Psychopharmacology (1998) 139 : 243–250

ORIGINAL INVESTIGATION

Richard J. Porter · R. Hamish McAllister-Williams
Brian S. Lunn · Allan H. Young

5-Hydroxytryptamine receptor function in humans is reduced by acute administration of hydrocortisone

Received: 6 October 1997/Final version: 19 February 1998

Abstract 5-Hydroxytryptamine$_{1A}$ (5-HT$_{1A}$) receptors have been shown to be suppressed by corticosteroid hormones in a variety of animal experimental paradigms. It has been suggested that this effect may be central to the pathophysiology of severe clinical depressive illness, a condition in which 5-HT$_{1A}$ receptor function is reduced and corticosteroid hormones are elevated. We report the effects of acute administration of hydrocortisone in normal volunteers on a neuroendocrine model of 5-HT$_{1A}$ receptor function. Fifteen healthy male volunteers took part in a random order, double blind, placebo controlled study, in which 100 mg hydrocortisone or placebo was administered 11 h before infusion of L-tryptophan (L-TRP). Pre-treatment with hydrocortisone significantly reduced the growth hormone (GH), but not the prolactin (PRL) response to the infusion. These data are consistent with the view that acute administration of corticosteroid hormones significantly impairs 5-HT$_{1A}$ receptor mediated function in healthy human volunteers and are in line with animal studies of the effects of corticosteroid hormones on 5-HT$_{1A}$ receptors. We propose that this finding is relevant to the pathophysiological processes which cause severe depressive illness.

Key words L-Tryptophan · Hydrocortisone · Serotonin · Cortisol · Growth hormone · Prolactin · Human volunteer

R.J. Porter · R.H. McAllister-Williams
B.S. Lunn · A.H. Young (✉)
Department of Neuroscience and Psychiatry,
University of Newcastle, Royal Victoria Infirmary,
Newcastle NE1 4LP, UK
e-mail: A.H.Young@ncl.ac.uk, Fax: +44-191-227-5108

Introduction

The 5-HT$_{1A}$ receptor is a 450 amino acid polypeptide, with seven interconnected transmembrane segments, that is a member of the G-protein linked receptor superfamily (Hartig 1989). Both binding sites and messenger ribonucleic acid (mRNA) for this receptor are located presynaptically on serotonin containing raphe neurones (somatodendritic autoreceptors) and postsynaptically on cells throughout the cortex, especially in the hippocampus and Ammon's Horn (Burnet et al. 1995; Azmitia et al. 1996; Pasqualetti et al. 1996). Animal investigations have suggested that treatments for depression, including a variety of different classes of antidepressant drugs and electroconvulsive shocks, have specific actions on the function of 5-HT$_{1A}$ receptors (Goodwin et al. 1985) and that post-synaptic serotonergic transmission can be enhanced by increasing post-synaptic 5-HT$_{1A}$ receptor sensitivity or attenuating somatodendritic 5-HT$_{1A}$ autoreceptors (Blier and de Montigny 1994). At present, there is little direct evidence to support this mechanism in humans, although early results suggest that pindolol, used in doses thought to cause blockade of somatodendritic 5-HT$_{1A}$ autoreceptors, may be effective in accelerating antidepressant response (Perez et al 1997). Human studies using the technique of L-tryptophan (L-TRP) infusion have suggested that depressed patients have an impairment in post-synaptic 5-HT$_{1A}$ receptor function (Heninger et al. 1984; Koyama and Meltzer 1986; Cowen and Charig 1987; Deakin et al. 1990; Price et al. 1991) and that this impairment is state dependant (Upadhyaya et al. 1991). It is therefore suggested that the functioning of 5-HT$_{1A}$ receptors is central both to the pathology of depression and its treatment.

An important but as yet unresolved question is why this possible impairment of 5-HT$_{1A}$ function may arise in depressive illness. One possible cause might be the elevated levels of corticosteroid hormones which are found to be associated with depressive illness (Murphy

1991). Recent work in rodents has demonstrated a myriad of interactions between the hypothalamic-pituitary-adrenal axis and the serotonergic system (Chaouloff 1993), including findings that corticosteroids may attenuate post-synaptic 5-HT_{1A} receptor function (Joels et al. 1991; Haleem 1992). This has led to the suggestion that the impairment in serotonergic neurotransmission seen in depression may be caused by the action of corticosteroids (Young et al. 1994).

Intravenous infusion of L-TRP causes a brief, robust rise in the anterior pituitary hormones growth hormone (GH) and prolactin (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), suggesting that this response is a measure of $5HT_{1A}$ function. L-TRP infusion has been used to study $5HT_{1A}$ function in five studies which have shown a reduction in growth hormone response in depressed patients compared with control subjects (Power and Cowen 1992). Two of these examined the relationship between the degree of reduction in neuroendocrine response to L-TRP and measures of cortisol secretion and negative feedback (Cowen and Charig 1987; Deakin et al. 1990) but gave conflicting results.

