

Project 3: Ethanol Dependence and Stress Effects on Ethanol Drinking: CRF & Neurosteroids

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A. SPECIFIC AIMS

A host of biological and environmental factors interact in a complex manner throughout the addiction process to influence ethanol (EtOH) drinking behavior. While stress has been viewed as an important contributing factor to EtOH abuse and alcoholism, the interaction between stress and EtOH drinking behavior is not well understood. Moreover, little is known about the dynamics associated with the relationship between stress and EtOH consumption, as well as mechanisms underlying this interaction in the context of dependence. A major tenet of our current work and this proposal is that chronic EtOH exposure and withdrawal experience produces fundamental changes in brain reward and neuroendocrine/stress systems that progressively drive excessive EtOH drinking, as well as alter vulnerability to stress as a trigger for provoking relapse behavior.

During the current funding period, we linked a model of EtOH dependence and drinking to demonstrate that repeated cycles of chronic EtOH exposure and withdrawal experience enhances subsequent voluntary EtOH consumption. Studies also examined whether stress associated with chronic intermittent EtOH exposure plays a role in the resultant enhanced voluntary EtOH intake. While plasma corticosterone (CORT) levels were elevated during acute withdrawal, the magnitude and duration of this effect does not appear to relate to the increased propensity to drink in animals with a history of dependence. This proposal builds and expands on this current work in two important ways. First, we have refined the drinking model by adding an operant component (mice need to respond to gain access to EtOH), which enables separate analysis of the appetitive (seeking) and consummatory (drinking) components of EtOH self-administration, as well as affords the opportunity to evaluate the influence of EtOH dependence on stress-induced relapse behavior. Second, we have extended analysis of the role of stress in this phenomenon from peripheral measures of hypothalamic-pituitary-adrenocortical (HPA) axis activation (plasma CORT levels) to central mechanisms. Specifically, proposed studies will focus on the neuropeptide CRF and the neuroactive steroid allopregnanolone because they are intimately related to stress responsiveness (involving both neuroendocrine-related and independent brain stress pathways), as well as EtOH dependence and EtOH self-administration behavior.

Thus, the overall focus of this proposal is aimed at utilizing an established **mouse model of EtOH dependence** to examine mechanisms by which **stress** associated with repeated cycles of chronic EtOH exposure/withdrawal (changes in brain **CRF** and **allopregnanolone** activity) influence subsequent **EtOH self-administration behavior**, as well as **stress-induced relapse** behavior. *The general working hypothesis is that repeated cycles of chronic EtOH exposure and withdrawal experience produce changes in CRF and allopregnanolone activity within brain reward and stress systems that subsequently engender enhanced EtOH seeking and drinking behavior, as well as alter the ability of acute stress to trigger EtOH relapse.* More specifically, the main objectives of this project are to:

(a) examine the relationship between brain regional CRF levels and EtOH self-administration behavior following repeated cycles of chronic EtOH exposure/withdrawal experience **(Aim I)**;

(b) examine the relationship between brain regional allopregnanolone levels and EtOH self-administration behavior following repeated cycles of chronic EtOH exposure/withdrawal experience **(Aim II)**;

(c) examine whether a history of repeated cycles of chronic EtOH exposure/withdrawal influences the ability of an acute environmental stressor to reinstate EtOH-seeking behavior as well as alter brain CRF and allopregnanolone levels **(Aim III)**; and

(d) examine the role of brain CRF and allopregnanolone in mediating stress-induced reinstatement of EtOHseeking behavior in dependent vs. non-dependent mice **(Aim IV)**.

As such, this project not only fills a void in the literature related to EtOH dependence and stress, but importantly, it targets the major overarching theme of the INIA-Stress Consortium as well as complements other projects with a similar research focus in the Consortium. The overall goal of this proposal is to provide new information about possible mechanisms underlying/mediating the interaction between EtOH dependence, stress, and EtOH drinking behavior that is relevant to the INIA-Stress Consortium, as well as the alcohol research community in general.