

Project 2: Stress and Ethanol Self-Administration in Monkeys
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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, we propose to characterize individual differences in HPA response to stress prior to, during and following chronic ethanol self administration. Further, the very nature of endocrine response to stress brings into focus 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 in the ethanol self-administration procedure. Finally, we will screen gene polymorphisms to identify those associated with an HPA response 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.