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# Neuroendocrine aspects of hypercortisolism in major depression

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**Abstract**

A consistent finding in biological psychiatry is that hypothalamic–pituitary–adrenal (HPA) axis physiology is altered in humans with major depression. These findings include hypersecretion of cortisol at baseline and on the dexamethasone suppression test. In this review, we present a process-oriented model for HPA axis regulation in major depression. Specifically, we suggest that acute depressions are characterized by hypersecretion of hypothalamic corticotropin-releasing factor, pituitary adrenocorticotropic hormone (ACTH), and adrenal cortisol. In chronic depressions, however, enhanced adrenal responsiveness to ACTH and glucocorticoid negative feedback work in complementary fashion so that cortisol levels remain elevated while ACTH levels are reduced. In considering the evidence for hypercortisolism in humans, studies of nonhuman primates are presented and their utility and limitations as comparative models of human depression are discussed.


*Keywords:* Adrenocorticotropin; Cortisol; Corticotropin-releasing factor; Hypothalamic–pituitary–adrenal axis; Major depression; Social separation; *Saimiri*; Squirrel monkey

Of all the many brain systems that have been studied in major depression (Schatzberg and Nemeroff, 1998), a consistent finding is that 40–60% of drug-free depressed patients present with hypercortisolism (Gold et al., 1986; Murphy, 1991). Because depressive episodes are frequently elicited or exacerbated by psychosocial sources of stress (McEwen, 1998; Schatzberg and Nemeroff, 1998), animal research has tended to focus on how stress affects hypothalamic–pituitary–adrenal (HPA) axis physiology and, ultimately, how HPA axis physiology becomes dysregulated in major depression. In this review, we examine neuroendocrine data from human and nonhuman primate research, and present a process-oriented model for HPA axis regulation in humans with major depression.

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## HPA axis physiology in major depression

More than 40 years ago, researchers reported that patients diagnosed with major depression hypersecrete cortisol (Board et al., 1956; Gibbons and McHugh, 1962). Since then, data from a variety of clinical studies clearly indicate that hormones of the HPA axis are dysregulated in patients with major depression (Carroll et al., 1976; Gold et al., 1986; for a review see also Plotsky et al., 1995). Some reports suggest that chronic hypersecretion of cortisol is due to prolonged hypersecretion of corticotropin-releasing factor (CRF) (Nemeroff et al., 1984) and adrenocorticotropic hormone (ACTH) (Kalin et al., 1982; Reus et al., 1982; Pfohl et al., 1985). Although CRF is frequently found to be elevated during episodes of depression (reviewed by Arborelius et al., 1999), data from studies of ACTH concentrations in depressed human patients are inconsistent. Specifically, some studies report greater ACTH levels (Kalin et al., 1982; Reus et al., 1982; Pfohl et al., 1985; Deuschle et al., 1997; Young et al., 2001), whereas other research indi-

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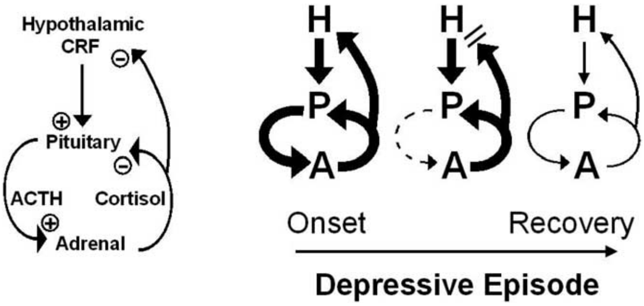


Fig. 1. Schematic representation of HPA axis regulation in major depression. The broken line reflects low levels of hormone, thin lines reflect normal levels of hormone, thick lines reflect increased levels of hormone, ⊕ signifies a stimulatory effect, and ⊖ signifies an inhibitory effect.

cates that depressed individuals present with normal to low ACTH concentrations (Fang et al., 1981; Yerevanien and Woolf, 1983; Sherman et al., 1985; Linkowski et al., 1985; Gold et al., 1986; Murphy, 1991; Posener et al., 2000).

One potential explanation for these findings is that the neurobiology of hypercortisolism during depressive episodes changes over time. According to this process-oriented perspective (Gold and Chrousos, 1985; Nemeroff, 1988; Amsterdam et al., 1989b; Sapolsky and Plotsky, 1990), in acute depressions, hypersecretion of CRF (and potentially other hypothalamic secretagogs) stimulates the synthesis and secretion of ACTH from pituitary corticotrophes. ACTH, in turn, stimulates the synthesis and secretion of cortisol from the adrenal cortex. Thus, hypersecretion of cortisol is initially driven by hypersecretion of both CRF and ACTH. In chronic depressions, however, two opposing processes apparently work in complementary fashion so that cortisol levels remain elevated while ACTH levels are reduced.

