Psychopharmacology (1999) 143 : 64–71

ORIGINAL INVESTIGATION

Richard J. Porter · R. Hamish McAllister-Williams
Samantha Jones · Allan H. Young

Effects of dexamethasone on neuroendocrine and psychological responses to L-tryptophan infusion

Received: 5 June 1998/Final version: 25 September 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. 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. Evidence suggests that the growth hormone (GH) response to L-tryptophan (L-TRP) is mediated by 5-HT$_{1A}$ receptors. This response has been shown to be reduced following acute administration of hydrocortisone. The purpose of this study was to examine the effects of acute administration of dexamethasone, in normal volunteers, on hormonal and psychological responses to L-TRP infusion. *Methods*: Sixteen healthy male volunteers took part in a random order, double blind study, in which 5 mg dexamethasone or placebo was administered 11 h before infusion of L-TRP. *Results*: Pretreatment with dexamethasone had no effect on the GH response to the infusion. However, baseline prolactin (PRL) was significantly reduced, as was the prolactin response to the infusion. *Conclusions*: These data contrast with a previous study using hydrocortisone in the same paradigm and demonstrate important functional differences between dexamethasone and hydrocortisone.

Key words L-Tryptophan · Dexamethasone · Serotonin · Cortisol · Growth hormone · Prolactin · Human volunteers

R.J. Porter · R.H. McAllister-Williams · S. Jones · 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

Deakin and Graeff (1991) have suggested that 5-HT neurones in the median raphé, which project onto postsynaptic 5-HT$_{1A}$ receptors in the hippocampus, maintain adaptive behaviours in the face of aversive stimuli. They further postulate that failure of this system leads to helplessness in animals and depression in humans. While it is not currently possible to measure 5-HT function in the hippocampus or other cortical structures in vivo in humans, neuroendocrine challenge tests allow measurement of the functioning of 5-HT pathways in the hypothalamus. In particular, the growth hormone (GH) response to L-tryptophan (L-TRP) infusion appears to be a useful measure of 5-HT$_{1A}$ receptor function in humans (Smith et al. 1991) and has consistently been shown to be blunted in depressive illness (Power and Cowen 1992). This abnormality appears to resolve following successful treatment (Upadhyaya et al. 1991), and there is evidence that specific antidepressant medications enhance 5-HT$_{1A}$ receptor function in both healthy volunteers and depressed subjects (Price et al. 1990).

Elevated levels of corticosteroid hormones are associated with depressive illness (Murphy 1991a), and 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 5-HT$_{1A}$ receptor function (Joels et al. 1991; Haleem 1992). Although there have been few human studies, it has been shown that in normal volunteers pre-treatment with 100 mg hydrocortisone the night before significantly reduced the GH response to infusion of L-TRP 11 h later (Porter et al. 1998). This supports the notion that the impairment in serotonergic neurotransmission seen in depression may be induced by corticosteroids (Young et al. 1992; Dinan 1994; Young 1994; McAllister-Williams et al. 1998).

In subjects with depressive illness, conflicting results have been reported regarding the relationship between the attenuation in L-TRP responses and abnormalities in hypothalamic-pituitary axis (HPA) function. Deakin et al. (1990) showed that basal cortisol concentrations were strongly and inversely predictive of PRL responses in depressives and controls and Price et al. (1991) showed a negative correlation between post-dexamethasone cortisol and GH response. However, Cowen and Charig (1987) showed a positive correlation between post-dexamethasone cortisol and PRL responses.

It has been suggested that agents such as ketoconazole, aminoglutethamide and metyrapone, which reduce cortisol levels, may be effective treatments in depression (Murphy 1991b). Dexamethasone has also been shown in open studies and in one double blind placebo controlled trial to improve symptoms of depression in a dose of 4 mg per day (Arana and Forbes 1991; Arana et al. 1995). Dexamethasone differs from the other agents used in that it is itself a potent corticosteroid. However, dexamethasone has important differences from the endogenous steroid cortisol. In particular, dexamethasone has both a different distribution of brain binding and greater affinity for glucocorticoid receptors (GRs) than cortisol but less affinity for mineralocorticoid receptors (MRs) (Caamano et al. 1994).

Because of this, a comparison of the effect of dexamethasone with that of hydrocortisone in healthy volunteers may be helpful in determining the relative roles played by MRs and GRs in the attenuation of post-synaptic 5-HT_{1A} function by corticosteroids. Previously, it has been shown that when dexamethasone is given in a dose of 1 mg (in the same paradigm used in our study with hydrocortisone; Porter et al. 1998), the PRL response to L-TRP is enhanced but the GH response is not (Traskman-Bendz et al. 1986). However, this dose of dexamethasone is well below that which is clinically equipotent to the dose of 100 mg hydrocortisone employed in our study.