The aim of this study was to investigate whether administration of corticosteroids to normal volunteers would affect $5HT_{1A}$ function. We used the hormonal responses to L-TRP as a measure of $5HT_{1A}$ function and observed the effects on this response of pre-treatment with hydrocortisone.

Materials and methods

Subjects and experimental design

Eighteen healthy male volunteers, aged 18–40 years (mean 27.9, SD 6.18), gave their informed consent to the study, which was approved by the local Ethics Committee. They had no history of significant psychiatric or physical illness and had been on no medication for at least 2 months.

Subjects were tested on two occasions, having taken pre-treatment medication at 2300 hours the night before. Pre-treatment medication consisted of either placebo or hydrocortisone 100 mg orally, administered in a balanced order, double blind, cross-over design. Following an overnight fast, subjects attended the research laboratory at 0900 hours, when an intravenous cannula was inserted. This was kept patent with heparinised saline. Subjects fasted throughout the experiment, remained semi-supine and were not allowed to sleep. After 1 h, an infusion of L-TRP (in aqueous solution 10 g/l) was given, at a dose of 100 mg/kg, over 25 min. Blood samples were taken every 15 min from 30 min before the infusion (−30 min, −15 min and time 0) and every 15 min from 5 min until 95 min after completion of the infusion (+5 min, +20 min etc.). Rating scales consisting of 100 mm visual analogue scales, measuring depression, dizziness, drowsiness, happiness, hunger, light-headedness and nausea, were administered immediately before infusion and at times +5, +35, +65 and +95 min. The Profile of Mood States (POMS: McNair et al. 1992) was administered at screening (baseline), −15 and +95 min. Beck depression inventory (BDI: Beck et al. 1961) was administered at baseline and at −15 min.

Biochemical measures

Blood samples were taken into EDTA tubes and centrifuged to remove plasma. This was stored at −20°C. Plasma was also ultrafiltered and stored until assay. Samples were analysed for prolactin, growth hormone and cortisol by standard radioimmunoassay. Free and total tryptophan were measured using high performance liquid chromatography (Marshall et al. 1987). Intra- and inter-assay coefficients of variation for PRL were 5.7% and 6.4%, respectively, for GH 2.7% and 7.4%, cortisol 8.1% and 10.4%, free tryptophan 3.4%, 4.4% and total tryptophan 3.3% and 4.4%.

Analysis

SPSS for Windows Release 7 (SPSS, Chicago, Ill., USA) was used for statistical analysis. In all cases, the Kolmogorov-Smirnov test was used to test for significant departure from a normal distribution. The biochemical and hormonal data, visual analogue measures and POMS were analysed using a two-way repeated measures analysis of variance (ANOVA) with treatment (cortisol or placebo) and time as the main variables. Hormonal responses were also calculated using the trapezoid area under the curve method measured from the average of the three baseline measures taken prior to infusion of L-TRP. These were then analysed using post hoc paired *t*-tests (two-tailed). These data are quoted as means ± SE. Order effects were analysed for each biochemical measure, by comparison of area under the curve (AUC) measures with an independent samples *t*-test.

Results

Eighteen subjects entered the study. Three did not complete both trials because of intolerance of side effects (nausea and vomiting) and were excluded from the analysis. Data are thus presented on 15 subjects.

Growth hormone

There was a significant effect of hydrocortisone pre-treatment on growth hormone response to L-TRP infusion ($F = 9.00$; $df = 14,1$; $P = 0.01$) (Fig. 1). In addition,

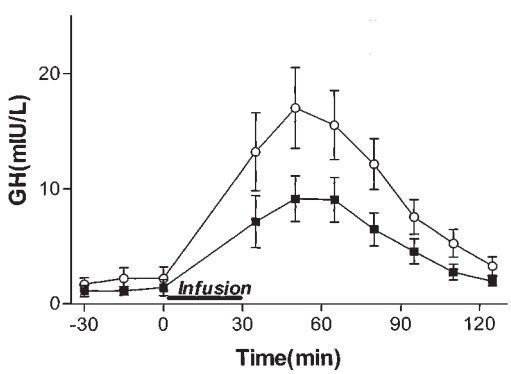

Fig. 1 Effect of pre-treatment with hydrocortisone or placebo on mean (SEM) growth hormone response to intravenous infusion of L-tryptophan (mIU/l) (see text for statistics). ■ Hydrocortisone, ○ placebo