The first proposed process involves changes in adrenal responsiveness to circulating ACTH. According to this hypothesis, normal responsiveness to high levels of ACTH occurs in acute depressions, whereas adrenal hyper-responsiveness to low levels of ACTH emerges in chronic depressions (see Fig. 1). This possibility is consistent with reports that prior exposure of the adrenal to acute elevations in ACTH subsequently enhances the responsiveness of the adrenal cortex. For example, when exogenous ACTH is administered to healthy humans, the adrenal cortex remains hyperresponsive to subsequent ACTH stimulation for days (Kolanowski et al., 1969). This long-lasting “potentiation” effect does not require continuous exposure to high levels of ACTH. Adrenal hyperresponsiveness persists after a single ACTH infusion even when chronic 7-day dexamethasone treatments are used to maintain low circulating levels of endogenous ACTH (Kolanowski et al., 1975). This outcome may reflect well-known trophic effects of ACTH on the adrenal cortex (Dallman, 1984), or long-lasting stimulatory effects on adrenocortical enzyme systems involved in glucocorticoid biosynthesis (Simpson and Waterman, 1983). In keeping with the former possibility, radiographic evidence suggests that the adrenal gland in depressed patients is enlarged (Amsterdam et al., 1987a; Nemeroff et al., 1992).

More recent evidence using magnetic resonance imaging techniques corroborates these earlier findings of adrenal hypertrophy in major depression (Rubin et al., 1996), and indicates that adrenal gland enlargement is state, rather than trait, dependent (Rubin et al., 1995). Specifically, following remission after treatment, adrenal gland volumes of depressed patients are indistinguishable from those of healthy controls. These reported changes in adrenal size are almost certainly due to adrenocortical rather than adrenomedullary enlargement, since the medulla constitutes a small part of the adrenal gland and has, unlike the adrenal cortex, not shown the capacity to change in size after perturbations such as chronic stress (Dallman, 1984). We also know that many depressed patients show an exaggerated cortisol response to supraphysiological doses of exogenous ACTH (Amsterdam et al., 1983, 1985, 1986; Gerken and Holsboer, 1986; Amsterdam et al., 1987b; Jaeckle et al., 1987; Amsterdam et al., 1989a). Additionally, in response to exogenously administered CRF, depressed patients often exhibit blunted ACTH but normal cortisol responses, indicating that depressed patients produce more cortisol per molecule of ACTH even in physiological circumstances (Holsboer et al., 1984; Gold et al., 1986; Amsterdam et al., 1987c; Young et al., 1990). Similar to the adrenal gland hypertrophy data (Rubin et al., 1995), adrenal hyperresponsiveness to ACTH is also a state-dependent phenomenon that subsides with clinical recovery (Gerken and Holsboer, 1986; Amsterdam et al., 1987b).

In addition to changes in adrenal responsiveness to ACTH, a second proposed process involves changes in pituitary responses to hypothalamic CRF. According to this hypothesis (see Fig. 1), high levels of CRF generate high levels of ACTH in acute depressions, whereas high CRF levels are associated with low ACTH levels in chronic depressions. This hypothesis is based on reports that exposure of the pituitary to high circulating levels of cortisol subsequently attenuates the responses of pituitary corticotrophes to hypothalamic CRF. Many hypercortisolemic depressed patients show an attenuated ACTH response to exogenous CRF (Holsboer et al., 1984; Gold et al., 1986; Amsterdam et al., 1987c; Holsboer et al., 1987; Amsterdam et al., 1988; Rubin et al., 1995), and ACTH responses tend to be most attenuated in depressed patients with the most severe hypercortisolism (Gold et al., 1986). Metyrapone blockade of cortisol biosynthesis effectively abolishes the attenuated ACTH response to exogenous CRF (von Bardeleben et al., 1988; Kathol et al., 1989), and metyrapone alone produces significant increases in baseline levels of circulating endogenous ACTH (Liansky et al., 1989; Young et al., 1997). The gradual 24-h increase in baseline ACTH suggests that pituitary corticotrophes in hypercortisolemic depressed patients are stimulated by excessive hypothalamic CRF [also see reports on CRF-like immunoreactivity in CSF (Ur et al., 1992; Nemeroff et al., 1984;