We postulated that equipotent doses of hydrocortisone and dexamethasone would have different effects on 5-HT_{1A}receptor function as a result of the different pharmacological profiles of these two corticosteroids. The purpose of this study was to test this hypothesis; therefore we have replicated the design used in our previous study (Porter et al. 1998) and that of Traskman-Bendz et al. (1986) to examine the effects of pre-treatment with 5 mg dexamethasone on the neuroendocrine response to L-TRP infusion.

Materials and methods

Subjects and experimental design

Nineteen 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 dexamethasone 5 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 (VAS), 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 -15 and +95 min. The 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 PRL, GH and cortisol by standard radioimmunoassay. Free and total TRP were measured using high performance liquid chromatography (Marshall et al. 1987). Intra- and inter- assay co-efficients of variation for PRL were 5.7% and 6.4%, respectively, for GH 2.6% and 7.4%, cortisol 8.1% and 10.4%, free TRP 3.4%, 4.4% and total TRP 3.3% and 4.4%.

Analysis

SPSS for Windows Release 7 (SPSS, Chicago, Illinois, USA) was used for statistical analysis. In all cases, the Kolmogorov-Smirnov test was used to exclude any significant departure from a normal distribution. The biochemical and hormonal data were analysed using a three-way repeated measures analysis of variance (ANOVA), with treatment (dexamethasone or placebo) and time as within-subject variables and order as a between-subject variable with significant results corrected using the Huynh-Feldt correction for repeated measures. Hormonal responses were also calculated using the trapezoid area under the curve (AUC) method. This was measured from the average of the three baseline measures taken prior to infusion of L-TRP for all analyses except prolactin, where the final measure before infusion was used because of a falling baseline. These were then analysed using post-hoc paired *t*-tests (two tailed). These data are quoted as means ± standard errors (SEM). Order effects were further analysed for each biochemical measure, by comparison of AUC measures with an independent samples *t*-test.

Pre-infusion psychological data were analysed by paired *t*-tests. VAS and POMS data were analysed using three-way repeated measures ANOVA. AUC was calculated for VAS and this was used to calculate correlations with hormonal measures.

Results

Three subjects 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 16 subjects of whom nine received placebo then dexamethasone, seven received dexamethasone then placebo.

Growth hormone

Two sets of data were excluded because of high baseline GH values (>10 mIU/l), since GH inhibits its own secretion (Checkley 1980). There was no significant effect of dexamethasone pre-treatment on GH response to L-TRP infusion ($F < 0.001$; $df = 12,1$; $P = 0.96$), or significant drug by time interaction (Table 2, Fig. 1). Post-hoc comparison of AUC measures also showed no significant difference (Table 1) and there was no significant effect on baseline. Of the 14 subjects, eight received placebo first. However, there was no significant effect of order or interaction between order and drug or time (data not shown).

Prolactin

One subject was excluded because of baseline PRL values, which were approximately 6–8 SD greater than the mean placebo baseline (610–744 mIU), and was referred for further endocrinological assessment. Baseline PRL levels were significantly lower following pre-treatment with dexamethasone (dexamethasone 102 ± 9.9; placebo 161 ± 17.5; $t = 3.8$; $df = 14,1$; $P = 0.002$) (Table 1). ANOVA showed a significant effect of pre-treatment with dexamethasone ($F = 16.91$; $df = 13,1$; $P = 0.001$) and a significant drug by time interaction ($F = 4.96$; $df = 117,9$; $P < 0.018$) (Table 2, Fig. 2). When change from baseline PRL values were examined, dexamethasone appeared to decrease the PRL response. ANOVA, however, showed no significant effect of dexamethasone ($F = 2.79$; $df = 13,1$; $P = 0.119$), though a significant dexamethasone by time interaction was found ($F = 7.52$; $df = 78,6$; $P = 0.005$). Post hoc comparison of AUCs showed no significant difference between the two conditions (Table 1). Of the 15 subjects, nine received placebo first. There was no significant effect of order or interaction between order and drug or time.

Cortisol

Cortisol levels were markedly decreased by dexamethasone. ANOVA showed a significant effect of dexamethasone on the cortisol response to L-TRP ($F = 155.44$; $df = 14,1$; $P < 0.001$) and a significant interaction between drug and time ($F = 6.45$; $df = 126,9$; $P < 0.001$). Pre-treatment with dexamethasone had a significant effect on baseline cortisol (dexamethasone 23.7 ± 2.3; placebo 295.8 ± 27.4; $t = 10.1$; $df = 135,9$; $P < 0.001$) (Fig. 3). AUC measures were not significantly different (Table 1). There was no significant effect of order or interaction between order and drug or time.

