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140. Chronic Stress in Infancy Results in Downregulation of Corticotropin-Releasing Hormone Gene Expression in the Hypothalamus

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Immediate and long-term effects of severe chronic stress in infancy on the hypothalamic-pituitary-adrenal stress system have not been defined. We have created an infant rat model of severe chronic stress manifested by abnormally increased secretion of the stress hormone corticosterone (CORT). The goal of the current study was to examine gene expression of hypothalamic corticotropin-releasing hormone (CRH), the neuropeptide controlling the release of stress hormones. Two-day-old rat pups ($n = 70$) were assigned to two treatment groups: a nonhandled group without access to cage bedding (NHNB), and a nonhandled control group. All pups were killed under stress-free conditions on postnatal day 9. Plasma CORT was measured by radioimmunoassay and CRH-mRNA levels were determined from serial sections of the hypothalamus of at least 5 rats per group using ISH

as previously described (Yi and Baram, *Endocrinology* 1994; 135:2364–2368). Mean and SEM from a minimum of 50 values per group were determined. Groups were compared using the nonparametric Mann-Whitney test. Levels of CRH-mRNA in the hypothalamus of NHNB animals were markedly decreased to 57% of that of nonhandled control pups ($p < 0.005$). Conversely, total CORT output (plasma levels \times time) by the chronically stressed animals (NHNB) was 142% that of nonhandled controls. The significant decrease in CRH-mRNA levels in NHNB animals is compatible with enhanced negative feedback of the high levels of circulating CORT. Markedly diminished levels of CRH-mRNA in the chronically stressed pups, however, may limit their ability to respond appropriately to subsequent acute stressors with increased CRH production. This may ulti-