Banki et al., 1987; Roy et al., 1987)], but this stimulatory effect is suppressed by high circulating levels of cortisol (Gold et al., 1986; Kathol et al., 1989; von Bardeleben et al., 1988; Young et al., 1995; Young et al., 1997). Because the pituitary ACTH response to hypothalamic CRF is normalized by metyrapone administration, these data argue against the possibility that pituitary CRF receptors are altered in major depression (Young et al., 1995). A more likely possibility is that high circulating levels of CRF are opposed at the pituitary by elevated glucocorticoid feedback signal, which contributes to the blunted ACTH profile frequently observed in patients with depression (Gold et al., 1986; Liansky et al., 1989).

## A model of hypercortisolism in monkeys

Although rodents often serve as valuable models in human biomedical research, in keeping with Selye's initial observations (1946), it has been nearly impossible to produce in experimental studies of rodents a sustained endogenous adrenocortical response (Bohus, 1969; Daniels-Severs et al., 1973; Sakellaris and Vernikos-Danellis, 1975; Katz et al., 1981; Vernikos et al., 1982; Young and Akil, 1985; Rivier and Vale, 1987). This problem undoubtedly contributed to Selye's formulation of an "exhaustion" phase in his General Adaptation Syndrome, and may account for the fact that most laboratory rodent models of adrenocortical hyperactivity rely on repetitive physical stressors that bear little resemblance to the psychosocial stressors generally associated with depression (Paykel et al., 1969; Fava et al., 1981; Brown et al., 1987) and hypercortisolism (Sonino et al., 1993; Breier et al., 1988) in humans.

Studies in our laboratory suggest that social separation-induced hypercortisolism in squirrel monkeys (*Saimiri sciureus*) provides unique opportunities for comparative research on the neuroendocrinology of chronic hypercortisolism and its neurobiological consequences during depressive disorders in humans. Specifically, because the loss or absence of valued social companionship is a well-known risk factor in major depression (Paykel et al., 1969; Aneshensel and Stone, 1982; Billings et al., 1983), and as the sudden unexpected absence of a social companion serves as a potent psychogenic stressor in squirrel monkeys (Hennessy, 1997), we have studied squirrel monkeys as a model by which to investigate how social separations alter HPA axis physiology. Findings from these studies are reviewed below.

## Adult grouping tendencies and cortisol responses to social separation

Squirrel monkeys are gregarious New World primates that typically live in social groups composed of males and females in all stages of life span development (Lyons et al., 1992). A salient characteristic of these groups is the segregation of males and females into same-sex subgroups. Around puberty at 2–3 years of age, juvenile males begin to associate primarily with other males, whereas juvenile females associate with other females (Coe and Rosenblum, 1974; Coe et al., 1988). In free-ranging, semi-free-ranging, and captive settings, adult males and females within a group also spend most of their time with same-sex companions, and social transactions between the sexes are generally limited to seasonal mating activities (Lyons et al., 1992).

When squirrel monkeys are separated from social companions they show unusually prolonged elevations in plasma cortisol. After separation from juvenile peers, for example, morning measures of cortisol in juveniles housed for 21 days without companions are 18–87% higher than control values observed when the same juveniles are housed in groups (Lyons and Levine, 1994). Whether this hypersecretion of cortisol is due specifically to the absence of same-sex companions remains to be determined for juveniles, but this is apparently the case for adults. Modest but prolonged elevations in cortisol are observed not only when adults are separated from companions and housed alone (Mendoza et al., 1992; Lyons et al., 1994), but also when adult males and females are housed together without same-sex companions in male–female pairs and when adult males are housed without male companions in single-male, multifemale groups (Mendoza et al., 1991). As generally found in diurnally active human and nonhuman primates, plasma cortisol levels in squirrel monkeys are highest just before or just after lights-on, and lowest just before or just after lights-off (Wilson et al., 1978). This pattern is maintained but at consistently higher levels across the 24-h cycle in individually housed squirrel monkey juveniles (Lyons et al., 1995) and adults (Mendoza et al., 1991).

## Separation-induced changes in adrenal responsiveness to ACTH

One explanation for the finding that squirrel monkeys hypersecrete cortisol when separated from social companions is that hypercortisolism reflects a deficiency in glucocorticoid-negative feedback mechanisms that normally inhibit the prolonged hypersecretion of ACTH (Saltzman et al., 1991; Mendoza et al., 1992; Lyons and Levine, 1994). To test this hypothesis, we initially examined longitudinal morning plasma samples collected from monkeys separated from social companions for evidence of prolonged elevations in both cortisol and ACTH. As predicted, separation-induced elevations in cortisol were initially driven by acute elevations in ACTH (see Fig. 2). However, contrary to prediction, subsequent morning measures of cortisol remained elevated in monkeys housed without companions despite reductions, below baseline control values, in simultaneous measures of ACTH.