Tryptophan

ANOVA showed no drug effect or drug by time interaction on both free and total TRP (Table 2). Post-hoc comparison of mean AUC and baseline measures showed no significant difference between the dexamethasone pre-treatment and placebo conditions (Table 1). There was a significant effect of order on both free ($F = 7.46$; $df = 14,1$; $P = 0.016$) and total TRP ($F = 8.13$; $df = 14,1$; $P = 0.013$) and a significant interaction between order and time for both free ($F = 3.93$; $df = 126,9$; $P = 0.021$) and total TRP ($F = 5.11$; $df = 126,9$; $P = 0.015$). For free TRP there were no significant differences in AUC between first and second visits. For total TRP, AUC was significantly higher following placebo pre-treatment on the second visit, and was higher but not significantly following dexamethasone on the first visit (placebo pre-treatment first 68 800 ± 4700; placebo pre-treatment second 98 000 ± 10 000; $t = 2.84$; $df = 14,1$; $P = 0.013$; dexam-

Table 1 Effect of pre-treatment with dexamethasone on baseline measures and responses (calculated as trapezoid area under the curve) to L-TRP infusion

		Placebo mean ± SEM	Dexamethasone mean ± SEM	95% CI[a]	Paired *t*-test
Growth hormone (mIU)	AUC	582 ± 257	527 ± 103	−539 to 428	0.81
Baseline		1.7 ± 0.6	2.1 ± 0.5	−0.3 to 1.0	0.31
Prolactin (mIU)[b]	AUC	9369 ± 3280	4621 ± 934	−10439 to 943	0.095
Baseline		160.9 ± 17.5	102.4 ± 9.9	−91.2 to −25.8	0.002
Cortisol (nmol/L)	AUC	–2501 ± 2029	−409.4 ± 73.9	−2215 to 6399	0.317
Baseline		296 ± 27.4	24 ± 2.3	−329 to −215	<0.001
Free tryptophan (ng/ml)	AUC	40477 ± 2514	33812 ± 3402	−15761 to 2430	0.14
Baseline		7.20 ± 0.52	6.93 ± 1.20	−2.67 to 2.14	0.82

[a]95% confidence interval of difference between the means
[b]AUC for prolactin calculated from a single baseline at $t = 0$

Table 2 The effect of dexamethasone pre-treatment on responses to L-TRP infusion: summary of analysis of variance results

	Effect of L-TRP (time)[a]		Effect of pre-treatment with dexamethasone (drug)[a]		Interaction between pre-treatment and infusion (drug by time)[a]	
	F value	*P*	*F* value	*P*	*F* value	*P*
Hormones						
GH[b]	11.32	0.001	<0.001	0.955	0.58	0.559
Prolactin[c]	11.65	0.001	16.91	0.001	4.96	0.018
Cortisol[d]	6.90	<0.001	155.44	<0.001	6.45	<0.001
Tryptophan						
Free TRP[d]	213.45	<0.001	2.24	0.156	1.26	0.301
Total TRP[d]	172.92	<0.001	0.03	0.861	0.36	0.646

[a]Analysis by three-way ANOVA. Results for order, order × drug, order × time and order × drug × time not given
[b]Degrees of freedom = time 108,9, drug 12,1, drug × time 108,9
[c]Degrees of freedom = time 117,9, drug 13,1, drug × time 117,9
[d]Degrees of freedom = time 126,9, drug 14,1, drug × time 126,9

ethasone pre-treatment first 93200 ± 14200; dexamethasone pre-treatment second 70400 ± 8000; $t = 1.47$; $df = 14,1$; $P = 0.163$).

Psychological responses

Pre-treatment with dexamethasone had no significant effect on baseline BDI (dexamethasone 1.47 ± 0.54; placebo 1.47 ± 0.55; $t < 0.001$; $df = 15,1$; $P = 1.00$). There were significant drug effects on VAS scores of "dizziness" ($F = 5.81$; $df = 14,1$; $P = 0.030$), and "light-headedness" ($F = 7.10$; $df = 14,1$; $P = 0.019$), which were reduced by dexamethasone, and on "happiness" ($F = 5.54$; $df = 14,1$; $P = 0.034$), which was increased by dexamethasone. There were no significant drug by time effects on these measures. There was a significant difference in the baseline VAS measure of depression (dexamethasone 3.6 ± 1.4; placebo 8.9 ± 3.1; $t = 2.4$; $df = 15,1$; $P = 0.028$) but no other significant differences in baseline between the two conditions (data not shown). Significant time effects occurred on VAS measures of dizziness ($F = 11.83$; $df = 56,4$; $P < 0.001$), drowsiness ($F = 3.59$; $df = 56,4$; $P = 0.027$), hunger ($F = 11.67$; $df = 56,4$; $P < 0.001$), light-headedness ($F = 6.99$; $df = 56,4$; $P < 0.001$) and nausea ($F = 11.45$; $df = 56,4$; $P < 0.001$). There were no significant order effects or interactions of order with other variables. There were no significant drug effects or drug by time interactions on POMS (Table 3). There were significant time effects on the vigor ($F = 5.80$; $df = 14,1$; $P = 0.030$), fatigue ($F = 5.50$; $df = 14,1$; $P = 0.034$) and tension ($F = 10.24$; $df = 14,1$; $P = 0.006$) subscales of the POMS. These significant time effects and those in VAS measures were as expected clinically.

