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# Chronic stress differentially regulates glucocorticoid negative feedback response in rats

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**Abstract**

Exposure to chronic stress is thought to play an important role in the etiology of depression. In this disorder, a disrupted negative feedback response to exogenous glucocorticoids on cortisol secretion has been indicated. However, the regulation of glucocorticoid negative feedback by chronic stress is not fully understood. In the present study, we investigated the effects of chronic stress administered by water immersion and restraint (2 h/day) for four weeks on the glucocorticoid feedback in rats. In the acutely (one-time) stressed rats, the basal plasma corticosterone (CORT) level was markedly elevated, remained at high levels for 5 h after the termination of stress, and then decreased. In the chronically stressed rats, the CORT level was initially elevated similarly, but rapidly decreased at 2 h. In the dexamethasone (DEX) suppression test, the peak CORT level in response to stress was not suppressed by DEX in the acutely stressed rats, but was significantly suppressed in the chronically stressed rats. In contrast, the suppressive effects of DEX on the basal CORT secretion in naive rats were attenuated in the chronically stressed rats. In the chronically stressed hippocampus, which plays an important role in the regulation of the glucocorticoid feedback response, the binding of [$^3$H]DEX was decreased and the increased response of activator protein-1 induced by acute stress was abolished. These results suggest that chronic stress induces a hypersuppressive state for induced CORT secretion in response to acute stress, which is caused by partial habituation,

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coping, and adaptation to the stressor, whereas it induces a hyposuppressive state for the basal CORT secretion, which is caused by glucocorticoid receptor downregulation. These mechanisms may be involved in the stress-induced neural abnormalities observed in depression.


*Keywords:* Chronic stress; Corticosterone; Dexamethasone suppression test; Glucocorticoid negative feedback; Glucocorticoid receptor; Hippocampus

## 1. Introduction

Exposure to chronic stress is thought to play an important role in the etiology of depression (Mazure, 1995). In this disorder, a number of studies indicate an abnormal neuroendocrine system. Thus, a reduced negative feedback response to exogenous glucocorticoids is one of the most consistent findings, and is characterized by the failure in suppression of plasma cortisol levels following administration of synthetic glucocorticoid, dexamethasone (DEX) (Carroll et al., 1981; Kalin et al., 1982; Holsboer, 1983; Arana et al., 1985). Hypersecretion of basal cortisol (Carroll et al., 1976) and increased adrenal weight (Rubin et al., 1995) are also observed. In addition, there is a significant correlation between the duration of the depression and the extent of hippocampal atrophy (Sheline et al., 1996). Although glucocorticoid secretion is negatively regulated by glucocorticoids at the level of the anterior pituitary gland (Miller et al., 1992), suprahypothalamic limbic structures such as the hypothalamus, hippocampus, and amygdala, and the mesoprefrontal system are also involved (Magarinos et al., 1987; Bradbury et al., 1991; Diorio et al., 1993; Feldman and Weidenfeld, 1999; Ferrini et al., 1999). In particular, hippocampal glucocorticoid receptors appear to be sensitive to elevated glucocorticoid levels (Reul and de Kloet, 1985) and these receptors or their messenger RNAs are downregulated by chronic stress (Sapolsky et al. 1984, 1986; Herman et al., 1995; Kitraki et al., 1999). These stress effects are thought to be involved in the reduced negative feedback response to exogenous glucocorticoids. Indeed, in chronically footshocked rats, elevated plasma corticosterone (CORT) levels in response to acute footshock are not decreased by DEX (Haracz et al., 1988), and ß-endorphin release upon subsequent presentation of swim stress is not inhibited by exogenous CORT (Young et al., 1990).

These findings from basic research have had a major impact on theories of the reduced glucocorticoid feedback that may involve altered glucocorticoid receptor regulation. However, since the chronic footshock-induced dysregulations of glucocorticoid feedback are evaluated for the elevated plasma levels of hormones in response to acute stress (Haracz et al., 1988; Young et al., 1990), it seems that these dysregulations may not reflect the reduced negative feedback response observed under resting, non-stressful, conditions in depressed patients.

In the present study, to clarify the involvement of chronic stress in the regulation of the glucocorticoid negative feedback response, we examined the plasma CORT levels during chronic stress exposure and the feedback response to DEX for the basal