Table 1 Effect of pre-treatment with hydrocortisone on baseline measures and responses (calculated as trapezoid area under the curve) to L-tryptophan infusion (*$P < 0.05$)

	Placebo mean ± SEM	Hydrocortisone mean ± SEM	Paired *t*-test
Growth hormone (mIU)AUC	824 ± 635	452 ± 414	0.03*
Baseline	2.1 ± 3.1	1.2 ± 1.7	0.19
Prolactin (ng/ml) AUC	405 ± 570	191 ± 254	0.16
Baseline	3.2 ± 1.8	2.7 ± 1.7	0.29
Cortisol (nmol/l) AUC	−4120 ± 3540	−8050 ± 2570	0.309
Baseline	362 ± 44	296 ± 41	0.179
Free tryptophan (ng/ml) AUC	38600 ± 1900	38400 ± 2200	0.94
Baseline	5.46 ± 0.41	5.49 ± 0.75	0.97
Total tryptophan (ng/ml) AUC	67100 ± 2800	68400 ± 2400	0.63
Baseline	51.17 ± 3.34	46.93 ± 5.48	0.51

Table 2 Two-way repeated measures analysis of variance (ANOVA) of responses to L-tryptophan infusion with condition (hydrocortisone/placebo) and time as variables (*$P < 0.05$; **$P < 0.001$)

	Effect of L-tryptophan (time)[a]		Effect of pre-treatment with hydrocortisone (drug)[b]		Interaction between pre-treatment and infusion (drug by time)[c]	
	F value	*P*	*F* value	*P*	*F* value	*P*
Hormones						
GH	17.93	<0.001**	9.00	0.01**	4.40	<0.001**
Prolactin	8.62	<0.001**	3.03	0.104	1.31	0.238
Cortisol	9.16	<0.001**	13.20	0.003**	1.04	0.409
Tryptophan						
Free TRP	143.4	<0.001**	0.60	0.452	2.41	0.078
Total TRP	208.82	<0.001**	0.15	0.706	0.64	0.763

[a]Degrees of freedom = 9,126
[b]Degrees of freedom = 1,14
[c]Degrees of freedom = 9,126

there was a significant Drug by Time interaction ($F = 4.40$; $df = 126,9$; $P < 0.001$). Post-hoc comparison of AUC measures showed the GH response to L-TRP to be significantly attenuated following pre-treatment with hydrocortisone (hydrocortisone 452 ± 414; placebo 824 ± 635; $t = 2.4$; $df = 14,1$; $P = 0.03$). There was no significant effect on baseline (Table 1).

Prolactin

ANOVA showed no significant effect of pre-treatment with hydrocortisone ($F = 3.03$; $df = 14,1$; $P = 0.104$) and no drug by time interaction ($F = 1.31$; $df = 14,1$; $P = 0.238$; Table 2). Post hoc comparison of AUCs showed no significant difference between the two conditions and there was no significant effect on baseline prolactin (Table 1).

Cortisol

ANOVA showed a significant effect of hydrocortisone on the cortisol response to L-TRP ($F = 13.2$; $df = 14,1$; $P = 0.003$) but there was no significant interaction between Drug and Time ($F = 1.04$; $df = 14,1$; $P = 0.409$; Fig. 2, Table 2). Pre-treatment with hydrocortisone had no significant effect on baseline cortisol and no significant difference in AUC measures (Table 1).

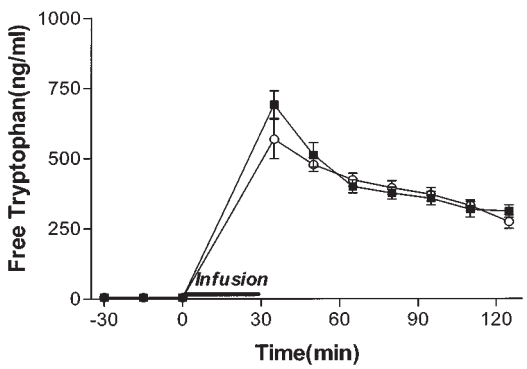

Fig. 2 Effect of pre-treatment with hydrocortisone or placebo on mean (SEM) plasma free tryptophan (nmol/l) in response to L-tryptophan infusion (see text for statistics). ■ Hydrocortisone, ○ placebo

Tryptophan

ANOVA showed no drug effect or Drug by Time interaction on both free and total tryptophan (Fig. 3,

Table 3 Two-way repeated measures analysis of variance (ANOVA) of visual analogue responses to L-tryptophan infusion with condition (hydrocortisone/placebo) and time as variables (*$P < 0.05$;**$P < 0.001$)

