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Hypothalamic–Pituitary–Adrenal Axis Early-Feedback Responses are Preserved in Melancholic Depression: A Study of Sertraline Treatment

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Major depression with melancholia is associated with hypercortisolaemia. Loss of the early-phase of negative feedback — acute suppression of ACTH in response to rising cortisol levels — is the subject of conflicting reports in patients with major depression. Using a within-subjects design, six patients with DSM-IIIR melancholic depression received a 60 min infusion of hydrocortisone at 0900 with measurement of ACTH and cortisol before and after 4 weeks of antidepressant treatment. All patients responded clinically. ACTH responses (early feedback) did not differ between test conditions. Baseline cortisol fell significantly following treatment response. This provides further evidence for the preservation of the acute phase of negative feedback, even in the presence of hypercortisolism.

KEY WORDS — hypothalamic–pituitary–adrenal axis; negative feedback; depression; melancholia; sertraline

INTRODUCTION

There is considerable evidence for overactivity of the hypothalamic–pituitary–adrenal axis (HPA) axis in major depression, but more specifically, in the melancholic subtype (Kupfer, 1991). Plasma levels of cortisol are elevated (Gibbons and McHugh, 1963; Sachar *et al*., 1973; Halbreich *et al*., 1985; Rubin *et al*., 1987) as are 24 h urinary free cortisol (Carroll *et al*., 1976). In contrast to patients with Cushing's syndrome, however, there is relative preservation of the normal diurnal variation in cortisol production (Van Cauter and Turek, 1994). The adrenal glands are enlarged and this is seen on both computerised tomographic (CT) scanning (Amsterdam *et al*., 1987; Nemeroff *et al*., 1992) and on magnetic resonance imaging (MRI) (Rubin *et al*., 1995, 1996). Elevation of corticotropin-releasing hormone (CRH) in the cerebro-spinal fluid has been reported by Nemeroff *et al*. (1991), an alteration that was ameliorated by effective treatment with electro-convulsive therapy.

Cortisol levels are determined by a complex homeostatic mechanism — the closed loop of the HPA axis. The secretion of cortisol is driven by the circadian rhythm and stress responsiveness which are mediated principally via release of hypothalamic secretagogues CRH and arginine-vasopressin (AVP) (Grossman, 1994). Inhibition of the HPA axis occurs via negative feedback. The observed HPA overactivity in depression arises from either increased forward drive and/or decreased negative feedback.

Negative feedback in the HPA has a number of components (Jones and Gilham, 1988). The immediate or fast-feedback response occurs in response to the rate of rise of cortisol and is followed by the early- and late-delayed phases within 1–2 h and 24 h respectively (Jones and Gilham, 1988). There is good evidence for the existence of fast-feedback in rats (Jones *et al*., 1972; Young, 1995), but the demonstration of an immediate fall in ACTH levels in response to rising cortisol has not been demonstrated in man. The studies cited as evidence of the existence of this phenomenon in humans either do not sample sufficiently frequently

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(Reader *et al*., 1982; Carr *et al*., 1984) or they demonstrate a lag of at least 5–10 min (Won *et al*., 1986; Young *et al*., 1991), or they administer a bolus of hydrocortisone rather than an infusion (Raff *et al*., 1988; Goodwin *et al*., 1992). What these and other studies are testing are the early or intermediate (Kellner *et al*., 1995) feedback mechanisms — the term early feedback is more accurate.

The early phase of negative feedback was previously reported to be impaired in major depression (Young *et al*., 1991). In contrast, a replication study by Cooney and Dinan (1996a,b) did not find any difference in the early feedback (reported as 'fast-feedback' in both studies) responses between patients with major depression and controls. The principal difference in these studies was that Adrenocorticotropin (ACTH) was measured directly in the latter study, whereas β-endorphin/β-lipotropin ratio was used to infer ACTH level in the former. This ratio may be altered in depressive illness (Rupprecht *et al*., 1989; Morphy *et al*., 1993; Young *et al*., 1993). However, Cooney and Dinan (1996a,b) failed to find an abnormality in feedback, which may be related to the fact that many of their patients did not fulfil criteria for melancholia.

Patients with melancholic depression may differ from those with 'simple' major depression without melancholia, endocrinologically. If an abnormality of early-feedback exists, it is likely to be detected in this more homogeneous group by correction of the state dependant hypercortisolaemia. The aim of this study is to examine early-feedback responses in a group of melancholically depressed patients before and after effective antidepressant treatment.