Discussion

The main finding of the study is that pre-treatment with 5 mg dexamethasone had no significant effect on the GH response to infusion of L-TRP (Fig. 1). This finding has to be regarded with some caution, given the relatively small numbers and consequently large confidence intervals (Table 1). Baseline PRL levels were significantly reduced and there was a significant attenuation of the PRL response to L-TRP infusion following dexamethasone pre-treatment (Fig. 2). The AUC for PRL was not significantly reduced, which may have been due to the large variance in PRL responses. Baseline cortisol was significantly reduced, as was the cortisol response to L-TRP, by dexamethasone pre-treatment (Fig. 3A).

The GH response to L-TRP has been shown to be attenuated by the 5-HT_{1A} antagonist pindolol (Smith et al. 1991), but was not attenuated by the non-selective 5-HT antagonist metergoline (McCance et al. 1987). The explanation for this may lie in a relative lack of effective antagonism of 5-HT_{1A} receptors by metergoline that has been demonstrated in functional studies in animals (Koenig et al. 1987). There is further evidence that pindolol has β antagonistic properties in dynamic tests of noradrenergic function (Aellig 1976). Propranolol, a β antagonist which has a much

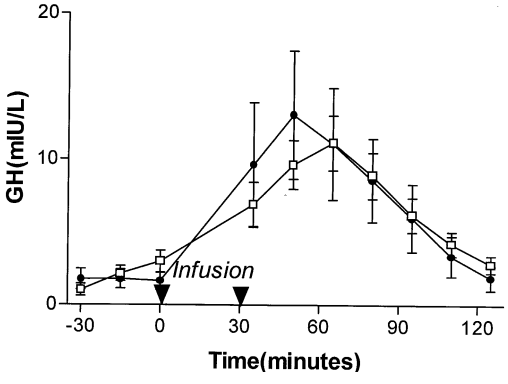

Fig. 1 Effect of pre-treatment with dexamethasone (□) or placebo (●) on GH response to IV infusion of L-TRP. GH levels (mIU/l) are plotted as mean ± SEM against time

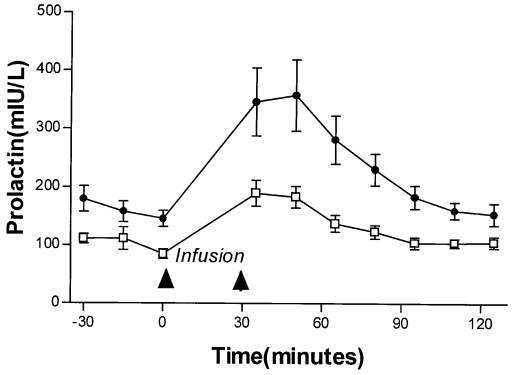

Fig. 2 Effect of pre-treatment with dexamethasone (□) or placebo (●) on PRL response to IV L-TRP. PRL levels (mIU/l) are plotted as mean ± SEM against time (see text for statistics)