Visual analogue	Effect of L-tryptophan (time)[a]		Effect of pre-treatment with hydrocortisone (drug)[b]		Interaction between pre-treatment and infusion (drug × time)[c]	
	F	*P*	*F*	*P*	*F*	*P*
Depression	2.50	0.053	2.37	0.146	0.39	0.815
Dizziness	10.98	<0.001**	0.97	0.342	0.75	0.564
Drowsiness	10.97	<0.001**	0.16	0.698	0.73	0.578
Happy	2.13	0.089	0.19	0.668	0.85	0.5
Hungry	3.10	0.023*	0.04	0.842	0.8	0.532
Light headed	12.21	<0.001**	0.14	0.709	1.21	0.317
Nausea	6.81	<0.001**	0.63	0.441	0.15	0.963

[a]Degrees of freedom = 56,4
[b]Degrees of freedom = 14,1
[c]Degrees of freedom = 56,4

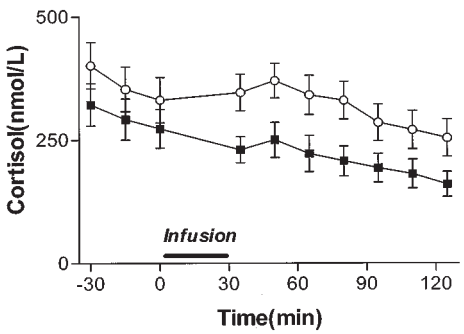

Fig. 3 Effect of pre-treatment with hydrocortisone or placebo on mean (SEM) plasma cortisol (nmol/l) in response to L-tryptophan (see text for statistics). ■ Hydrocortisone, ○ placebo

Table 2). Post-hoc comparison of mean AUC and baseline measures showed no significant difference between the hydrocortisone pre-treatment and placebo conditions (Table 1).

Psychological responses

Pre-treatment with hydrocortisone had no significant effect on baseline BDI (hydrocortisone 1.27 ± 0.47; placebo 0.87 ± 0.34; $t = 0.74$; $df = 14,1$; $P = 0.47$).

Visual analogues

Significant Time effects occurred on scales measuring dizziness, drowsiness, light headedness and nausea. There were no significant Drug or Drug by Time effects (Table 3).

Profile of mood states

The "vigor" subscale showed an effect of Time ($F = 10.20$; $df = 1,14$; $P = 0.006$) and "vigor" was significantly reduced, immediately after the infusion, but only during the placebo phase (pre-infusion 16.1 ± 1.4; post-infusion 12.9 ± 1.4; $f = 3.3$; $df = 14,1$; $P = 0.006$; paired *t*-test). There were no significant effects of hydrocortisone or interaction between hydrocortisone and time, and paired *t*-tests showed no difference between conditions at any parallel time points (data not shown).

Analysis of covariance

ANOVA revealed no significant independent effect of free tryptophan level ($F = 0.53$; $df = 13,1$; $P = 0.480$) or of cortisol level ($F = 0.10$; $df = 13,1$; $P = 0.761$) on the effect of hydrocortisone on the GH response to L-TRP.

Order effects

There were no significant order effects for any variable and in particular none for GH (hydrocortisone pre-treatment first 352 ± 217; hydrocortisone pre-treatment second 602 ± 103; $t = 1.2$; $df = 13,1$; $P = 0.266$; placebo pre-treatment first 902 ± 213; placebo pre-treatment second 772 ± 242; $t = 0.376$; $df = 13,1$; $P = 0.713$).

Discussion

The main finding of the study is that pre-treatment with hydrocortisone 100 mg orally significantly attenuates the growth hormone response to infusion of L-TRP. The cortisol and PRL responses were also reduced but only the former was significant. The GH response to L-TRP has been shown to be attenuated by the 5-HT_{1A} antagonist pindolol (Smith et al. 1991), which suggests that it is mediated by 5-HT_{1A} receptors. These data are therefore consistent with the hypothesis that the

Table 4 Individual data showing response to L-tryptophan infusion (AUC) for GH and prolactin, following hydrocortisone and placebo, and % change (see text for statistical analysis)

GH (mIU/l)			Prolactin (ng/ml)		
Placebo	Hydrocortisone	% change	Placebo	Hydrocortisone	% change
1185.65	134.15	−88.7	82.77	−396.30	−578.8
1436.53	195.03	−86.4	118.25	−2.50	−102.1
2103.65	417.10	−80.2	2206.30	114.03	−94.8
1273.23	304.12	−76.1	436.50	29.45	−93.3
676.28	256.63	−62.1	−249.27	−26.00	−89.6
233.15	106.63	−54.3	244.80	68.03	−72.2
507.65	256.35	−49.5	733.23	343.00	−53.2
1722.63	1135.88	−34.1	444.40	302.50	−31.9
354.62	270.45	−23.7	831.73	700.80	−15.7
312.73	260.63	−16.7	297.30	267.78	−9.9
891.65	954.85	7.1	396.47	428.45	8.1
1222.80	1528.08	25.0	325.30	426.80	31.2
170.10	236.05	38.8	180.80	291.15	61.0
189.30	348.78	84.2	19.00	123.02	547.5
80.38	376.00	367.8	3.23	195.77	5961.0

function of 5-HT_{1A} receptors is reduced by pre-treatment with hydrocortisone.