Because plasma cortisol concentrations remain elevated

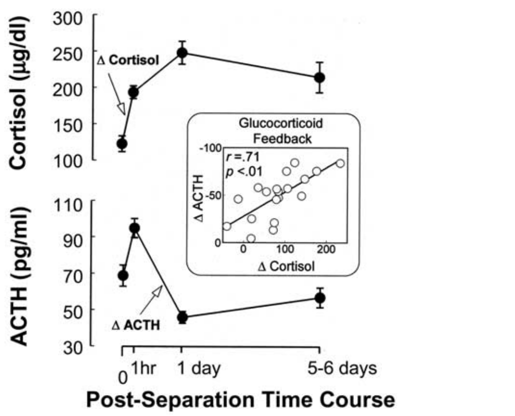


Fig. 2. Plasma levels of cortisol (top) and ACTH (bottom) in monkeys separated from groups and housed alone (mean + SEM). Inset: Monkeys who responded to separation with greater baseline to 1-h increases in cortisol subsequently show greater 1-h to 1-d decreases in ACTH, which suggests that reductions in ACTH are due to glucocorticoid feedback. Adapted from Lyons et al. (1999).

despite prolonged reductions in plasma ACTH, we hypothesized that a state-dependent change occurs by which adrenal responsiveness to ACTH is enhanced. To test this hypothesis, squirrel monkeys were assessed in standard ACTH stimulation tests administered 7 days after subjects were separated from like-sex social groups and temporarily housed alone (Lyons et al., 1995). All monkeys were pretreated overnight with dexamethasone to temporarily suppress the secretion of endogenous ACTH, and then challenged the following morning with a bolus injection of exogenous ACTH. Monkeys housed without companions responded to the challenge with greater, more prolonged elevations in cortisol relative to monkeys housed in groups (see Fig. 3).

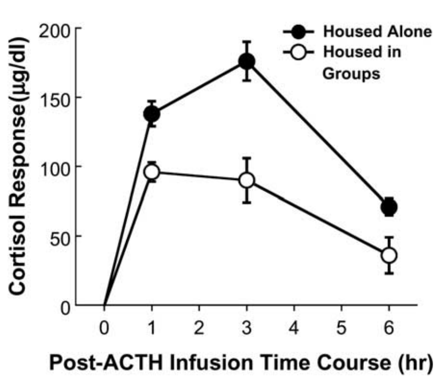


Fig. 3. Incremental cortisol responses (mean + SEM) to administration of exogenous ACTH in dexamethasone-pretreated monkeys housed alone (solid circles) or with same-sex companions in established social groups (open circles). Adapted from Lyons et al. (1995).

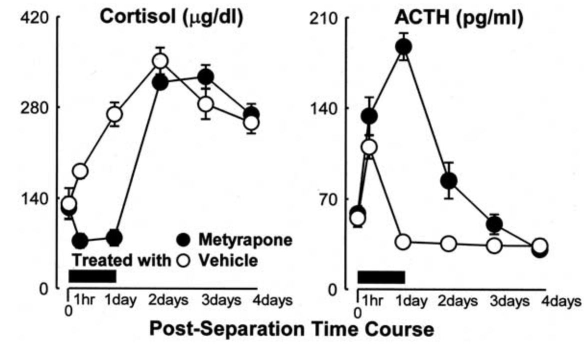


Fig. 4. Plasma levels of cortisol (left) and ACTH (right) in monkeys separated from groups and administered metyrapone (solid circles) or fruit drink vehicle (open circles) for the first 24 h. With the onset of glucocorticoid feedback delayed by the 24-h metyrapone blockade, overdriven pituitary corticotrophes are revealed by long-lasting increases in plasma levels of ACTH (mean + SEM). Adapted from Lyons et al. (1999).