METHODS AND MATERIALS

Six subjects with DSM-IIIR major depression with melancholia participated in this study. All gave written consent in accordance with the guidelines of the local ethics committee that granted approval for the study. There were four males and two females with a mean age of 35 years. Severity of depression was assessed using the 17-item HAMD (Hamilton, 1960) and the Beck Depression Inventory (BDI) (Beck *et al*., 1961). All subjects were physically healthy, non-obese and more of the females were using oral contraceptives. There was no history of endocrinopathy, peptic ulcer disease, asthma or irritable bowel disease. Four of the group were drug naive and all had been free of medication for at least 4 weeks prior to the first test.

All subjects studied were outpatients and agreed to attend on a weekly basis for review and to ensure compliance. Additionally, patients were encouraged to make contact earlier than their scheduled appointments if problems arose with side-effects. Antidepressant medication was started the morning after the initial hydrocortisone challenge. All were initially started on sertraline 50 mg per day. This was increased to 100 mg at one week. The medication was well tolerated after initial nausea in two of the subjects.

A within-subjects design was used; all subjects were tested on two separate occasions, 4 weeks apart. Females were studied in the follicular phase of their menstrual cycle. On each of the test days, subjects had fasted from midnight and had 22G cannulae inserted into forearm veins bilaterally by 0830 h. These were sealed with a rubber bung and kept patent using a heparin/saline solution. The volunteers remained recumbent for the duration of the testing period. Infusions of either hydrocortisone (Solu-Cortef, hydrocortisone as the sodium succinate, Upjohn, Crawley, UK) 5 μg/kg/min in 0·9 per cent normal saline were administered. The infusions were given over a 60 min period between 0900 and 1000 h using a metered syringe pump (IVAC P2000, Wellmed, Hampshire, UK). Blood samples were taken from the arm contralateral to the infusion at -15 min (0845), 0, $+15$, $+30$, $+45$, $+60$, $+90$. The first 1 ml of each sample was discarded and then 4 ml were taken in an EDTA containing tube and 4 ml in a plain tube without an anticoagulant. Blood was immediately centrifuged and stored at -70°C.

Plasma cortisol and $ACTH_{1-39}$ were analysed in batch blind to subject status. Cortisol was measured with an immunoradiometric assay (Dash *et al*., 1975) with a sensitivity of 3–5 nmol/l and inter- and intrassay precision of 1·5 per cent and 4·5 per cent, respectively. ACTH was measured using a commercially available IRMA (Raff and Findling, 1989) with a detection limit for plasma ACTH of $<0{\cdot}44$ pmol/l. The inter- and intrassay coefficients of variation were <5 per cent across the working range of the assay (0·44–308 pmol/l).

Basal cortisol and ACTH were calculated as the mean of -15 and 0 min samples. ΔACTH was calculated as the maximal difference between basal ACTH and ACTH response up to 120 min. Student's *t*-test was used to compare these means. One- and two-way repeated measures analysis of variance were used where appropriate. Data were analysed by means of Statgraphics, Version 7 (Statistical Corporation, 1993).

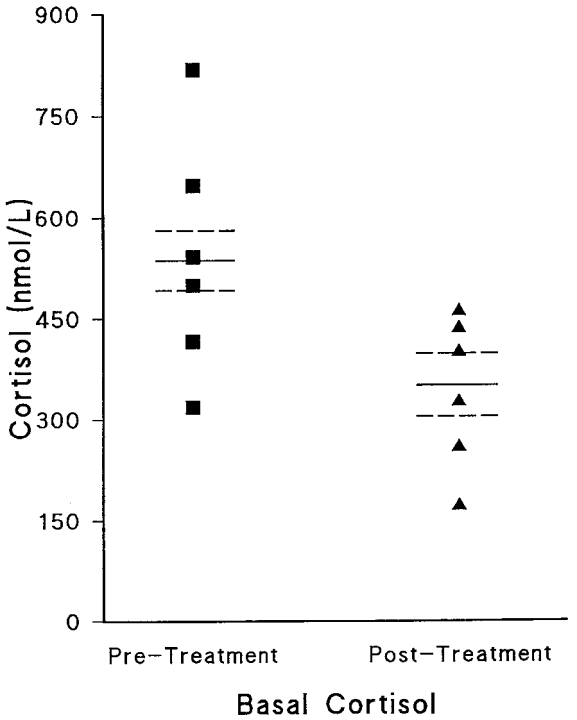

Figure 1. Basal cortisol levels with means (±SEM) before and after 4 weeks treatment with sertraline 100 mg daily ($n = 6$)