Hydrocortisone did not significantly attenuate the PRL response to intravenous infusion of L-TRP. One reason for this may have been the greater variance in PRL responses (Table 1) and in fact, in the majority of subjects, the prolactin response was lower following administration of hydrocortisone (Table 4). However, there may be additional mediators of the PRL response. Pindolol causes markedly less attenuation of the PRL response than the GH response to L-TRP (Smith et al. 1991). L-TRP competes with tyramine for transport across the blood-brain barrier (Wurtman 1982) and may reduce dopamine synthesis. This is supported by evidence that intravenous 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 may therefore be mediated in part by a reduction in dopamine synthesis, which releases PRL secretion from inhibition by dopamine.

Previously, it has been suggested that the effects of cortisol on brain 5-HT may be mediated by reduction in plasma levels of the aminoacid, L-TRP (Green and Curzon 1968). However, in this study, the effects of cortisol are unlikely to be due to an alteration of plasma levels of L-TRP, as these did not differ between the cortisol and placebo phases of the study (Fig. 2 and Table 1). In addition, L-TRP levels were not a significant covariant in the hydrocortisone effect on the GH response (see Results).

Our findings are in keeping with a large body of animal work which suggests that 5HT_{1A} receptors are suppressed by corticosteroids. Post-synaptic 5-HT_{1A} receptor binding is increased following adrenalectomy, an effect which 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). Putative postsynaptic 5-HT mediated behaviour (forepaw treading) is reduced by corticosteroid administration in rodents (Haleem 1992). Chronic administration of corticosterone also causes a reduction in the function and binding of somato-dendritic 5-HT_{1A} receptor (Young et al. 1992; Laaris et al. 1995). It should be noted, however, that stress initially produces a transient increase in post synaptic 5-HT_{1A} receptors (Mendelson and McEwen 1991) which is not in keeping with the findings in this study.

The effects of the synthetic corticosteroid dexamethasone on the response to L-TRP has previously been examined in normal volunteers (Traskman-Bendz et al. 1986). In contrast to our data, an increase in PRL response, but no effect on GH response, to L-TRP infusion was seen following pre-treatment with dexamethasone 1 mg 10 h before infusion. There are two possible reasons for these differences. Firstly, it has been shown in animals that the pattern of binding of dexamethasone in the brain is different from that of corticosterone (de Kloet et al. 1975), binding being particularly high in the pituitary. Secondly, there is a different pattern of binding to the subtypes of brain corticosteroid receptors. Thus glucocorticoid receptors (GRs) have a much higher affinity for dexamethasone than corticosterone (in rats), while for mineralocorticoid receptors (MRs) these relative affinities are reversed (Caamano et al. 1994). There is considerable evidence that 5-HT_{1A} function may be regulated differentially by these receptors (Meijer and de Kloet 1995; Hesen and Joels 1996).

Our results differ from those of Young et al. (1994), who used buspirone as a neuroendocrine probe of 5-HT_{1A} function in healthy volunteers and found no blunting of growth hormone responses following a regimen of treatment with hydrocortisone 20 mg twice a

day for 1 week. This regime was, however, found to cause blunting of the hypothermic response to buspirone which evidence now suggests may also be a measure of post-synaptic 5-HT_{1A} receptor function (Blier et al. 1994). The results of this study are therefore difficult to interpret. It is possible that the difference in the effects of corticosteroids on these two putative measures of post-synaptic 5-HT_{1A} receptor function could be explained by corticosteroids having effects on GH control mechanisms in addition to those involving 5-HT_{1A} receptors, such as somatostatin. These mechanisms are discussed further below. Buspirone has the additional disadvantage of having dopaminergic antagonistic activity (Tunnicliff 1991), and the neuroendocrine findings in depressed patients with this drug have been inconsistent. The one study in depressed patients to have used ipsapirone, a relatively selective 5-HT_{1A} agonist, demonstrated a reduction in the cortisol and ACTH response and in hypothermia, all effects believed to mediated by 5-HT_{1A} receptors (Lesch 1992). This is consistent with the findings in studies using L-TRP infusion and further suggests that buspirone may not be an ideal probe of 5-HT_{1A} function. However, it is also possible that in the normal volunteers studied by Young et al. (1994), an acute down- regulation of 5-HT_{1A} function produced by corticosteroids is compensated for after 1 weeks treatment. Depressed patients may lack such an ability to compensate for the effects of elevated corticosteroids and this may be central to the pathophysiology of this disorder.