## Glucocorticoid feedback and hypothalamic drive

As indicated above, social separations induce an initial hypersecretion of both ACTH and cortisol, whereas prolonged social separations result in hypersecretion of cortisol but hyposecretion of ACTH (see Fig. 2). To test the hypothesis that these low circulating levels of ACTH are maintained by glucocorticoid negative feedback, monkeys were separated from groups as in previous studies and longitudinal samples of plasma ACTH and cortisol concentrations were evaluated (Lyons et al., 1999). Separated monkeys initially responded with significant increases in cortisol and ACTH, but over time, while cortisol remained elevated above preseparation levels, significant reductions occurred in plasma ACTH. Interestingly, monkeys that responded with greater initial increases in cortisol subsequently demonstrated greater reductions in ACTH, suggesting that reductions in ACTH are, indeed, mediated by glucocorticoid feedback. Additional data also support this conclusion: squirrel monkeys responded to social separation with long-lasting increases in circulating ACTH when the onset of glucocorticoid feedback was delayed by metyrapone blockade of cortisol biosynthesis (see Fig. 4).

In healthy humans, normal concentrations of ACTH are evident within hours of termination of an equivalent metyrapone blockade (Jubiz et al., 1970). However, in our studies, after termination of metyrapone, ACTH concentrations in monkeys separated from groups remained elevated for several days. This suggests that hypersecretion of CRF is typically opposed at the pituitary by a robust glucocorticoid negative feedback signal. Although direct analysis of cerebrospinal fluid (CSF) concentrations of CRF in socially isolated versus group-housed squirrel monkeys did not reveal differences in CRF drive (Lyons et al., 1999), this likely occurs because CSF samples of CRF reflect extrahypothalamic sources that do not act synchronously with hypothalamic sources of CRF (Kalin et al., 1987).

## Summary and conclusions

In squirrel monkeys, the unexpected loss of social companions mobilizes the HPA axis and results in acute hypersecretion of both plasma ACTH and cortisol (Lyons et al., 1999). However, following prolonged social separation, cortisol remains elevated above preseparation levels, whereas simultaneous reductions occur in ACTH (Lyons et al., 1995; Lyons and Levine, 1994). Following ACTH challenge (with dexamethasone pretreatment), socially separated squirrel monkeys respond with greater, more prolonged elevations in cortisol compared with monkeys housed in groups. This suggests that adrenal responsiveness to ACTH is enhanced. Monkeys that initially respond to social separation with greater increases in cortisol exhibit greater subsequent reductions in ACTH (Lyons et al., 1999). Squirrel monkeys also respond to social separations with long-lasting increases in ACTH when the onset of glucocorticoid feedback is delayed by 24-h metyrapone blockade of cortisol biosynthesis (Lyons et al., 1999). Following termination of metyrapone, ACTH concentrations remain elevated for several days, which suggests that hypersecretion of CRF is opposed at the pituitary by a robust glucocorticoid negative feedback signal.

These results parallel findings in humans that suggest that excessive central stimulation by hypothalamic CRF is opposed at the pituitary by glucocorticoid negative feedback in depressed patients that present with hypercortisolism (Ur et al., 1992; von Bardeleben et al., 1988; Young et al., 1995, 1997). Like monkeys, humans also exhibit increased adrenal responsiveness to ACTH (Kolanowski et al., 1969, 1975; Simpson and Waterman, 1983; Dallman, 1984), and depressed patients with hypercortisolism exhibit attenuated ACTH responses to exogenously administered CRF (Gold et al., 1986). However, metyrapone blockade of cortisol biosynthesis effectively abolishes the attenuated ACTH response to exogenous CRF (von Bardeleben et al., 1988; Kathol et al., 1989). Following metyrapone blockade, hypercortisolemic depressed patients exhibit a gradual increase in baseline ACTH, suggesting that pituitary corticotrophes are stimulated by excessive hypothalamic CRF, but this stimulatory effect is suppressed by high circulating levels of cortisol (Gold et al., 1986; Kathol et al., 1989; von Bardeleben et al., 1988; Young et al., 1995, 1997). With removal of glucocorticoid feedback, the overdriven corticotrophes are revealed (Liansky et al., 1989).

Comparative assessment of HPA axis physiology is thought to provide a window into the neuroendocrinology of human depression. However, many of the diagnostic criteria for major depression involve aspects of cognition and emotion that are probably unique to humans [e.g., suicidal ideation, low self-esteem, feelings of worthlessness (DSM-IV-TR, 2000)]. Moreover, despite the similarities in HPA axis physiology between human and nonhuman primates, adult monkeys show little evidence of depression-like behavior evident in humans with commensurate changes in HPA axis physiology. Taken together, these observations raise the intriguing possibility that the pituitary adrenal physiology in humans with major depression is not dysregulated per se, but instead reflects basic mechanisms underlying adrenal physiology and glucocorticoid negative feedback.

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