



# Acute and chronic stress increase DHEAS concentrations in rhesus monkeys

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Received 22 March 2009; received in revised form 13 January 2010; accepted 14 January 2010

## KEYWORDS

Hypothalamic–pituitary–adrenal (HPA) axis;  
Dehydroepiandrosterone sulfate;  
DHEAS;  
Cortisol;  
Stress;  
Rhesus monkey;  
Dexamethasone

**Summary** Most studies on the stress-responsiveness of the hypothalamic–pituitary–adrenal (HPA) axis have focused on glucocorticoids, while few studies have investigated the adrenal secretion of dehydroepiandrosterone sulfate (DHEAS), which is unique to primates. Monkeys were chair-restrained for 2 h per day for seven consecutive days, and blood samples were collected upon placement in the chair, and at 15, 30, 60 and 120 min later. Like cortisol, DHEAS concentrations increased throughout the initial session of chair restraint (acute stress). Unlike the cortisol response, which decreased after repeated exposure to the stressor, the DHEAS response was sustained throughout the seventh session of restraint (chronic stress) and response to the seventh session of restraint did not differ from the DHEAS response to the initial session. Like cortisol, DHEAS concentrations showed a diurnal rhythm with higher concentrations in the morning compared to the evening and a decrease in response to dexamethasone (DEX) administration. After repeated exposure to the stressor, the suppression of DHEAS in response to dexamethasone was more complete, suggesting an increase in negative feedback sensitivity. These data show that DHEAS concentrations increase in response to both acute and chronic (repeated) stress and provide another measure of HPA activity that parallels cortisol during acute responses to stress but diverges in chronic or repeated stress.

Published by Elsevier Ltd.

## 1. Introduction

While most studies on the stress-responsiveness of the hypothalamic–pituitary–adrenal (HPA) axis have focused

on adrenal secretion of glucocorticoids, little research has been done on the secretion of the adrenal androgen dehydroepiandrosterone (DHEA) and its more stable sulfate ester DHEA-sulfate (DHEAS). In part, this is because androgen secretion by the adrenal cortex is restricted to primate (human and non-human) species due to a unique three-layered cortex. While both primates and rodents (rats and mice) have a zona glomerulosa layer that secretes mineralocorticoids (e.g., aldosterone) and a zona fasciculata layer that secretes glucocorticoids (e.g., cortisol), only primates

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have a zona reticularis layer that expresses cytochrome P450c17 (the enzyme responsible for the synthesis of DHEA from pregnenolone) and secretes DHEA and DHEAS (Conley et al., 2004; Nguyen and Conley, 2008). DHEAS is the major secretory steroid of the adrenal gland (Vaitukaitis et al., 1969) and the most abundant steroid hormone in the human body (Orentreich et al., 1984). Despite high circulating concentrations, DHEAS' mechanisms of action are not completely understood as no unique steroid hormone receptor for DHEAS (or DHEA) has been found (Rehman and Carr, 2004; Maninger et al., 2009). We do know that DHEA and DHEAS (jointly referred to in this article as "DHEA(S)") have neuroprotective actions, and are precursors to more potent androgens and estrogens, such as testosterone and estradiol (Kurata et al., 2004; Labrie, 2004; Maninger et al., 2009). Exogenous administration of DHEA (which gets converted to DHEAS *in vivo*) has been found to improve symptoms of depression in patients with major depression, as well as improve negative symptoms in patients with schizophrenia (Wolkowitz et al., 1999; Strous et al., 2007; Wolkowitz et al., 2008; Maninger et al., 2009).

Like humans, rhesus macaque monkeys show an increase in plasma DHEAS in response to corticotropin releasing hormone (CRH) administration (Goncharova and Lapin, 2002). Cortisol and DHEAS are secreted from the adrenal cortex in response to corticotropin (ACTH) stimulation in both humans (Nieschlag et al., 1973) and rhesus monkeys (Koritnik et al., 1983). Therefore, given the similar mechanism of secretion, it is reasonable to predict that both hormones would increase in response to a stressor. A concomitant increase in serum DHEAS and salivary cortisol concentrations has been demonstrated in military personnel experiencing the stressors associated with mock prisoner of war camp, including food and sleep deprivation (Morgan et al., 2004). In a study of hormonal response to blood sampling procedures in animals' individual home cages (with squeeze mechanisms), female rhesus monkeys showed an increase in serum cortisol and DHEAS concentrations over time (Fuller et al., 1984). In this study, animals were restrained for 2–4 min with the squeeze mechanism of their cages and bled at 30-min intervals for 2 h. Although serum concentrations of both hormones increased after animals were restrained, cortisol concentrations were significantly elevated from baseline at 30 min while DHEAS concentrations were significantly increased from baseline at 90 min (Fuller et al., 1984). While these results suggest similar regulation in healthy individuals (i.e., both cortisol and DHEAS concentrations increase in response to a stressor), the difference in time course suggests a more complex picture; in fact, other data also indicate differences in the regulation of these two adrenal steroids.