We postulate that cortisol reduces the function of hypothalamic $5HT_{1A}$ receptors and so reduces growth hormone releasing hormone (GHRH) release in response to L-TRP. GH release in response to L-TRP is therefore reduced by this mechanism. An alternative explanation is that cortisol increases hypothalamic somatostatin release which inhibits GH release from the pituitary. Evidence suggests that GH release in response to a number of stimuli is altered by corticosteroids but that this appears to be dependant on the length of exposure and the type of corticosteroid (Thakore and Dinan 1994). The effects of hydrocortisone on GHRH-mediated GH release, in a similar paradigm to the one used here, have not been studied. It is extremely unlikely that the observed reduction in GH response to LTP in depressed patients could be secondary to increased somatostatin tone, since studies have consistently shown somatostatin concentrations in CSF to be reduced in depression (Gerner and Yamada 1982; Rubinow et al. 1983; Agren and Lundqvist 1984).

There appears to be a small increase in cortisol secretion following L-TRP infusion on a background of declining cortisol levels (Fig. 3). Pre-treatment with hydrocortisone significantly reduced the cortisol response to L-TRP infusion and caused a general reduction in cortisol levels (see Fig. 3), although baseline values were not significantly different. It could be argued that the effects of hydrocortisone on the GH response to L-TRP infusion was due to reduced cortisol levels arising during the test. Such rapid neurosteroidal effects of corticosteroids, which could act over this time scale, have been demonstrated (Majewska et al. 1985). However, cortisol levels did not prove to be a significant co-variant in the growth hormone response, which makes this mechanism unlikely.

The biological half-life of hydrocortisone is approximately 90 min (Rang and Dale 1991). Feedback inhibition of cortisol secretion is rapid and it is therefore likely that in this design endogenous cortisol secretion was quickly suppressed to return total cortisol levels to normal. Hydrocortisone administration, in this study, was timed to coincide with the normal nadir of cortisol secretion. Therefore, the effect of our manipulation is likely to have been to increase cortisol levels at a time when they would normally have been low, simulating, as found in depression, the loss of the evening trough. However, although there was no statistically significant reduction in baseline cortisol the following morning, the cortisol levels throughout the study were consistently lower (Fig. 3). This implies that the increase in cortisol levels at 2300 hours, although short in duration, did cause a longer term down-regulation of cortisol secretion, with the overall effect that the normal circadian pattern of low nocturnal levels followed by a morning peak was abolished. In terms of receptor occupancy, GRs exist in higher numbers than MRs and are thought to be fully occupied only in response to stress (de Kloet et al. 1991). In this study, it is likely that we created a more even pattern of GR occupation through the night and early morning in the experimental compared with the control condition. Although it is generally assumed that MRs are fully occupied at all stages in the circadian rhythm, recent work suggests that they are responsive to high levels of circulating corticosteroids (de Kloet et al. 1994). There is also animal evidence that the MR receptor is a more important mediator of the effects of corticosteroids on $5HT_{1A}$ function (Meijer and de Kloet 1994). Therefore, in this study, the effects of hydrocortisone may be mediated by GRs or MRs or both of these subtypes of receptors working in concert.

We conclude that acute administration of hydrocortisone to healthy male subjects appears to impair 5-HT_{1A} receptor mediated function. This finding is consistent with a large body of animal work, and demonstrates a possible causative link between the findings, in depression, of reduced 5-HT_{1A} receptor function and hypercortisolaemia. Further work is needed to determine whether these findings apply to chronic cortisol excess, what the role of GRs and MRs is in this effect and whether a correlation between cortisol levels and 5-HT_{1A} receptor function can be demonstrated in depressed patients.

Acknowledgements This work was supported by a grant from The Mental Health Foundation – North East Branch. We are grateful to Professor I.N. Ferrier for his helpful advice.

References

Agren H, Lundqvist G (1984) Low levels of somatostatin in human CSF mark depressive episodes. Psychoneuroendocrinology 9: 233–248

Azmitia EC, Gannon PJ, Kheck NM, Whitaker-Azmitia PM (1996) Cellular localization of the 5-HT_{1A} receptor in primate brain neurons and glial cells. Neuropsychopharmacology 14:35–46

Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J (1961) An inventory for measuring depression. Arch Gen Psychiatry 4:53–63

Blier P, de Montigny C (1994) Current advances and trends in the treatment of depression. Trends Pharmacol Sci 15:220–226

Blier P, Seletti B, Young S, Benkelfat C, de Montigny C (1994) $Serotonin_{1A}$ receptor activation and hypotherma: evidence for a postsynaptic mechanism in humans. Neuropsychopharmacology 10[3S]:92

