

Project 2: Stress and Ethanol Self-Administration in Monkeys

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A. SPECIFIC AIMS

Stress is believed to be an etiological factor in the abuse of ethanol. However, the role of stress in the risk for excessive ethanol consumption is difficult to untangle from the stress derived from excessively drinking alcohol. A starting point is to operationally define stress as activation of the hypothalamic-pituitary-adrenal (HPA) axis through measurable changes in circulating levels of the hormones adrenocorticotropin (ACTH) from the pituitary and cortisol from the adrenals. Monkeys show clear individual differences in endocrine response of the HPA axis to stressful events and also clear individual differences in the amount of ethanol they choose to self-administer. To address the causal interaction of stress and excessive ethanol interaction, this renewal application proposes to further characterize individual differences in HPA response to stress prior to, during and following chronic ethanol self-administration. The very nature of endocrine response to stress brings to the forefront the concept of neurocircuitries underlying information flow, integration and functional output. Viewing the HPA response as an intermediate determinant of behavior guides a translational endeavor into the realm of intermediate phenotypes or “endophenotypes”. To address the predictive validity of an HPA response as an endophenotype underlying the risk of excessive ethanol self-administration, we will screen a large population of monkeys for specific HPA responses. Individuals that are on the extreme ends of the population distribution of the potential endophenotype will be characterized for ethanol self-administration. Finally, we will screen gene polymorphisms to identify those associated with an HPA endophenotype. We will assess the predictive value of the genetic polymorphisms by screening the rhesus colony to select animals with the “risk” alleles and then characterize them in the alcohol self-administration procedure.

The specific aims of this research are:

- 1) **To complete the characterization of HPA response and ethanol self-administration in outbred cynomolgus monkeys begun in the previous funding cycle.** We hypothesize that baseline measures of stress will predict ethanol intake in an open access self-administration paradigm and that HPA adaptations to chronic ethanol self-administration are influenced by ethanol intake, social status, and housing conditions.
- 2) **To determine the effects of chronic ethanol self-administration and periods of abstinence on measures of stress in cynomolgus monkeys.** We hypothesize that excessive ethanol self-administration will alter HPA stress response and the time course for HPA axis recovery will be directly proportional to the length of ethanol abstinence. We further hypothesize that not all aspects of HPA response will show “recovery” in abstinence and these long-term changes will predict increases in ethanol self-administration following abstinence.
- 3) **To explore specific HPA endophenotypes in predicting ethanol self-administration in rhesus monkeys.** We hypothesize that monkeys chosen for divergent HPA response to pharmacological challenge will have differential risk for excessive ethanol self-administration.
- 4) **To use a candidate gene approach to identify genes associated with excessive alcohol consumption in rhesus monkeys.** We hypothesize that the genes that underlie the HPA response will also predict alcohol consumption in rhesus macaques.