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

The effects of sub-chronic administration of hydrocortisone on hormonal and psychological responses to L-tryptophan in normal male volunteers

Received: 14 December 2001 / Accepted: 4 March 2002 / Published online: 10 July 2002 © Springer-Verlag 2002

Abstract Rationale: 5-Hydroxytryptamine₁A (5-HT₁A) receptor function has been shown to be attenuated 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 depressive illness in humans, a condition in which 5-HT₁A receptor function is reduced and corticosteroid hormone levels are elevated. Evidence suggests that the hormonal response to L-tryptophan (L-TRP) is mediated by 5-HT₁A receptors. This response has been shown to be reduced following acute administration of hydrocortisone, and we hypothesised that sub-chronic administration of hydrocortisone would also blunt it. Objectives: To examine the effects of sub-chronic administration of hydrocortisone on hormonal and psychological responses to L-TRP infusion in healthy male subjects. To ascertain whether cortisol was exerting effects on prolactin release directly at the pituitary rather than via hypothalamic 5-HT₁A receptors, a thyroid-releasing hormone (TRH) challenge test was performed. Methods: Fourteen healthy male volunteers took part in a random-order, double-blind, placebo-controlled study, in which 20 mg hydrocortisone or placebo was administered twice daily for 7 days before infusion of L-TRP. A TRH challenge was administered to eight of the subjects following the L-TRP infusion. Results: Pre-treatment with hydrocortisone significantly reduced the growth hormone (GH) and cortisol responses, but not the prolactin (PRL) response to the infusion. TRH administration caused a robust increase in PRL, but this response was not attenuated by hydrocortisone pre-treatment. The TSH response to TRH was blunted. There was no effect of pre-treatment on psychological responses to L-TRP. Conclusions: The attenuation in GH response following hydrocortisone pre-treatment could indicate a reduction in 5-HT₁A receptor function, although it is probable that it is attributable to the action of hydrocortisone at the pituitary level. More precise, non-neuroendocrine models of 5-HT₁A receptor function are necessary to clarify this.

Keywords L-Tryptophan · Hydrocortisone · Serotonin · Cortisol · Growth hormone · Prolactin · Human volunteers

Introduction

Dysfunction of brain serotonin (5-hydroxytryptamine, 5-HT) systems may be central to the pathophysiology of many psychiatric disorders, with the role of the 5-HT₁A receptor being of particular interest. Deakin and Graeff (1991) have hypothesised that adaptive behaviour in the face of aversive stimuli is maintained by 5-HT neurones which project from the raphe onto post-synaptic 5-HT₁A receptors in the hippocampus. It has been suggested that a failure of this system leads to learned helplessness in animals and depression in humans.

In humans, intravenous infusion of the 5-HT precursor L-tryptophan (L-TRP) causes a robust increase in growth hormone (GH) and prolactin (PRL) from the anterior pituitary (Cowen et al. 1990). These responses are blocked by the 5-HT₁A antagonist pindolol (Smith et al. 1991) and by the non-selective 5-HT antagonist metergoline (McCance et al. 1987), but not by the 5-HT₂C antagonist ritanserin (Chargié et al. 1987) or the selective 5-HT₁A antagonist BRL 43694 (Anderson et al. 1988). This suggests that the GH and PRL responses to L-TRP are mediated by the 5-HT₁A receptor (Cowen et al. 1990; Cleare and Bond 2000). Five of six previous studies have demonstrated that one or both of these neuroendocrine responses to infusion with L-TRP is blunted in patients with depressive disorder (Heninger et al. 1984; Koyama and Meltzer 1986; Cowen and Chargié 1987; Deakin et al. 1990; Price et al. 1991), although no attenuation is
observed in the absence of hypercortisolaemia (Porter et al. 2001).

Abnormalities of the hypothalamic–pituitary–adrenal (HPA) axis are also well documented in depressive illness (Holboer 1995), and it has been suggested that serotonergic dysfunction may be secondary to glucocorticoid hypersecretion (Dinan 1994; Pitchot et al. 2001). Previous studies have investigated the relationship between hypercortisolaemia and 5-HT function by examining the effects of administration of glucocorticoids to healthy volunteers. Sub-chronic administration of hydrocortisone (20 mg twice daily for 7 days) gives rise to corticosteroid levels similar to those found in patients with severe depressive illness, providing a useful model of basal HPA axis dysfunction (Young et al. 1999). It has been demonstrated that pre-treatment with this regime attenuates the hypothalamic effects of the 5-HT₁₆ partial agonist buspirone, which may indicate a decreased sensitivity of 5-HT₁₆ autoreceptors in raphé nuclei (Young et al. 1994). It has also been shown that the buspirone-induced PRL response is highly correlated with endogenous cortisol in healthy volunteers (Dinan et al. 2001), but that sub-chronic hydrocortisone treatment does not blunt the PRL or GH response to buspirone (Young et al. 1994). There are however problems inherent in the use of buspirone as a neuroendocrine challenge agent, in part because buspirone also acts as a dopamine D₂ receptor antagonist (Gregory et al. 1990; Meltzer et al. 1992) and has a pharmacologically active metabolite 1-pyrimidinylpiperazine (1-PP) (Mahmood and Sahajwalla 1999).