Burnet PW, Eastwood SL, Lacey K, Harrison PJ (1995) The distribution of 5-HT_{1A} and 5-HT_{2A} receptor mRNA in human brain. Brain Res 676:157–168

Caamano CA, Morano MI, Watson SJ, Dalman FC, Pratt WB, Akil H (1994) The functional relevance of the heteromeric structure of corticosteroid receptors. Ann NY Acad Sci 746:68–77

Chaouloff F (1993) Physiopharmacological interactions between stress hormones and central serotonergic systems. Brain Res Rev 18:1–32

Charney DS, Heninger GR (1982) The effect of IV L-tryptophan on prolactin, growth hormone, and mood in healthy subjects. Psychopharmacology 78: 38–43

Cowen PJ, Charig EM (1987) Neuroendocrine responses to intravenous tryptophan in major depression. Arch Gen Psychiatry 44:958–966

de Kloet ER, Wallach G, McEwen BS (1975) Differences in corticosterone and dexamethasone binding to rat brain and pituitary. Endocrinology 96:598–609

de Kloet ER, Reul JM, de Ronde FS, Bloemers M, Ratka A (1986) Function and plasticity of brain corticosteroid receptor systems: action of neuropeptides. J Steroid Biochem 25:723–731

de Kloet ER, Joels M, Oitzl MS, Sutanto W (1991) Implication of brain corticosteroid receptor diversity for the adaptation syndrome concept. Methods Achieve Exp Pathol 14:104–132

de Kloet ER, Rots NY, Van den Berg DT, Oitzl MS (1994) Brain mineralocorticoid receptor function. In: de Kloet ER, Azmitia EC, Landfield PW (eds) Annals of the New York Academy of Sciences. New York Academy of Sciences, Arlington, Virginia, pp 8–21

Deakin JF, Pennell I, Upadhyaya AJ, Lofthouse R (1990) A neuroendocrine study of 5HT function in depression: evidence for biological mechanisms of endogenous and psychosocial causation. Psychopharmacology 101:85–92

Gerner RH, Yamada T (1982) Altered neuropeptide concentrations in cerebrospinal fluid of psychiatric patients. Brain Res 238: 298–302

Goodwin GM, De Souza RJ, Green AR (1985) Presynaptic serotonin receptor-mediated response in mice attenuated by antidepressant drugs and electroconvulsive shock. Nature 317:531–533

Green AR, Curzon G (1968) Decrease of 5-hydroxytryptamine in the brain provoked by hydrocortisone and its prevention by allopurinol. Nature 220:1095–1097

Haleem DJ (1992) Repeated corticosterone treatment attenuates behavioural and neuroendocrine responses to 8-hydroxy-2-(di-*n*-propylamino) tetralin in rats. Life Sci 51:PL225–230

Hartig PR (1989) Molecular biology of 5-HT receptors. Trends Pharmacol Sci 10:64–69

Heninger GR, Charney DS, Sternberg DE (1984) Serotonergic function in depression. Prolactin response to intravenous tryptophan in depressed patients and healthy subjects. Arch Gen Psychiatry 41:398–402

Hesen W, Joels M (1996) Modulation of $5HT_{1A}$ responsiveness in CA1 pyramidal neurons by in vivo activation of corticosteroid receptors. J Neuroendocrinol 8:433–438

Joels M, Hesen W, de Kloet ER (1991) Mineralocorticoid hormones suppress serotonin-induced hyperpolarization of rat hippocampal CA1 neurons. J Neurosci 11:2288–2294

Koyama T, Meltzer HY (1986) A biochemical and neuroendocrine study of the serotonergic system in depression. In: Hippius H et al. (eds) New results in depression research. Springer, Berlin Heidelberg New York, pp 169–188

Kuroda Y, Watanabe Y, Albeck DS, Hastings NB, McEwen BS (1994) Effects of adrenalectomy and type I or type II glucocorticoid receptor activation on 5-HT_{1A} and 5-HT_2 receptor binding and 5-HT transporter mRNA expression in rat brain. Brain Res 648:157–161

Laaris N, Haj-Dahmane S, Hamon M, Lanfumey L (1995) Glucocorticoid receptor-mediated inhibition by corticosterone of 5-HT_{1A} autoreceptor functioning in the rat dorsal raphe nucleus. Neuropharmacology 34:1201–1210

Lesch KP (1992) The ipsapirone/5-HT_{1A} receptor challenge in anxiety disorders and depression. In: Stahl SM, Gastpar M, Keppel Hesselink JM, Traber J (eds) Serotonin-$_{1A}$ receptors. Raven Press, New York, pp 135–163