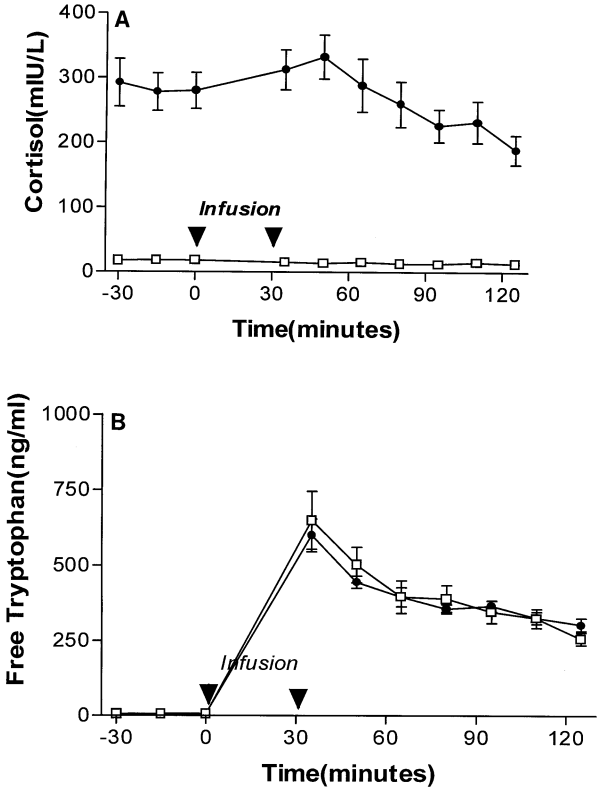

Fig. 3A,B Effect of pre-treatment with dexamethasone (□) or placebo (●) on: **A** plasma cortisol (mean ± SEM, nmol/l) response to L-TRP. **B** Plasma free TRP (mean ± SEM, ng/ml) following IV L-TRP

lower affinity for 5-HT_{1A} receptors than pindolol (Hoyer 1988), increases rather than decreases the GH response to L-TRP (Upadhyaya et al. 1990). This suggests that the effect of pindolol in inhibiting the GH response to L-TRP is not mediated via β adrenoceptor blockade, but probably involves 5-HT_{1A} receptor antagonism. These findings therefore support a role for post-synaptic 5-HT_{1A} receptors in the GH response to L-TRP.

In a previous study, we have shown a reduction in the GH response to L-TRP following pre-treatment with hydrocortisone 100 mg, (Porter et al. 1998), suggesting that in this paradigm hydrocortisone reduces 5-HT_{1A} function. Both the study of Traskman-Bendz et al. (1986) (using 1 mg dexamethasone) and the current study (using 5 mg dexamethasone, which is clinically equipotent to 100 mg hydrocortisone) have found no effect of dexamethasone on the GH response to L-TRP. This suggests that systemically administered dexamethasone does not have the same effect on post-synaptic 5-HT_{1A} function as hydrocortisone.

The differences in the effects of dexamethasone and hydrocortisone on L-TRP induced GH release may be explained by a number of differences between dexamethasone and cortisol. Firstly, dexamethasone has a much higher affinity for GRs than corticosterone, while for MRs these relative affinities are reversed (Caamano et al. 1994). There is considerable evidence from animal studies that 5-HT_{1A} function may be regulated differentially by MRs and GRs. MR activation appears to lead to tonic suppression of $5HT_{1A}$ function (Meijer and de Kloet 1995). When GRs are also activated, for instance at times of stress, $5HT_{1A}$ function is increased (Hesen and Joels 1996). Therefore steroids with different affinities for these receptors are expected to have different effects (see Meijer and de Kloet 1998 for review).

A second possible explanation for differences in effects between dexamethasone and hydrocortisone following systemic application is that relatively little dexamethasone crosses the blood-brain barrier, being actively pumped out by mdr 1A P-glycoprotein (Meijer et al. 1998). In rats, dexamethasone binding is found primarily in pituitary while hydrocortisone binding occurs widely, including hypothalamus and hippocampus (de Kloet et al. 1975). Miller et al. (1992) have investigated corticosteroid receptor effects of different doses of dexamethasone and found that while central MRs are tonically activated at low levels of corticosterone, even very high doses of dexamethasone failed to activate them.

A third theoretical reason for the differences between the results of our studies using hydrocortisone and dexamethasone may be differences in the direct effects of these steroids on GH secretion. At 12 h (approximately the same time scale as used in this study) a single dose of dexamethasone 8 mg orally suppresses growth hormone releasing hormone (GHRH)-induced GH release (Burguera et al. 1990), an effect thought to be mediated by an increase in inhibitory somatostatin tone. In the current study, we would therefore expect a reduced GH response as a result of this effect. The dose of dexamethasone used in this study is, however, slightly lower (5 mg versus 8 mg). We also note that there was an apparent rise in baseline GH prior to the infusion following dexamethasone pre-treatment. This does not fit with previous studies in which

oral administration of dexamethasone stimulated GH release between 3 and 5 h but not after this (see Thakore 1994 for review). No similar data is available regarding the effects on GH release of administration of hydrocortisone.

