Abstract  Rationale: In depression, the growth hormone (GH) response to clonidine and L-tryptophan (L-TRP) is reduced, suggesting reduced alpha2-adrenergic and serotonin (5-HT)1A receptor function. Pretreatment with hydrocortisone (100 mg, orally 11 h before) also blunts the GH response to L-TRP. This effect may be mediated at the hypothalamic level via reduced 5-HT1A receptor function or at the pituitary level, either by a direct effect on somatotrope cells or via enhanced insulin-like growth factor-1 (IGF-1) or somatostatin (SS) release. Objectives: To examine the effects of acute and chronic exposure to hydrocortisone on baseline and stimulated GH release from the pituitary. Methods: Twelve healthy male volunteers received pretreatment with acute hydrocortisone (100 mg, 11 h before), chronic hydrocortisone (20 mg twice a day for 1 week) and placebo in a double blind, balanced order, crossover design. Serial measurements of plasma GH, IGF-1 and thyroid stimulating hormone (TSH) levels were made at baseline and following intravenous administration of 1 mcg/kg GHRH. Results: The GH response to growth hormone releasing hormone (GHRH) was significantly blunted by pretreatment with both acute and chronic hydrocortisone. Baseline IGF-1 levels were significantly lower at baseline after chronic hydrocortisone compared with placebo. Baseline TSH levels were significantly lower after acute hydrocortisone compared with placebo, suggesting an increase in somatostatin levels. Conclusions: These data suggest that hydrocortisone acts at the pituitary level to reduce GH release. The TSH and IGF-1 data support the hypothesis that hydrocortisone reduces GH release by enhancing somatostatin and IGF-1 release.

Key words  Somatotropin-releasing hormone · Somatotropin · Adrenal cortex hormone · 5-HT1A receptor · Hydrocortisone · Insulin-like growth factor-I

Introduction  Neuroendocrine tests of monoaminergic synaptic function measure the hormonal response to agents that exert an effect on monoamine receptors in the hypothalamus. Because of the practical difficulties involved in measuring hypothalamic output directly, pituitary hormones such as growth hormone (GH) and prolactin (PRL) are assayed as a proxy measure (Checkley 1980). GH release from anterior pituitary gland is influenced by the antagonistic actions of two hypothalamic hormones, growth hormone releasing hormone (GHRH) and somatostatin (SS), which are themselves regulated by a variety of neurotransmitter systems and which reach their receptors on the somatotropes via portal vessels. Responsiveness of somatotrophic cells is also reduced by insulin-like growth factor-1 (IGF-1) (Scanlon et al. 1996).

PRL is secreted from the anterior pituitary in a circadian pulsatile fashion with nocturnal elevation. Its release is inhibited powerfully by dopamine and regulated by a number of other substances, including thyrotropin releasing hormone (TRH), vasopressin, oxytocin and 5-HT (Nicholas et al. 1998). Neuroendocrine tests have been used extensively to study monoamine function in depression, a condition in which hypothalamo-pituitary-adrenal (HPA) axis abnormalities have been clearly demonstrated (Murphy 1991). The interaction between the HPA axis and the monoamine system may be of central importance in the pathophysiology of depression (Dinan 1994; McAllister-Williams and Young 1998). This interaction has been specifically examined in a number of neuroendocrine studies with GH and PRL as proxy measures of neurotransmitter function (Dolan and Calloway 1986; Price et al. 1991; Porter et al. 1998). These have suggested that high levels of circulating cortisol in both normal and depressed subjects act to reduce monoamine function. However, these results may also be subject to direct effects of corticosteroids on pituitary output.

In depression, studies of basal GH (Mendlewicz et al. 1985; Jarrett et al. 1990; Rubin et al. 1990), basal PRL
in depression induces a reduction in 5-HT1A function providing support for the theory that hypercortisolaemia hypothalamic 5-HT1A function by hydrocortisone, thus by the 5-HT1A antagonist pindolol and is therefore response to L-tryptophan (L-TRP) (Porter et al. 1998). In volunteers orally 11 h before testing, reduced the GH re-

1989). Studies using metyrapone to reduce cortisol levels in states of chronic hypocortisolaemia (Giustina et al. 1990) and no significant effect (Burguera et al. 1990). There are, however, a number of important differences between dexamethasone and the physiological corticosteroid, cortisol, in terms of its profile of receptor binding and its entry into the brain (Meijer et al. 1998). Thompson et al. (1995) demonstrated a reduction in GH release in response to GHRH in sheep 4 h after the commencement of a 5-h cortisol infusion. In humans, Franz and Rabkin (1964) demonstrated a reduced GH response to insulin-induced hypoglycaemia following pretreatment with hydrocortisone. GHRH-induced GH release is reduced in a dose-dependent manner by acute pretreatment with cortisone acetate (Giustina et al. 1990) and enhanced in states of chronic hypocortisolaemia (Giustina et al. 1989). Studies using metyrapone to reduce cortisol levels have shown both an enhanced response (Dinan et al. 1994) and no significant effect (Burguera et al. 1990). Corticosteroids influence prolactin release probably via enhancement of dopamine transmission (Schatzberg et al. 1985).