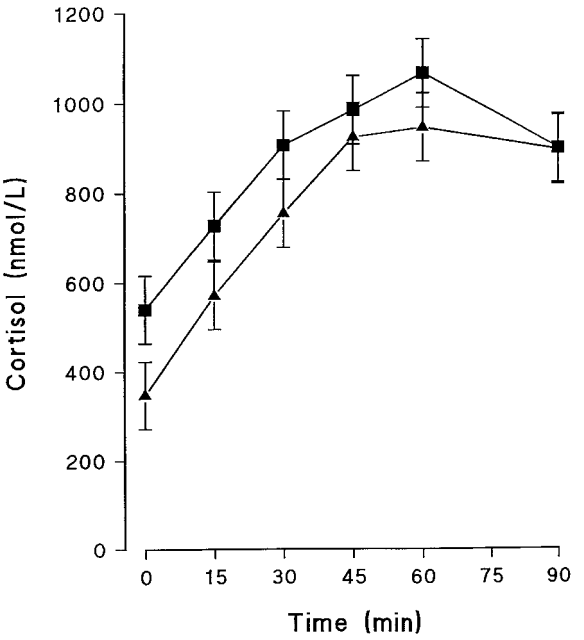

Figure 2. Cortisol levels (±SEM) before (■) and after treatment (▲) in melancholically depressed patients ($n = 6$) following infusion of hydrocortisone at 5 μ/kg/min

RESULTS

All subjects improved clinically in the severity of depressive symptoms. Mean HAMD (±SEM) score fell from 28·16 (±4·9) to 14·5 (±5·3) over 4 weeks ($t = 3{\cdot}9$, $df = 5$; $p = 0{\cdot}02$). Mean scores on the BDI also fell from 36·3±5 to 15·5±5·6 ($t = 6{\cdot}3$; $df = 10$; $p = 0{\cdot}0008$).

Mean basal cortisol levels before treatment (540±55 nmol/l) fell significantly after antidepressant treatment (347±65 nmol/l) ($t = 2{\cdot}25$; $df = 10$; $p = 0{\cdot}04$) (Figure 1). Mean basal ACTH levels before treatment (12·72±6·7 pmol/l) fell following treatment (6·30±5·1 pmol/l) and this approached statistical significance ($p = 0{\cdot}1$).

The infusion of hydrocortisone was well tolerated by all subjects. Δcortisol before treatment (549±151 nmol/l) did not differ significantly from Δcortisol after (726±229 nmol/l). ΔACTH was greater before (9·91±5·9 pmol/l) than after (4·64±4·4 pmol/l), but the difference does not reach statistical significance.

Two-way ANOVA was used to examine for group (before and after treatment) × time differences in cortisol ($F = 0{\cdot}39$; $df = 5,60$; $p = 0{\cdot}8$) (Figure 2) and ACTH responses ($F = 1{\cdot}05$; $df = 5,60$; $p = 0{\cdot}4$) (Figure 3), but failed to reveal any significant interactions.

Basal cortisol values correlated significantly with basal ACTH ($r = 0{\cdot}8$; $p = 0{\cdot}0007$) and ΔACTH ($r = 0{\cdot}8$; $p = 0{\cdot}0006$). Before treatment, the correlations with basal cortisol ($r = 0{\cdot}8$; $df = 5$; $p = 0{\cdot}04$) and ΔACTH ($r = 0{\cdot}8$; $df = 5$; $p = 0{\cdot}04$) were significant, but not after treatment ($p = 0{\cdot}1$ for both). Basal ACTH was highly significantly correlated with ΔACTH both before ($r = 0{\cdot}99$; $df = 5$; $p = 0{\cdot}0001$) and after treatment ΔACTH ($r = 0{\cdot}9$; $df = 5$; $p = 0{\cdot}00001$).