Fourthly, dexamethasone has a half life of 36–54 h (Organon, data sheet) while that of hydrocortisone is approximately 100 min (Merck Sharp and Dohme, data sheet). We previously postulated that with hydrocortisone pre-treatment the main effect was an increased and short-lived occupation of central GRs during the nocturnal trough of cortisol secretion (Porter et al. 1998). In the current study, the main effect may be a prolonged occupation of pituitary GRs leading to suppression of cortisol and a prolonged state of reduction in occupation of central MRs and GRs. This is the same effect centrally as would be seen following adrenalectomy. In animals, $5HT_{1A}$ hyperpolarisations (a measure of post-synaptic $5HT_{1A}$ function) are increased following adrenalectomy (Hesen and Joels 1996). Therefore, we might expect an increase in GH response in this study. The difference may lie in the fact that studies in adrenalectomised animals are done at least 2 days after the manipulation allowing time for a variety of adaptive changes to occur, while our study was done 11 h after first administering dexamethasone. It is also possible that at the relatively high dose of dexamethasone employed in this study, some dexamethasone entered the brain and resulted in GR activation without concurrent MR activation as has been previously shown in animals (Miller et al. 1992).

In this study, baseline PRL was significantly reduced by pre-treatment with dexamethasone 5 mg. In addition, there was a significant drug and drug by time interaction with a reduction in the PRL response to L-TRP infusion. This is different from the findings of Traskman-Bendz et al. (1986) who found no significant effect of 1 mg dexamethasone on baseline PRL and an increase in PRL response to L-TRP infusion. These differences may be related to differences in the dose of dexamethasone used in the two studies. At the dose used in this study, some central activation of GRs may have resulted which would perhaps be unlikely (see above) following pre-treatment with 1 mg as used by Traskman-Benz et al. (1986). The lack of an effect on baseline levels in the study, of Traskman-Benz is in contrast to previous consistent findings of a reduction in baseline prolactin levels after pre-treatment 10 h before with 1 mg dexamethasone in healthy volunteers (Meltzer et al. 1982; Rupprecht et al. 1987). The discrepancy may be because of the small numbers in the Traskman-Bendz et al. (1986) study ($n = 5$).

There is evidence that the PRL response to L-TRP infusion may have a dopaminergic component (van Praag et al. 1987). 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 by reducing brain tyramine. This is supported by evidence that an 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 to L-TRP may therefore be mediated in part by a reduction in dopamine synthesis, which releases PRL secretion from tonic inhibition by dopamine.

The effect of dexamethasone on baseline PRL may also occur via an effect on dopaminergic transmission. There is some evidence that in both animals (see Schatzberg et al. 1985 for review) and humans (Rothschild et al. 1984; Wolkowitz et al. 1985), dopaminergic transmission is increased by corticosteroids, in particular by dexamethasone. It has been suggested that this may be of relevance to the aetiology of psychotic depression (Schatzberg et al. 1985) in which there appears to be a particularly high incidence of HPA abnormalities (Nelson and Davis 1997). Further studies, however, have not always found a significant increase in free dopamine levels following administration of dexamethasone (Rupprecht et al. 1989; Lupien et al. 1995). Dexamethasone may also have a direct effect on the pituitary, decreasing PRL release (Naess et al. 1980). It has therefore been suggested that dexamethasone may have both a primary effect on the pituitary and a secondary effect on inhibitory dopaminergic activity, both of which lead to decreased PRL release (Lupien et al. 1995).

The attenuation of the PRL response may have been a consequence of an attenuation in post-synaptic $5HT_{1A}$ function. However, if this was the case then it would have been expected that an attenuated GH response would also have been seen. As this was not the case, we believe that other mechanisms are more likely, such as a direct effect of dexamethasone on PRL release from pituitary or effects on dopaminergic activity as described above.

In our previous study, using pre-treatment with hydrocortisone, there was a reduction in the prolactin response to L-TRP, but this was not significant. One reason for this may have been the large degree of variance in the prolactin responses (Porter et al. 1998). At present, there is no direct evidence that increased cortisol affects dopaminergic function.

We have shown a mild effect of dexamethasone on mood with a significant increase in VAS measures of "happiness" during the test and a reduction in VAS measures of "depression" at baseline. These results agree with previous observations of a euphoriant effect of exogenous corticosteroids (Murphy 1991a). This may be related to increased dopamine function, but the evidence for this is equivocal. Previous controlled studies in healthy volunteers have failed to find consistent effects of corticosteroids on mood. Wolkowitz

et al. (1990) examined the behavioural effects of prednisone 80 mg each morning for 5 days in healthy volunteers. VAS measures including those of "sadness" and "well-being" were used. The only consistent effects at any time point were on "sensory sharpness", which was rated as being higher during prednisone administration. Of interest, no significant increase in HVA levels was found. There is some evidence that a single dose (4 mg IV: Arana and Forbes 1991) or a short oral course (4 mg orally for 4 days: Arana et al. 1995) of dexamethasone may result in an early antidepressant effect in patients with major depression. It has been suggested that an increase in dopaminergic function may be responsible for early improvements in certain symptoms of depression, for instance following electroconvulsive therapy (Browning and Cowen 1986). However, there is evidence that the effects of dexamethasone on HVA levels in depressed subjects are much less even than in controls (Wolkowitz et al. 1987). Further research is required to elucidate the mechanism of action of dexamethasone, if it is confirmed as an effective antidepressant agent.