Using the 5-HT releaser d-fenfluramine (d-FEN), Young et al. (1998) found no attenuation in d-FEN-induced PRL release following hydrocortisone pre-treatment for 10 days relative to placebo. However, following acute pre-treatment with hydrocortisone, Dinan and Scott (1996) found the prolactin response to be attenuated, while pre-treatment with metyrapone, a cortisol synthesis inhibitor, enhanced the response. The prolactin response to d-FEN depends on the 5-HT-releasing properties of d-FEN and is mediated by post-synaptic 5-HT₂₃ receptors (Goodall et al. 1993; Park and Cowen 1995). Therefore, this test is a measure of general 5-HT function and of the integrity of receptors other than the 5-HT₁₆ receptor. Recent studies in healthy volunteers have shown that the PRL response to intravenous l-TRP is blunted by pre-treatment with dexamethasone (Porter et al. 1999) and the GH response is blunted by acute administration of hydrocortisone (Porter et al. 1998).

In this study, we further examined the interaction of the HPA axis with the 5-HT₁₆ system by examining the effects of sub-chronic pre-treatment with hydrocortisone on the hormonal responses to l-TRP infusion. The mechanism of glucocorticoid-induced blunted hormonal responses to serotonergic challenge may occur via a direct action on hypothalamic 5-HT₁₆ receptors or, alternatively, downstream by a 5-HT-independent effect at the level of the pituitary (Watson et al. 2000). To investigate the role of the pituitary in the regulation of PRL secretion in this context, we subsequently administered a thyroid-releasing hormone (TRH) challenge. TRH stimulates PRL release through direct action on pituitary lactotrophs (Anderson et al. 1992). We predicted that sub-chronic pre-treatment with hydrocortisone would blunt 5-HT₁₆-mediated GH and PRL release.

Materials and methods

Subjects and experimental design

Fourteen healthy male volunteers, aged 19–28 years (mean±SD 21.6±2.5 years), 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, verified by non-structured clinical interview and examination, and had been on no medication for at least 2 months.

Subjects were tested on two occasions, having taken pre-treatment medication at 0800 hours and 2000 hours during the 7 days prior to the testing session. A minimum 2-week washout period was left between phases of the study. Pre-treatment medication consisted of either placebo or hydrocortisone (20 mg orally, twice daily), 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 then every 15 min from +5 min until +95 min after completion of the infusion (+5 min, +20 min, etc.).

At +95 min, a standard TRH challenge test was administered. TRH (200 µg: Protirelin, Cambridge Laboratories, UK) was administered as a single bolus injection. Blood samples continued to be taken at 15-min intervals until +185 min. Immediately before infusion and at times +5, +35, +65 and +95 min, subjects rated their mood using 100-mm visual analogue scales. These scales measured depression, dizziness, drowsiness, happiness, hunger, light-headedness and nausea.

Biochemical measures

Blood samples were taken into tubes containing ethylene diamine tetracetic acid (EDTA) and centrifuged to remove plasma. This was stored at −20°C. Plasma was also ultra-filtered and stored until assay. Samples were analysed for PRL, GH and cortisol using standard radioimmunoassays. Free and total TRP were measured using high-performance liquid chromatography (Marshall et al. 1987). Respective inter- and intra-assay coefficients of variation for PRL were 7.9% and 4.8%, for GH 10.8% and 13.4%, for cortisol 10.4% and 6.7%, for free TRP 3.4% and 4.4% and for total TRP 3.3% and 4.4%. TSH was measured using standard radioimmunoassay, with an inter- and intra-assay coefficient of variation of 11.7% and 9.6%, respectively.

Statistical analysis

Baseline levels were calculated from the average of the three pre-infusion samples and were analysed using one-way, repeated-measures analysis of variance (ANOVA). Biochemical and hormonal responses were analysed using a three-way, repeated-measures ANOVA, with treatment (hydrocortisone or placebo) and time as within-subject variables and order as a between-subject variable. Where the assumption of sphericity was violated, within-subject degrees of freedom were corrected using the Huynh-Feldt correction and the adjusted F values reported. For clarity,