Under conditions of chronic medical illness, levels of DHEA(S) and cortisol have been observed to become dissociated (Parker et al., 1985); for example, cortisol concentrations either increase or do not change, and DHEAS concentrations tend to decrease (Semple et al., 1987; Wade et al., 1988). This has also been observed in people with acquired immunodeficiency syndrome (AIDS) (Villette et al., 1990), rheumatoid arthritis (Masi et al., 2006), type 2 diabetes mellitus (Yamauchi et al., 1996), and other medical illnesses (for a review, see Kroborth et al., 1999). Although these "conditions" are sometimes referred to in the literature as "chronic stress" – these refer to the chronic stress of

medical illness and not other types of psychological chronic stress, such as unemployment, which are not associated with a disease process. The "imbalance" of levels of cortisol and DHEA(S) in medical illness is thought to be important since the actions of cortisol and DHEA(S) can be antagonistic. For example, while cortisol is a catabolic hormone, DHEA(S) is a precursor to more potent anabolic steroids, such as testosterone (Labrie, 2004). DHEA has also been described as having anti-glucocorticoid properties because it buffers or antagonizes the effects of cortisol (Kalimi et al., 1994; Hennebold et al., 1995; Maninger et al., 2009). Because of these properties, DHEA(S) has been proposed to play a role in modulating the vulnerability of an organism to the negative consequences of stress (Charney, 2004; Morgan et al., 2004).

To our knowledge, no study has examined the DHEAS response to an acute novel stressor and to repeated exposure to the same stressor (laboratory model of chronic stress). Rhesus monkeys are an ideal animal model to examine this question. In addition to the advantage of increased experimental control (compared to human participants), rhesus monkeys are similar to humans in their zona reticularis zone of the adrenal cortex, which mice and rats do not have (Conley et al., 2004; Nguyen and Conley, 2008). Like humans, rhesus monkeys show a decrease in DHEAS concentrations in response to the synthetic glucocorticoid dexamethasone (Wickings and Nieschlag, 1978; Koritnik et al., 1983), presumably due to its negative feedback effect on pituitary secretion of ACTH, which in turn suppresses adrenal output of both cortisol and DHEAS. While ACTH administration following dexamethasone (DEX) suppression results in an increase in DHEAS concentrations in rhesus monkeys (Koritnik et al., 1983), administration of human chorionic gonadotropin (hCG) following DEX suppression does not (Wickings and Nieschlag, 1978). This evidence, along with the localization of DHEA sulfotransferase (DST, the enzyme that sulfonates DHEA) to the zona reticularis layer of the adrenal cortex but not the ovary or testis in rhesus monkeys (Parker et al., 2000), suggests that DHEAS is primarily of adrenal origin in rhesus monkeys. Because DHEA can be secreted by both the testis and the adrenal gland (Wickings and Nieschlag, 1978) and we are interested in HPA activity, this study focuses on DHEAS.

In order to better understand the stress responsive nature of DHEAS, the current investigation takes advantage of banked blood samples from a previous study in our laboratory that examined changes in plasma glucocorticoid levels and behavior in adult male rhesus monkeys exposed to repeated physical restraint (Ruys et al., 2004). The animals were restrained in primate chairs for 2 h each day for seven consecutive days, and blood samples were collected at regular intervals during each 2-h chairing session. Animals showed a sustained increase in cortisol concentrations throughout their first consecutive session of chair restraint, but the cortisol response to the seventh session of restraint was substantially reduced (Ruys et al., 2004). Chair restraint sessions in which DEX was administered prior to restraint revealed that animals had an increase in glucocorticoid negative feedback sensitivity after 7 days of consecutive chair restraint (Ruys et al., 2004). Morning basal cortisol concentrations on the day after the initial session of restraint were increased in comparison to pre-restraint samples. After

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