

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

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A complex interplay among numerous biological and environmental factors governs both ethanol (EtOH) seeking and drinking behavior. While stress has been viewed as an important contributing factor to EtOH abuse and alcoholism, the interaction between stress and EtOH drinking and behavior is not well understood. This is especially true when one considers the role/impact of stress on EtOH self-administration in the context of EtOH dependence. Chronic excessive consumption of EtOH can lead to the development of dependence, and repeated experience with associated withdrawal episodes may constitute a powerful motivational force that contributes to the perpetuation of EtOH use/abuse. Further, functional changes in brain/neuroendocrine stress and reward systems as a result of chronic EtOH exposure may render subjects not only more vulnerable to engage in excessive EtOH drinking, but also more susceptible to events (stress) that may trigger re-initiation of EtOH use after periods of abstinence (relapse). Unfortunately, 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. 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. This proposal builds and expands on this work, with an emphasis on elucidating mechanisms underlying the phenomenon. 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. 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. 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. Results from this research proposal will provide new and novel information about possible mechanisms underlying/mediating the interaction between EtOH dependence, stress, and EtOH drinking/relapse behavior that is relevant to the INIA-Stress Consortium, as well as the alcohol field in general. The overall goal is to provide a more complete and comprehensive analysis of the biological underpinnings and environmental circumstances in which stress contributes to excessive EtOH drinking and the development of alcoholism.