Majewska MD, Bisserbe JC, Eskay RL (1985) Glucocorticoids are modulators of $GABA_A$ receptors in brain. Brain Res 339: 178–182

Marshall EF, Kennedy WN, Eccleston D (1987) Whole blood serotonin and plasma tryptophan using high-pressure liquid chromatography with electrochemical detection. Biochem Med Metab Biol 37:81–86

Martire M, Pistritto G, Preziosi P (1989) Different regulation of serotonin receptors following adrenal hormone imbalance in the rat hippocampus and hypothalamus. J Neural Transm 78: 109–120

McNair DM, Lorr M, Droppleman LF (1992) Edits manual for the profile of mood states. Educational and Industrial Testing Service, San Diego

Meijer OC, de Kloet ER (1994) Corticosterone suppresses the expression of 5-HT_{1A} receptor mRNA in rat dentate gyrus. Eur J Pharmacol 266:255–261

Meijer OC, de Kloet ER (1995) A role for the mineralocorticoid receptor in a rapid and transient suppression of hippocampal 5-HT_{1A} receptor mRNA by corticosterone. J Neuroendocrinol 7:653–657

Mendelson SD, McEwen BS (1991) Autoradiographic analyses of the effects of restraint-induced stress on 5-HT_{1A}, 5-HT_{1C} and 5-HT_2 receptors in the dorsal hippocampus of male and female rats. Neuroendocrinology 54: 454–461

Mendelson SD, McEwen BS (1992a) Autoradiographic analyses of the effects of adrenalectomy and corticosterone on 5-HT_{1A} and 5-HT_{1B} receptors in the dorsal hippocampus and cortex of the rat. Neuroendocrinology 55:444–450

Mendelson SD, McEwen BS (1992b) Quantitative autoradiographic analyses of the time course and reversibility of corticosterone-induced decreases in binding at 5-HT_{1A} receptors in rat forebrain. Neuroendocrinology 56:881–888

Murphy BE (1991) Steroids and depression. J Steroid Biochem Mol Biol 38:537–539

Pasqualetti M, Nardi I, Ladinsky H, Marazziti D, Cassano GB (1996) Comparative anatomical distribution of serotonin 1A, 1D alpha and 2A receptor mRNAs in human brain postmortem. Brain Res Mol Brain Res 39:223–233

Perez V, Gilaberte I, Faries D, Alvarez E, Artigas F (1997) Randomised, double-blind, placebo-controlled trial of pindolol in combination with fluoxetine antidepressant treatment. Lancet 349:1594–1597

Power AC, Cowen PJ (1992) Neuroendocrine challenge tests: assessment of 5-HT function in anxiety and depression. Mol Aspects Med 13:205–220

Price LH, Charney DS, Delgado PL, Heninger GR (1991) Serotonin function and depression: neuroendocrine and mood responses to intravenous L-tryptophan in depressed patients and healthy comparison subjects [see comments]. Am J Psychiatry 148: 1518–1525

Rang HP, Dale MM (1991) Pharmacology, 2nd edn. Churchill Livingstone

Rubinow DR, Gold PW, Post RM, Ballenger JC, Cowdry R, Bollinger J, Reichlin S (1983) CSF somatostatin in affective illness. Arch Gen Psychiatry 40:409–412

Smith CE, Ware CJ, Cowen PJ (1991) Pindolol decreases prolactin and growth hormone responses to intravenous L-tryptophan. Psychopharmacology 103:140–142

Thakore JH, Dinan TG (1994) Growth hormone secretion: the role of glucocorticoids. Life Sciences 55:1083–1099

Traskman-Bendz L, Haskett RF, Zis AP (1986) Neuroendocrine effects of L-tryptophan and dexamethasone. Psychopharmacology 89:85–88

Tunnicliff G (1991) Molecular basis of buspirone's anxiolytic action. Pharmacol Toxicol 69:149–156

Upadhyaya AK, Pennell I, Cowen PJ, Deakin JF (1991) Blunted growth hormone and prolactin responses to L-tryptophan in depression; a state-dependent abnormality. J Affect Disord 21:213–218

van Praag HM, Lemus C, Kahn R (1987) Hormonal probes of central serotonergic activity: do they really exist? Biol Psychiatry 22:86–98

Wurtman RJ (1982) Nutrients that modify brain function. Sci Am 246:50–59

Young AH, MacDonald LM, St John H, Dick H, Goodwin GM (1992) The effects of corticosterone on 5-HT receptor function in rodents. Neuropharmacology 31:433–438

Young AH, Sharpley AL, Campling GM, Hockney RA, Cowen PJ (1994) Effects of hydrocortisone on brain 5-HT function and sleep. J Affect Disord 32:139–146