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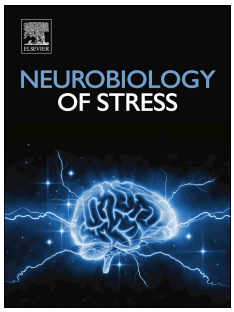

Neuroendocrine and neuroimmune adaptation to Chronic Escalating Distress (CED): A novel model of chronic stress

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Abstract

Acute and chronic stress challenges have a profound influence on the development and expression of subsequent affective disorders, alcohol use disorders, and natural aging processes. These experiments examined adaptation in neuroimmune and neuroendocrine responses that occurred as a result of exposure to a novel model of chronic stress, termed chronic escalating distress (CED). This model involves exposure to highly predictable daily stress challenges involving a systematic escalation in both the intensity and length of daily stress challenges, and has recently been shown to profoundly alter alcohol sensitivity. Male Sprague-Dawley rats were exposed to an 11 day procedure where days 1-5 consisted of 60 min of restraint, days 6-10 consisted of 60 min of restraint immediately followed by 30 min of forced swim, and on day 11 subjects were exposed to a 2 hr session of intermittent footshock. Experiment 1 examined adaptation in the corticosterone (CORT) response at key points in the 11 day procedure, and found that the escalation in stressors disrupted habituation to restraint, whereas the CORT response to daily forced swim exposure increased across days. Experiment 2 investigated the impact of this stress paradigm on the expression of several cytokine (IL-1β, IL-6, TNF-α) and cellular activation marker (c-Fos, CD14, CD200R) genes in key brain regions (PVN, HPC, & PFC) known to be influenced by stress. Interestingly, a history of CED had no effect on footshock-induced neuroimmune changes (increased IL-1 in the PVN; increased IL-6 in the HPC and PFC). In addition, acute footshock and CED produced similar c-fos induction within the PVN whereas CED led to enhanced c-fos induction in both the HPC and PFC. These findings support recent work indicating that neuroimmune responses to acute stress challenges persisted in rats with a recent history of repeated stress exposure, and that these effects occured contemporaneously with ongoing changes in HPA axis reactivity. Overall, this CED model may serve as a highly tractable model for studying adaptation to chronic stress, and may have implications for understanding stress-induced alterations in alcohol sensitivity and natural aging processes.