

**Grant # DA16556**

**Center Director: Rajita Sinha, Ph.D.**

### **Center Overview**

Cocaine addiction is a chronic relapsing disorder with devastating psychosocial, health and societal consequences. Emerging data clearly indicate the importance of studying sex-specific effects in cocaine dependence - a growing problem for women in this country. Stress has been identified as one of the key factors in increasing the vulnerability to develop cocaine dependence in women. Women also report stress and negative mood as playing a pivotal role in the continued drug use and relapse cycle. While there have been attempts to understand the mechanisms underlying the association between stress and cocaine addiction, systematic research on sex-specific factors that contribute to this association has been rare. The goal of this Center is to use interdisciplinary approaches of examination: (A) to assess the effects of early life stress, sex hormones and stress hormones on cocaine reinforcement and the risk of developing cocaine dependence; and (B) to understand the contribution of sex-based factors in the association between stress and cocaine relapse. These goals will be achieved using multidisciplinary laboratory and clinical research conducted in animals and in humans. A greater understanding of the interactions between sex, stress and cocaine dependence will be significant in the development of sex-specific prevention and treatment approaches that will specifically affect the health of women with cocaine dependence. The following specific aims will be achieved by the SCOR: (1) To establish a collaborative multidisciplinary research Center that will address the study of sex-specific factors in the relationship between stress and cocaine addiction. (2) To conduct a series of programmatic animal and human research studies aimed at understanding sex-specific factors in the relationship between stress and cocaine addiction. (3) To develop a collaborative research program that will utilize SCOR core resources to facilitate the investigation of sex-specific factors in ongoing independently funded research at Yale relating to the etiology, neurobiology and treatment of cocaine addiction. (4) To assist a range of young investigators from different disciplines in conducting sex-specific research on stress and cocaine addiction through mentorship activities of Center staff.

**Principal Investigator: Jane R. Taylor, Ph.D.**

**Project 1: Molecular Basis of Sex Differences in Cocaine Addiction**

Studies with both rats and nonhuman primates demonstrate that sex can be an important vulnerability factor for cocaine abuse. Females are more sensitive than males to the reinforcing effects of drugs. Estrogen, in particular, may play an important role in modulating the reinforcing and locomotor activating effects of psychomotor stimulants. An additional factor in the vulnerability to initiate drug self-administration is stress. We hypothesize that estrogen, stress and cocaine converge to activate the dopamine-regulated molecule DARPP32, and that this underlies the enhanced vulnerability to behavioral effects of cocaine seen in female animals. This may also increase the risk of female animals to stress-induced relapse to cocaine self-administration. In Specific Aim 1 we will identify interactions between sex, stress, and ovarian hormones on acquisition of cocaine self-administration. The effect of maternal separation stress on acquisition of cocaine self-administration will be compared in male and female rats and in ovariectomized females with and without estrogen replacement. An additional goal of this study is to explore the molecular neuroadaptations that underlie the effects sex, estrogen, and stress on cocaine self administration. Cocaine increases synaptic dopamine, which acts at D1 receptors, leading to phosphorylation and activation of DARPP32, an inhibitor of protein phosphatase 1, by PKA. This signaling pathway is critical for modulating both the reinforcing properties of drugs of abuse and the persistent neuroadaptations associated with cocaine exposure, stress and estrogen treatment. In Aim 2 we will investigate whether sex and ovarian hormones modulate cocaine self-administration through activation of the DARPP-32 signaling pathway. Although DARPP-32 is critical for the reinforcing properties of cocaine in male mice, it is unknown whether this is influenced by sex, estrogen or stress. In Aim 3, genetic manipulation of DARPP-32 will be used to examine the ability of this molecule to modulate the effects of sex, estrogen, and stress hormones on the rewarding properties of cocaine using knockout mice that lack either DARPP32 or its homologue I-1. It is hypothesized that female mice lacking DARPP-32 or I-1 may show a greater attenuation in the behavioral properties of cocaine than males. These experiments are of great significance for women's health since they may help to identify a molecular mechanism underlying the convergent behavioral effects of cocaine, estrogen and stress and thus lead to novel treatment strategies for cocaine abuse in women.