Previously, it has been suggested that the effects of cortisol on brain 5-HT may be mediated by reduction in plasma levels of the amino acid, L-TRP (Green and Curzon 1968). However, in this study, the effects of dexamethasone are unlikely to be due to an alteration of plasma levels of L-TRP, as these did not differ between the dexamethasone and placebo phases of the study. We did find a significant order effect and order by time effect on free and total TRP. Closer analysis revealed that in the placebo arm of the study, subjects who had previously received dexamethasone had a significantly higher rise in both free and total TRP, as measured by AUC, during the infusion than subjects who had received placebo first. This is contrary to what might have been expected given the evidence that dexamethasone can, in vivo, induce TRP metabolism by tryptophan 2,3-dioxygenase (Salter and Pogson 1985) and evidence that dexamethasone can reduce serum TRP levels in healthy subjects (Maes et al. 1990). However, the time scale of the effect in the current study is different and the effects of administration of a large dose of L-TRP complicate the situation.

This study demonstrates that dexamethasone has a different effect on the PRL and GH response to L-TRP from that of an equipotent dose of hydrocortisone administered in an identical paradigm. This may be because of different effects of these two steroids on serotonergic and dopaminergic function. The relative contribution of GR and MR activation in the attenuation of post-synaptic $5HT_{1A}$ function, seen with hydrocortisone administration, remains unclear. In addition, further work is needed to investigate the relationship between corticosteroid levels and $5HT_{1A}$ function in clinically depressed subjects.

References

Aellig WH (1976) Beta-adrenoceptor blocking activity and duration of action of pindolol and propranolol in healthy volunteers. Br J Clin Pharmacol 3:251–257

Arana GW, Forbes RA (1991) Dexamethasone for the treatment of depression: a preliminary report. J Clin Psychiatry 52:304–306

Arana GW, Santos AB, Laraia MT, McLeod-Bryant S, Beale MD, Rames LJ, Roberts JM, Dias JK, Molloy M (1995) Dexamethasone for the treatment of depression: a randomized, placebo-controlled, double-blind trial. Am J Psychiatry 152: 65–267

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

Browning SM, Cowen PJ (1986) Changes in mood, appetite and psychomotor retardation in depressed patients given ECT. Br J Psychiatry 149:371–373

Burguera B, Muruais C, Penalva A, Dieguez C, Casanueva FF (1990) Dual and selective actions of glucocorticoids upon basal and stimulated growth hormone release in man. Neuroendocrinology 51:51–58

Caamano CA, Morano MI, Watson SJ Jr, 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. Br Res Brain Res Rev 18:1–32

Checkley SA (1980) Neuroendocrine tests of monoamine function in man: a review of basic theory and its application to the study of depressive illness. Psychol Med 10:35–53

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

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

Deakin JFW, Graeff FG (1991) 5-HT and mechanisms of defence. J Psychopharmacol 5:305–315

Deakin JFW, 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

Dinan TG (1994) Glucocorticoids and the genesis of depressive illness. A psychobiological model. Br J Psychiatry 164:365–371

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 51:225–230

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

Hoyer D (1988) Functional correlates of serotonin $5\text{-}HT_1$ recognition sites. J Recept Res 8:59–81

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

Koenig JI, Gudelsky GA, Meltzer HY (1987) Stimulation of corticosterone and β-endorphin secretion in the rat by selective 5-HT receptor subtype activation. Eur J Pharmacol 137:1–8

Lupien S, Richter R, Risch S, Mirow A, Gillin J, Hauger R (1995) Time course of the corticosteroid-dopaminergic interaction during metyrapone and dexamethasone administration. Psychiatr Res 58:23–35

Maes M, Jacobs MP, Suy E, Minner B, Leclercq C, Christiaens F, Raus J (1990) Suppressant effects of dexamethasone on the availability of plasma L-tryptophan and tyrosine in healthy controls and in depressed patients. Acta Psychiatr Scand 81:19–23

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

McAllister-Williams RH, Ferrier IN, Young AH (1998) Mood and neuropsychological function in depression: the role of corticosteroids and serotonin. Psychol Med 28:573–584

McCance SL, Cowen PJ, Waller H, Grahame-Smith DG (1987) The effects of metergoline on endocrine responses to L-tryptophan. J Psychopharmacol 2:90–94