In a previous study, we demonstrated that pretreatment with 100 mg hydrocortisone given to normal volunteers orally 11 h before testing, reduced the GH response to L-tryptophan (L-TRP) (Porter et al. 1998). In normal volunteers, the GH response to L-TRP is blunted by the 5-HT1A antagonist pindolol and is therefore thought to be an indicator of 5-HT1A function (Smith et al. 1991). The mechanism of this may be a reduction of hypothalamic 5-HT1A function by hydrocortisone, thus providing support for the theory that hypercortisolaemia in depression induces a reduction in 5-HT1A function (Deakin 1991). However, an alternative mechanism explaining these results is a direct effect of hydrocortisone on GH release at the pituitary level, either directly or via enhancement of feedback mechanisms (Kendler and Davis 1977). In order to elucidate this, we investigated the effect of hydrocortisone on the GH response to GHRH in healthy volunteers. We administered GHRH at a dose of 1 mcg/kg, which is sufficient to produce a maximal GH response (Gelato et al. 1984). With respect to the hydrocortisone, we utilised the acute dosage schedule used by Porter et al. (1998) and the chronic schedule used by Young et al. (1994) in a study of the neuroendocrine response to the 5-HT1A agonist buspirone. The acute schedule increases cortisol levels during the normal nocturnal nadir, providing a short-term model of the situation found in depression. The chronic schedule mimics the cortisol hypersecretion and loss of the normal diurnal rhythm, which is seen in depression. Our null hypothesis was that neither schedule would affect baseline GH, PRL or GHRH-stimulated GH release, demonstrating that the effects of corticosteroids in neuroendocrine tests are truly secondary to alterations in hypothalamic monoamine function.

Materials and methods

Subjects and experimental design

Twelve healthy male volunteers, aged 21–32 years (mean 27.1, SD 3.8) with BMI between 20.1 and 24.7 (mean 22.7, SD 1.6), who had been on no medication for at least 2 months and had not recently lost weight, gave their informed consent prior to the study, which was approved by the local Ethical Committee. They were screened for past or current psychiatric disorder by an experienced psychiatrist (S. W.). Subjects were tested on three occasions at least 1 month apart, having taken pretreatment medication. This consisted of (1) placebo twice daily for 1 week (placebo), (2) placebo twice daily for a week with a final dose of hydrocortisone 100 mg at 11 p.m. on the evening before testing, 11 h before testing (acute hydrocortisone) and (3) hydrocortisone 20 mg twice a day for 1 week with the final dose at 11 p.m. on the evening before testing, 11 h before testing (chronic hydrocortisone).

These treatments were 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 sited. This was kept patent with heparinised saline. Subjects fasted throughout the experiment, remained semi-supine and did not sleep. After 1 h, an intravenous bolus of GHRH (1 µg/kg) was given. Blood samples were taken every 15 min from 30 min before the injection (–30 min, –15 min and time 0) and every 15 min until 120 min after completion of the infusion (+15 min, +30 min etc.).

Biochemical measures

Blood samples were taken into EDTA tubes and centrifuged to remove plasma which was stored at –20°C. Samples were analysed for growth hormone, cortisol, prolactin and thyroid stimulating hormone (TSH) by standard radio-immunoassay. IGF-1 was measured by immunoassay, using the Nichols Advantage System from the Nichols Institute, California. Inter- and intra-assay coefficients of variability for GH were 7.25% and 6.53%, respectively, for cortisol 6.6% and 6.8%, for prolactin 4.26% and 6.18%, TSH 6.13% and 10.04% and for IGF-1 6.81% and 6.18%.

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 hormonal data was analysed using a two-way repeated measures analysis of variance (ANOVA) with pretreatment (chronic hydrocortisone, acute hydrocortisone or placebo) and time as the main variables. The P values of all ANOVAs used the Huynh-Feldt correction factor when the sphericity assumption was not met. For clarity, uncorrected degrees of freedom are reported.