**Principal Investigator: Rajita Sinha, Ph.D.**

**Project 2: Sex Differences in Stress Related Relapse**

Cocaine dependent individuals, particularly women, frequently cite psychological stress/negative mood as reasons for relapse to drug use. However, there is little understanding of how stress/negative mood increases the risk of relapse in men and women. Preclinical research indicates that stress increases cocaine self-administration and cocaine reinstatement involves via interaction of brain stress systems, namely corticotrophin releasing factor (CRF)-hypothalamic-pituitary-adrenal (HPA) axis and central noradrenergic-sympatho-adrenomedullary pathways with reward circuits. Our previous work with cocaine dependent individuals has shown that imagery exposure to stress and to drug cue situations reliably increases cocaine craving, physiological arousal and activates the above brain stress systems. Pilot data also suggests sex differences in stress-induced and drug cue-induced activation of these systems. In addition, early trauma, stress/drug cue reactivity and recent stressors each are significantly associated with cocaine relapse in women as compared to men. Thus, in a sample of 150 treatment-seeking cocaine dependent men and women (75 men and 75 women), we will systematically examine sex differences in the association between early trauma, recent stressors, stress/drug cue reactivity and cocaine relapse. The following specific aims will be addressed: (1) To examine sex differences in measures of cocaine craving, emotion state, HPA activation, plasma catecholamine response and physiological arousal in response to stress imagery, drug cue imagery and neutral imagery; (2) To examine sex differences in the association between early trauma, recent stressors and stress/drug cue reactivity. (3) To assess sex differences in the effects of recent stressors, early trauma history and reactivity to stress/drug cues on cocaine relapse after inpatient cocaine treatment; (4) To explore whether demographic and individual difference variables such as race, age, psychiatric co-morbidity, frontal executive functioning and cocaine dependence severity are significantly associated with stress/drug cue reactivity and cocaine relapse. Findings from this study will have important implications for the development of sex-specific treatment approaches in preventing cocaine relapse in women.

**Principal Investigator: Thomas R. Kosten, M.D.**

**Project 3: Gender in fMRI Response to Stress in Cocaine Dependence**

Our research group has been examining stress disorders and gender differences for over 20 years and discovered a variety of biological abnormalities and pharmacotherapies. Responses to stress and to cocaine cues strongly affect the propensity to become dependent and to relapse after attaining abstinence and may differ in men and women. Gender differences in functional brain imaging responses to emotional stimuli and in the neuroendocrine response to stress are well documented. Our current fMRI work has shown that, in response to cocaine cues the anterior cingulate (AC) activates positively in cocaine dependent subjects compared to healthy controls. However, in response to stress, healthy controls activate the AC more than cocaine dependent individuals. This difference in AC activation is an important difference between cocaine cues and stressors as precipitants to cocaine use. Gender differences in these vulnerabilities may be related to different neural pathways and may form the basis for differences between genders in coping strategies and treatment outcome. A specific environmental vulnerability factor for gender differences in these neural pathways may be early life stress of physical and sexual abuse, which is a linking concept to the animal studies in this SCOR Center. In a sample of 25 male and 25 female healthy controls and 25 male and 25 female cocaine dependent subjects we will use blood oxygen level dependent (BOLD) functional magnetic resonance imaging (fMRI) to measure brain activation in two imaging sessions on each subject. Each imaging session will measure the response to personalized stressful, cocaine cue and neutral audiotaped scripts. The specific aims are: (1) To assess gender differences in brain activation patterns in response to stress and cocaine cues in cocaine dependent and healthy subjects. (2) To examine gender differences in intrasubject variability on fMRI responses to stressful, cocaine cue and neutral audiotaped scripts. (3) To explore whether frontal brain activation in response to stress varies as a function of the presence or extent of early trauma and whether or not this effect is greater in women compared to men.