dexamethasone cortisol in depressed patients. However, there was a significant negative correlation between baseline cortisol and cortisol response to 5-HTP in healthy controls. The degree to which the cortisol response depends on the feedback status of the HPA axis rather than effects of cortisol on 5-HT function is not clear.

Responses to D-fenfluramine

Mitchell and Smythe (1990) found a negative correlation between the PRL response to DL-fenfluramine and baseline cortisol (average of three measures 9–10 a.m.). This correlation was found in a combined group of 27 depressed patients and 14 healthy controls (presumably there was no interaction between diagnostic group and baseline cortisol in the ANCOVA, although this is not explicitly stated), but this was only significant when one outlying depressed patient was excluded. Rajewska et al. (2003) found an inverse relationship between the PRL and cortisol responses to D-fenfluramine and baseline cortisol in a combined group of post-menopausal depressed women (n=60) and controls (n=30).

In contrast, Park et al. (1996) found no correlation between baseline cortisol and PRL or cortisol response to D-fenfluramine in either 31 depressed or 29 control subjects and Duval et al. found no correlation between hormonal responses to D-fenfluramine and cortisol levels (basal or post-DST) in 71 drug-free depressed and 34 hospitalised healthy control subjects (Duval et al. 2001). Maes et al. (1991b) found no relationship between 8:00 a.m. post-dexamethasone cortisol and responses to D-

Table 2 Studies involving correlation of HPA axis measures with 5-HT function measures

Subject investigated	HPA axis measure	Output measure	Results	Notes	Reference
Depressed subjects (26)	24-h UFC	L-TRP, tyrosine, L-TRP/LNAA ratio, TYR/LNAA ratio	No correlation between UFC and output measures	–	(Maes et al. 1990b)
Depressed subjects (140)	Post-dexamethasone cortisol	L-TRP and TRP/LNAA ratio	Negative correlation between cortisol and both tryptophan measures	–	(Maes et al. 1987b)
Depressed inpatients (51)	Post-dexamethasone cortisol	L-TRP and TRP/LNAA ratio	Negative correlation between cortisol and both tryptophan measures	–	(Maes et al. 1988)
Depressed females (64)	Post-dexamethasone cortisol	TRP/LNAA ratio	Negative correlation between cortisol and TRP/LNAA	–	(Maes et al. 1990c)
Depressed females (64)	Basal cortisol (8 am)	TRP/LNAA ratio	No correlation	–	(Maes et al. 1990c)
Depressed subjects (100)	Plasma cortisol—average of 3 measures between 9 and 10 a.m.	TRP/LNAA ratio	No correlation (r=−0.094, P=0.352)	Data not included in original report	(Mulder et al. 2003)
Full time carers of patients with dementia (30), age and gender matched controls (28)	Midday and 10 p.m. salivary cortisol	Total plasma tryptophan	No correlation between TRP and mid day cortisol	Cortisol was increased and TRP decreased in carers compared with controls	(Da Roza Davis and Cowen 2001)
Depressed females (64)	Post-dexamethasone cortisol	Cortisol response to 5-HTP	No correlation between cortisol response to 5-HTP and cortisol	No data on the prolactin response reported	(Maes et al. 1990c)
Depressed patients (44)	Post-dexamethasone cortisol	Cortisol response to 5-HTP	No relationship between the two	–	(Meltzer et al. 1984)
Healthy controls (24)	Single baseline cortisol	Cortisol response to 5-HTP	Significant negative correlation between the two measure	–	(Meltzer et al. 1984)
Depressed patients (27), healthy controls (14)	Baseline plasma cortisol (3 measures 9–10 a.m.)	PRL response to dL- FEN	Negative correlation	Correlation reported only in combined group	(Mitchell and Smythe 1990)
Depressed patients (31), healthy controls (29)	Baseline plasma cortisol (3 measures 9–10 a.m.)	PRL and cortisol responses to D-FEN	No correlations	–	(Park et al. 1996)
Depressed inpatients (52)	Post-dexamethasone cortisol	PRL and cortisol responses to D-FEN	No difference in responses between suppressors and non-suppressors	–	(Mokrani et al. 1997)
Post menopausal depressed women (60), healthy controls (30)	Baseline plasma cortisol (single sample, 8 a.m.)	PRL and cortisol responses to D-FEN	Negative correlation	Correlation only in combined group	(Rajewska and Rybakowski 2003)
Depressed patients (19)	Baseline plasma cortisol (single sample, 9.15 a.m.)	PRL and cortisol responses to D-FEN	Negative correlation with cortisol but not PRL	–	(Cleare et al. 1996)
Depressed inpatients (71), hospitalised controls (34)	Baseline plasma cortisol (single sample, 9 a.m.) Post-dexamethasone cortisol	PRL and cortisol responses to D-FEN	No correlation with either measure of cortisol	–	(Duval et al. 2001)
Depressed patients (108)	Average of 3 measures between 9 and 10 a.m.–plasma cortisol	Prolactin and cortisol response to dL-FEN	Interaction between baseline cortisol and melancholia	See text for details	(Mulder et al. 2003)

