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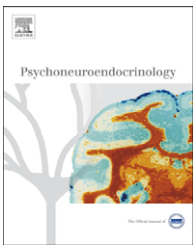

The acute effects of a mineralocorticoid receptor (MR) agonist on nocturnal hypothalamic–adrenal–pituitary (HPA) axis activity in healthy controls

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KEYWORDS
Mineralocorticoid receptor;
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HPA axis;
Insomnia;
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Summary
Introduction: Both glucocorticoid and mineralocorticoid receptors (GRs and MRs) help modulate cortisol feedback on the hypothalamic–adrenal–pituitary (HPA) axis. In brain, MRs inhibit the HPA axis and are thought to be fully occupied. Thus, prior studies of the effects of an MR agonist on HPA axis activity have first used metyrapone to inhibit cortisol production and to consequently deplete the receptors. Herein, we propose that an MR agonist may inhibit the HPA axis without first "unloading" receptors of endogenous cortisol.
Methods: Healthy subjects were admitted to the General Clinical Research Center. Blood was sampled for cortisol and adrenocorticotropic hormone (ACTH) from 16:00 to 24:00 h, when greatest MR activity is expected, on two consecutive nights. The first night established a baseline and the second night established response. On the second afternoon, all subjects were given 0.5 mg fludrocortisone. Mean cortisol and ACTH were computed from 16:00 to 24:00 h.
Results: Fludrocortisone acutely decreased mean cortisol ($p = 0.003$; effect size (ES) 1.65) and mean ACTH ($p = 0.000$, ES 4.46). Additionally, post hoc analysis showed that fludrocortisone tended to decrease the cortisol/ACTH ratio ($p = 0.0686$, ES 0.92) across the same time period.
Conclusions: Fludrocortisone significantly inhibits nocturnal HPA axis activity without first depleting MR receptors with metyrapone. This suggests that brain MRs are not fully occupied by endogenous cortisol and can be further activated by an agonist. The decrease in cortisol/ACTH ratio suggests a possible role on adrenal sensitivity as well. The ability to

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lower nocturnal HPA axis activity has interesting implications in disorders of HPA axis excess, such as insomnia, depression and healthy aging.

1. Introduction

Various forms of nocturnal hypothalamic–adrenal–pituitary (HPA) axis hyperactivity are associated with conditions such as chronic insomnia (Rodenbeck and Hajak, 2001; Vgontzas et al., 2001; Buckley and Schatzberg, 2005b), depression and healthy aging (Born and Fehm, 1998). In insomnia, HPA axis hyperactivity has been reported. In depression, cortisol amplitude is lowered and the magnitude at the nadir appears to depend on the sub-type of depression studied (Posener et al., 2000). In healthy aging, cortisol rhythm is similarly decreased in amplitude; its magnitude at nadir is elevated (van Coevorden et al., 1991; Ferrari et al., 1995, 1996; Van Cauter et al., 1996; Deuschle et al., 1997; Born and Fehm, 1998).

Hypothalamic–adrenal–pituitary axis control includes release of corticotropin releasing hormone (CRH) from the hypothalamus, adrenocorticotropic hormone (ACTH) from the pituitary gland and cortisol from the adrenal cortex (Figure 1). In turn, cortisol feeds back on the hypothalamus and pituitary to control release of ACTH and cortisol. Two key receptors effecting this feedback are mineralocorticoid and glucocorticoid receptors (MRs and GRs).

In addition to feedback of cortisol on CRH and ACTH at the level of the pituitary and hypothalamus, additional pathways act on the hypothalamus to modify CRH output. For example, via the hippocampus and the bed nucleus of the stria terminalis activation of MR in the hippocampus inhibits the HPA axis. In contrast to its negative feedback function at the hypothalamus and pituitary, GR stimulation at the level of the amygdala leads to enhanced CRH and HPA axis activity (Reul and Holsboer, 2002).

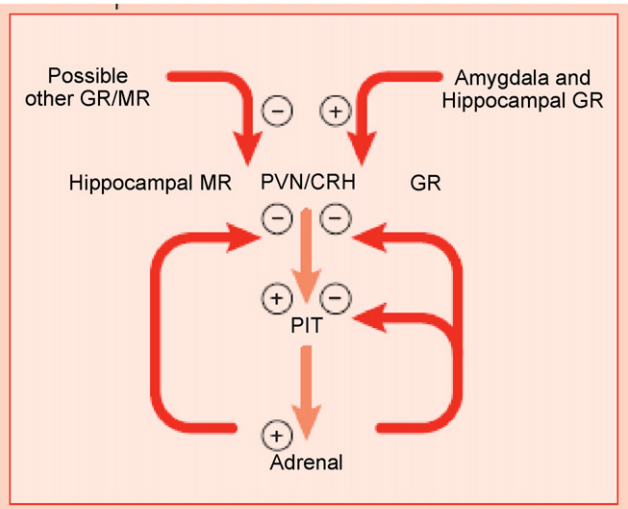

Figure 1 HPA axis feedback relationships (figure used with permission from Buckley, T., 2006. Hippocampal mineralocorticoid receptors in healthy aging and depression: overlapping cortisol circadian rhythm, sleep, and memory change. Depression: Mind and Body 2 (2), 47).

In brain, endogenous cortisol is a key activator of both MR and GR receptors. Cortisol has a much higher affinity for MRs than it does for GRs such that MRs fill preferentially before GRs (Reul and de Kloet, 1985). Mineralocorticoid receptor activity is greatest at the nocturnal nadir (Spencer et al., 1998) and plays an important role in decreasing the nocturnal level of cortisol. It is a commonly held belief that in the brain, MRs are almost completely occupied by endogenous cortisol before GRs fill. In this context, in two recent studies of healthy and aged subjects (Otte et al., 2003b), metyrapone was used to first reduce endogenous cortisol and "unload" mineralocorticoid and GRs before the MR agonist fludrocortisone was administered. Cortisol and ACTH levels at the nocturnal nadir were subsequently decreased by the MR agonist.

The ability of an MR agonist, alone, to additionally activate MR (above and beyond that from endogenous brain cortisol) and inhibit nocturnal HPA axis activity in man has not been reported to the best of our knowledge. Recent research in rat indicates that brain MR may not be fully occupied (Kalman and Spencer, 2002). Thus, we expect an additional biologic response with further MR occupancy. Herein, the MR agonist fludrocortisone was given without first depleting MRs and GRs with metyrapone. Its effect on nocturnal HPA axis activity was measured. We predicted that an MR agonist would decrease nocturnal HPA axis activity and that this would manifest in terms of decreased cortisol and ACTH (Buckley and Schatzberg, 2005a). Preliminary results are presented.

2. Methods

2.1. Subjects

Nine healthy subjects were recruited from the community via flyers and internet postings. Subjects responding to ads were phone screened to determine if they met the eligibility criteria. Those subjects meeting criteria underwent a physical examination, screening labs (complete blood count, comprehensive metabolic panel, urine analysis, urine toxicology screen, TSH, FT4, serum pregnancy test) and an EKG. A SCID was performed to rule out Axis I and Axis II DSMIV-TR pathology.

This analysis is a sub-study from a larger 5-year NIH parent study which will ultimately recruit 25 healthy controls, 25 subjects with depression and 50 subjects with psychotic major depression. The larger NIH study was designed for a different purpose; to evaluate secondary, longitudinal effects of another medication on MR activity. In the parent