

## **Project 4: Early Stress & Alcoholism: Neurobiological Analysis**

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### **A. SPECIFIC AIMS**

Stress is believed to be an etiological factor in the abuse of ethanol. Chronic stress is known to alter the behavioral effects of ethanol, including its reinforcing effects, and available evidence also suggests that chronic stress alters neurotransmission in specific brain regions that are important for mediating the reinforcing effects of many drugs of abuse, including ethanol. Little is known, however about the neurobiological basis of the response to stress that leads to excessive ethanol consumption in both people and animals.

While the response to stress is complex, involving many brain regions and transmitter systems, there is compelling evidence indicating that serotonin, acting especially in forebrain limbic structures, may mediate crucial aspects of the response to stress. Importantly, the same structures, including the orbito- and medial prefrontal cortex (OMPFC), amygdala, and hippocampus, have been implicated in ethanol self-administration as well. Along with the hypothalamus and raphe nuclei, these structures may be viewed as a tightly integrated system that participates both in the response to stress and the self-administration of ethanol.

One model of chronic stress is produced when infant rhesus monkeys are separated from their mothers at birth and reared in a nursery. Nursery-reared monkeys show an array of behavioral, cognitive, and physiological differences from similar animals raised by their mothers. We are now requesting support to continue a series of studies designed to examine the effects this early stress has on ethanol self-administration when ethanol is available either in a limited or free-access environment. We further propose to examine the status of the HPA axis and central serotonin system both before and after exposure to self-administered alcohol in each environment. Taken together, these studies will be the first of their kind in any primate species and will help to illuminate the residual neurobiological effects of childhood stress, the effects of long-term alcohol self-administration in normal monkeys, and the interaction of childhood stress with alcohol self-administration later in life. The "early stress – later alcohol" interaction is an important research area that has largely been unexamined in primates.

These experiments will permit us to test two sets of hypotheses. First, that early stress fundamentally alters the neuroendocrine and central serotonin systems, and that these alterations may be related to increased ethanol self-administration. Second, that the presence or absence of early childhood stress creates alternative developmental pathways that will determine the way the neuroendocrine and serotonin systems respond to the long-term self-administration of ethanol later in life.

To test these hypotheses we will examine the following specific aims:

**Aim 1** will test the hypothesis that early stress fundamentally alters the neuroendocrine and serotonin systems. Specifically, we hypothesize that compared to mother-reared controls, nursery-reared young adult monkeys will:

**Aim 1a:** show blunted neuroendocrine responses to a variety of pharmacological challenges.

**Aim 1b:** show higher levels of serotonin transporters, and lower densities of 5-HT1A receptors and

higher densities of 5-HT1D, 5-HT2A, and 5HT3 receptors, as measured with quantitative *in vitro* autoradiography.

**Aim 2** will test the hypothesis that early stress will lead to drinking patterns indicative of excessive alcohol consumption. Specifically, we hypothesize that compared to mother-reared controls, nursery reared monkeys will drink daily fixed doses of alcohol more rapidly and will consume greater amounts of alcohol when it is available *ad libitum*.

**Aim 3** will test the hypothesis that early stress will lead to alterations in the response of the neuroendocrine and brain serotonin systems resulting from exposure to alcohol. Specifically, we propose that compared to mother-reared controls, nursery-reared young adult monkeys who have consumed large amounts of alcohol will:

**Aim 3a** show a blunted neuroendocrine responses to a variety of pharmacologic challenges.

**Aim 3b** show higher densities of serotonin transporters, lower densities of 5-HT1A receptors, and higher densities of 5-HT1D, 5-HT2A , and 5HT3 receptors, as measured with quantitative *in vitro* autoradiography.

**Aim 4** will create a tissue bank. The tissue to be acquired in this study will be very valuable, but we will only be able to study a portion of it. Aim 4 is therefore to catalogue and bank the rest of the brain tissue and samples collected from other organs to assure that it is available for future study when resources become available or when other investigators are able to use it.