Table 2 (continued)

Subject investigated	HPA axis measure	Output measure	Results	Notes	Reference
Depressed patients (20) (ICD-10 defined), Vulnerable healthy women (65), non-vulnerable healthy women (60)	Baseline plasma cortisol (average of 9:30 a.m. and 10:30 a.m.)	PRL response to D-FEN	Baseline cortisol not a significant covariate. No correlation of response with salivary cortisol measures (P. Strickland–personal communication)	–	(Strickland et al. 2002)
Depressed subjects (24), controls (13)	Baseline plasma cortisol (one measure)	Cortisol response to 5-HTP	Significant negative correlation in control subjects. Similar trend but not significant in depressed subject	–	(Koyama and Meltzer 1986)
Depressed patients (23)	Post-dexamethasone cortisol	GH and PRL response to IV L-TRP	Positive correlation between PRL response and cortisol. No correlation with GH response	–	(Cowen and Charig 1987)
Depressed patients(18), healthy controls (11)	Plasma cortisol—average of 2 measures (8.30 and 9.30am)	GH and PRL response to IV L-TRP	Negative correlation between PRL response and baseline cortisol	–	(Deakin et al. 1990)
Depressed patients (69)	Post-dexamethasone cortisol	GH and PRL response to IV L-TRP	Negative correlation between GH response and cortisol	–	(Price et al. 1991)
Depressed patients (20), Healthy controls (20)	Salivary cortisol area under the curve (8 a.m., midday, 4 p.m., 8 p.m., averaged over 3 days)	GH and PRL response to IV L-TRP	Negative correlation between salivary cortisol and PRL response	–	(Porter et al. 2003)
Healthy volunteers (50)	Baseline cortisol (single 9 a.m. measure)	PRL response to buspirone	Negative correlation between PRL response and baseline cortisol	–	(Dinan et al. 2001)
Depressed patients (21)	Post-dexamethasone cortisol	PRL, cortisol, ACTH and hypothermic responses to flesinoxan	No correlations. Significantly lower ACTH response in non-suppressors	–	(Pichot et al. 2001)
Depressed in-patients (10)	Plasma cortisol (single morning measure)	Cortisol response to ipsapirone	Negative correlation between baseline cortisol and cortisol response	–	(Shapira et al. 2000)

fenfluramine in controls, minor depressives, simple major and melancholic depressives (DSM-III; American Psychiatric Association 1980).

Mulder et al. (2003), in a study of 108 outpatients with DSM-III-R major depression, showed an interaction between baseline cortisol (three single morning measurements) and DSM-III-R melancholic sub-type of depression. Non-melancholic patients showed a positive correlation and melancholic patients a negative correlation between the PRL response to fenfluramine and basal cortisol levels. A possible interpretation of these results is that there is a difference between melancholic and non-melancholic subjects in their ability to alter sensitivity of 5-HT_{2C} receptors in response to alterations in cortisol levels. Thus, non-melancholic subjects appear to increase 5-HT_{2C} receptor function in response to high cortisol while the opposite is the case for melancholic subjects. It should be noted that this study used the less selective racemic mixture DL-fenfluramine and may be contaminated by noradrenergic effects.

A recent study by Strickland et al. (2002) demonstrated an increased response to D-fenfluramine in depressed women compared with large numbers of control women. The study employed a placebo control and co-varied for D-fenfluramine and baseline PRL levels and was therefore particularly methodologically robust. However, the depression was relatively mild, only eight of 20 women meeting DSM-IV criteria for depression (20 in total met ICD-10 criteria). The same group had a reduced average morning serum cortisol compared with non-depressed subjects. Baseline plasma cortisol was not a significant covariate in analysis of the PRL response to fenfluramine and there was no correlation between salivary cortisol levels over the preceding days and PRL response to fenfluramine (P. Strickland, personal communication).

