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### Authors
Gilles, EE
EghbalAhmadi, M
Haltalski, CG
et al.



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## 23. Corticotropin-Releasing Factor Receptors Are Downregulated in Chronically Stressed Developing Rats

*Elizabeth E. Gilles, M. Eghbal-Ahmadi, Carolyn G. Haltalski, Mark Bounthavong, and Tallie Z. Baram; Columbus, OH, and Irvine, CA*

The effects of chronic early life stress on the development of CNS-controlled stress responses and their functional integrity later in life are not fully understood. We have been in-vestigating the neuroendocrine components of the stress re-sponse using an infant rat model of chronic stress. Previous studies have shown dramatic increases in basal and stress-evoked glucocorticoid secretion and decreased levels of hypothalamic corticotropin-releasing factor (CRF) messenger RNA (mRNA). Because the magnitude of the stress-mediating effects of CRF is determined by the levels of both CRF and the peptide's target receptors, the goal of the current study was to determine whether CRF receptors in the CNS are altered in chronically stressed developing rats. Two-day-old rat pups were assigned to one of two treatment groups: a chronically stressed group reared by mothers deprived of nesting material (NHNB; n = 19) and a control nonhandled group (NH; n = 16). All pups were sacrificed under stress-free conditions on postnatal day 9. The plasma corticosterone concentration was determined by radioimmunoassay and the $CRF_1$ receptor–mRNA level in hippocampus and the $CRF_2$ receptor–mRNA level in hypothalamic ventromedial nucleus (VMH) were determined by in situ hybridization histochemistry. NHNB plasma corticosterone levels were higher (1.9 ± 0.1 vs. 1.3 ± 0.05 μg/dl; $p < 0.05$) and adrenal weight increased (30.2 ± 0.9 vs. 24.3 ± 1.6 mg; $p < 0.01$), consistent with a chronically stressed state. In this chronic stress model, $CRF_1$ receptor–mRNA levels in the hippocampus were lower (80 ± 10 nCi/gm) in the NHNB pups (versus 130 ± 10 nCi/gm in the NH group; $p < 0.01$). The $CRF_2$ receptor–mRNA signal in the VMH of NHNB pups (100 ± 5 nCi/g) was lower than that in NH pups (120 ± 4 nCi/gm; $p < 0.05$). The finding of decreased levels of both types of CRF receptors is consistent with an increased secretion of the CRF itself, which is known to downregulate its own receptors. Enhanced CRF release is expected in response to stress and (mediated by pituitary corticotropin) probably underlies the markedly increased secretion of corticosterone in the stressed group. The downregulation of $CRF_1$ receptors would prevent chronically stressed people from responding appropriately to further stress. $CRF_2$ in the VMH is involved with satiety and the anorectic effects of CRF. A decreased level of VMH-$CRF_2$ may thus be an important factor in the poor growth observed in those exposed to chronic early-life stress.

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