Scores on the HAMD and BDI correlated significantly after treatment with basal ACTH ($r = 0{\cdot}8$; $p = 0{\cdot}05$; $r = 0{\cdot}8$; $p = 0{\cdot}04$, respectively) and with ΔACTH for the HAMD ($r = 0{\cdot}8$; $p = 0{\cdot}03$), which was approaching statistical significance for the BDI ($p = 0{\cdot}06$). The change in HAMD (ΔHAMD) and BDI (ΔBDI) scores were not significantly related to the change in ΔACTH (ΔΔACTH) (Table 1).

DISCUSSION

Patients with melancholic-type major depression have intact early feedback responses. This is evident

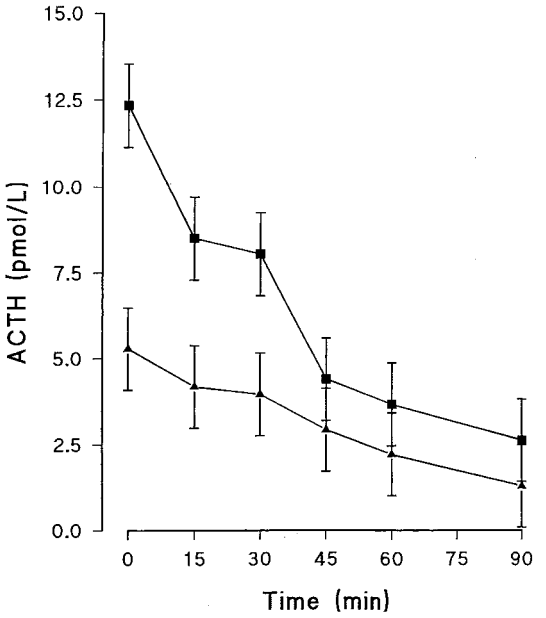

Figure 3. ACTH levels (±SEM) before (■) and after treatment (▲) in melancholically depressed patients ($n = 7$) over time following infusion of hydrocortisone at 5 μ/kg/min

from the near perfect correlation between basal ACTH and ÄACTH and the lack of significant difference between early feedback (ÄACTH) both before and after effective antidepressant treatment. The acute response to an elevation in serum cortisol is to inhibit further ACTH output proportionally, both while depressed and following clinical response to antidepressants. Clinical improvement was reflected by measurements in the HAMD and BDI scores. Basal cortisol was significantly lower after treatment and there was a trend for such a fall in basal ACTH values. Changes in basal cortisol and ACTH values were parallelled by improvements in HAMD and BDI.

A type II statistical error could explain the findings of an intact early feedback mechanism. Basal cortisol levels are higher pre-treatment in these patients with melancholic depression that is consistent with overactivity of the HPA axis in melancholically depressed subjects (Carroll *et al.*, 1981). The study was able to demonstrate a significant change in cortisol and a trend for the same in basal ACTH, suggesting that it had sufficient power to demonstrate an abnormality of HPA axis function. There was no significant change in early-feedback (ÄACTH) before and after treatment. However, there was a highly significant correlation between basal ACTH and ÄACTH (before and after), indicating that the acute homeostatic mechanism was intact.

In this group of melancholically depressed patients, there is hypercortisolaemia, despite an intact acute HPA mediated stress response. Following symptomatic improvement, there is a reduction in cortisol levels which parallels clinical improvement. Antidepressants upregulate both type I and type II steroid receptors (Holsboer and Barden, 1996). Previous work on the early-feedback response has demonstrated that it is a response mediated through the type II or glucocorticoid receptor (Cooney and Dinan, 1996a,b). This suggests that antidepressants reset HPA axis tone independently of early feedback, type II steroid receptor responses. Different mechanisms mediate acute and chronic responses of the type II receptor. Evidence for this observation is provided by the demonstration of inhibition of CRH-stimulated cAMP accumulation in late inhibition (Bilezikjian and Vale, 1983) and cAMP-induced activation of PKA (Shipston, 1995), neither of which changes occur in early feedback.

HPA axis activity is regulated by a complex interaction of forward drive and negative feedback. The early phase of negative feedback continues to function in patients with major depression with or without melancholia. Antidepressant treatment upregulates steroid receptors and results in a reduction of circulating cortisol, indicating that the mechanism mediating chronic stress responsivity may be implicated in the hupercortisolaemia of depression. This is consistent with animal data showing impaired chronic stress responsivity while retaining the ability to mount a response to acute stressors (Young, 1995).

The finding of intact early feedback, despite lowering of serum cortisol by treatment with sertraline, is further evidence for the preservation of this phase of negative feedback.

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