Responses to 5-HT_{1A} receptor agonists

Pichot (2001) used neuroendocrine challenge with the specific 5-HT_{1A} receptor agonist flesinoxan, in 21 depressed in-patients. There was no relationship between cortisol, ACTH, PRL and hypothermic responses and post-dexamethasone cortisol. Although the authors go on to report a significant difference in ACTH response between DST suppressors and non-suppressors (suppressors had a significantly higher response), none of the other responses were significantly different between these groups. Shapira et al. (2000) showed an inverse correlation between cortisol response to ipsapirone and baseline plasma cortisol. Correlations with the GH or hypothermic responses are not reported. In both studies, responses could have been inhibited by negative feedback by cortisol at the pituitary level.

In 50 healthy volunteers, buspirone-induced PRL response was highly negatively correlated with a single morning measure of plasma cortisol (Dinan et al. 2001).

Responses to L-TRP

Four studies have investigated the relationship between HPA axis function and hormonal responses to IV L-TRP. Deakin et al. (1990) found that increased baseline cortisol levels were associated with reduced PRL responses, but there was no association with GH responses. Cowen and Charig (1987) found that DST non-suppressors had greater PRL responses than DST suppressors but there was no difference in GH response. Price et al. (1991) showed a negative correlation between post-dexamethasone cortisol and GH response, but no correlation with PRL response. Porter et al. (2003) found an increased PRL response to IV L-TRP in depressed patients compared with control subjects. Across both groups, there was an inverse correlation between PRL response and total salivary cortisol secretion (measured at 8:00 a.m., midday, 4:00 p.m. and 8:00 p.m. over 3 days prior to testing). Depressed subjects did not, in this study, secrete more cortisol than control subjects. Our preferred interpretation of this finding is that it reflects an effect of cortisol secretion, within a normal physiological range, on dopamine function rather than on 5-HT_{1A} function.

Summary

Both acute and sub-acute treatment with hydrocortisone reduce GHRH mediated GH release. This is therefore likely to be an important factor in alterations in GH release in response to 5-HT neuroendocrine challenge agents following treatment with hydrocortisone. This is less likely to be the case when PRL is used as a measure. It is unlikely that measuring HPA axis hormonal output (cortisol and ACTH) following 5-HT stimulation will give rise to useful data regarding the relationship between the two systems.

Effects of manipulations of corticosteroids on other responses are inconsistent, although generally there is no effect especially following sub-acute manipulations. This probably reflects the ability of healthy subjects to compensate for such manipulations. The study of Bhagwagar et al (2002a) suggests that healthy subjects may up-regulate 5-HT_{1A} receptor function in response to acute pre-treatment with hydrocortisone while subjects with a recurrent depressive illness do not. This is of interest since the study of Smith et al. (2000) suggests that subjects with previous depression are less able to up-regulate 5-HT_{1A} receptor function in response to low TRP than healthy controls. These two challenges may be linked, since studies in depressed subjects have suggested that TRP availability correlates with measures of HPA axis feedback. That this is the case while there is no good evidence of a correlation between L-TRP availability and measures of cortisol output suggests that the link may be via control of HPA axis feedback by the 5-HT system.

Apart from the relationship between L-TRP availability and HPA axis feedback noted above, studies investigating correlations between HPA axis measures and 5-HT

measures are inconsistent. This is perhaps not surprising given the inconsistent evidence regarding abnormalities of 5-HT neuroendocrine challenge tests in depression. The most consistent findings have been of reduced responses (GH and/or PRL) to IV L-TRP thought to reflect reduced 5-HT_{1A} function in depression. Much animal research has focused on corticosteroid effects on the 5-HT_{1A} receptor, which is believed to mediate these responses. However, there is no consistent evidence of a relationship between HPA axis function and these responses to IV L-TRP

One study (Mulder et al. 2003) suggests that there may be a difference in the ability of the 5-HT system to adapt to altered cortisol levels between melancholic and non-melancholic patients. Whether this reflects a distinct abnormality in melancholia or a one end of a spectrum of failure of homeostatic mechanisms in depression is not clear.

Future research

Animal studies have convincingly demonstrated bi-directional interactions between the HPA axis and the serotonin system. In humans, existing neuroimaging methods are able to examine only structural rather than functional changes and the validity of newer methods of examining brain function has not yet been proven. There are methodological difficulties inherent in examining these systems using traditional neuroendocrine methods. Data from existing neuroendocrine research needs to be considered in light of these and non-neuroendocrine models of receptor function such as EEG measures of 5-HT function (McAllister-Williams and Massey 2003) may be more suited to investigate this further. Future studies might also use more sophisticated methods of manipulating and measuring the HPA axis and 5-HT system, for instance flattening the diurnal cortisol rhythm using the model piloted in laboratory rats by Leitch et al. (2003) and using more selective serotonergic agonists. Further investigation of the effects of low L-TRP availability on HPA axis function is also likely to be useful.

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