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 (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

Meijer OC, de Kloet ER (1998) Corticosterone and serotonergic neurotransmission in the hippocampus: functional implications of central corticosteroid receptor diversity. Crit Rev Neurobiol 12:1–20

Meijer OC, de Lange EC, Breimer DD, de Boer AG, Workel JO, de Kloet ER (1998) Penetration of dexamethasone into brain glucocorticoid targets is enhanced in mdr1 A P-glycoprotein knockout mice. Endocrinology 139:1789–1793

Meltzer HY, Fang VS, Tricou BJ, Robertson A, Piyaka K (1982) Effect of dexamethasone on plasma prolactin and cortisol levels in psychiatric patients. Am J Psychiatry 139:763–768

Miller AH, Spencer RL, Pulera M, Kang S, McEwen BS, Stein M (1992) Adrenal steroid receptor activation in rat brain and pituitary following dexamethasone: implications for the dexamethasone suppression test. Biol Psychiatry 32:850–869

Murphy BE (1991a) Steroids and depression. J Steroid Biochem Mol Biol 38:537–559

Murphy BE (1991b) Treatment of major depression with steroid suppressive drugs. J Steroid Biochem Mol Biol 39: 239–244

Naess O, Haug E, Gautvik K (1980) Effects of glucocorticosteroids on prolactin and growth hormone production and characterization of the intracellular hormone receptors in rat pituitary tumour cells. Acta Endocrinol 95:319–327

Nelson JC, Davis JM (1997) DST studies in psychotic depression: a meta analysis. Am J Psychiatry 154:1497–1503

Porter R, McAllister-Williams RH, Lunn B, Young A (1998) 5-Hydroxytryptamine receptor function in man is reduced by acute administration of hydrocortisone. Psychopharmacology 139:243–250

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, Goodman WK, Krystal JH, Woods SW, Heninger GR (1990) Clinical studies of 5-HT function using i.v. L-tryptophan. Prog Neuro-Psychopharmacol Biol Psychiatry 14:459–472

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. Am J Psychiatry 148:1518–1525

Rothschild AJ, Langlais PJ, Schatzberg AF, Walsh FX, Cole JO, Bird ED (1984) Dexamethasone increases plasma free dopamine in man. J Psychiatr Res 18:217–223

Rupprecht R, Barocka A, Jecht E, Noder M, Pichl J, Schwarz W (1987) Prolactin response to dexamethasone: a study on normal controls and depressed patients. Acta Psychiatr Scand 76: 139–143

Rupprecht R, Rupprecht M, Rupprecht C, Sofic E, Barocka A, Beck G, Noder M, Riederer P (1989) Effects of glucocorticoids on plasma catecholamines in depression. Psychiatr Res 29:187–198

Salter M, Pogson CI (1985) The role of tryptophan 2,3-dioxygenase in the hormonal control of tryptophan metabolism in isolated rat liver cells. Effects of glucocorticoids and experimental diabetes. Biochem J 229:499–504

Schatzberg AF, Rothschild AJ, Langlais PJ, Bird ED, Cole JO (1985) A corticosteroid/dopamine hypothesis for psychotic depression and related states. J Psychiatric Res 19:57–64

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 Sci 55:1083–1099

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

Upadhyaya AK, Deakin JF, Pennell I (1990) Hormonal response to L-tryptophan infusion: effect of propranolol. Psychoneuroendocrinology 15:309–312

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

Wolkowitz OM, Doran AR, Breier A, Roy A, Jimerson DC, Sutton ME, Golden RN, Paul SM, Pickar D (1987) The effects of dexamethasone on plasma homovanillic acid and 3-methoxy-4-hydroxyphenylglycol. Evidence for abnormal corticosteroid-catecholamine interactions in major depression. Arch Gen Psychiatry 44:782–789

Wolkowitz OM, Sutton ME, Doran AR, Labarca R, Roy A, Thomas JW, Pickar D, Paul SM (1985) Dexamethasone increases plasma HVA but not MHPG in normal humans. Psychiatry Res 16:101–109

Wolkowitz OM, Rubinow D, Doran AR, Breier A, Berrettini WH, Kling MA, Pickar D (1990) Prednisone effects on neurochemistry and behavior. Preliminary findings. Arch Gen Psychiatry 47:63–68

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

Young AH (1994) Glucocorticoids, serotonin and mood. Br J Psychiatry 165:271–272

Young AH, MacDonald LM, St John H, Dick H, Goodwin GM (1992) The effects of corticosterone on 5-HT receptor function in rodents. Neuropharmacology 31:433–4387