Yale University

Theme: Sex, stress, and substance use disorders

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Abstract

Competitive Renewal of the Yale SCOR on Women Health: Sex, Stress and Substance Abuse
Substance use disorders (SUDs) are chronic relapsing illnesses with devastating psychosocial, health and societal consequences. Differential susceptibility to SUDs in men and women is well known. Historically, prevalence of disorders such as cocaine abuse is higher in men than women, but emerging evidence indicates that adolescents girls are as likely or slightly more likely to use and abuse substances, such as cocaine, than adolescent boys. Stress is a major factor increasing the vulnerability to develop SUDs in girls and in women. Our current SCOR findings indicate that females are more vulnerable to the addictive properties of abusive drugs and that stress markers such as early trauma and altered stress neurobiology plays a pivotal role in the continued drug use and relapse cycle in women. In this SCOR competitive renewal, we propose translational research that will systematically examine mechanisms of such increased vulnerability in girls and in women. Continued support is requested to conduct interdisciplinary studies to address the following three scientific goals: (1) to examine sex differences in the neural and psychobiological effects of prenatal cocaine exposure (PCE) on stress responses affecting risk of developing SUDs; (2) to evaluate the effects of sex-specific factors in the association between stress, drug seeking and vulnerability to cocaine relapse; and (3) to build scientific collaborations through consultation and research support so as to increase the study of sex-specific effects on stress and drug abuse among investigators locally, regionally and nationally. These goals will be accomplished by means of basic science and clinical studies conducted in animals and in humans. A greater understanding of these interactions will directly

affect the development of sex-specific prevention and treatment approaches that will enhance the health of addicted women and their families. The following specific aims will be achieved by the SCOR: (1) To conduct a series of translational research projects on the interdisciplinary study of sex-specific effects in the association between stress and SUDs across the lifespan; (2) To extend the SCOR collaborative research program utilizing SCOR core scientific resources to facilitate the investigation of sex-specific factors in ongoing independently-funded research relating to the etiology, neurobiology and treatment of SUDs that includes faculty and research at other institutions; (3) To assist a range of young investigators from different disciplines both at Yale and at other institutions in conducting sex-specific research on stress and drug abuse through mentorship, research support and scientific consultation;(4) To establish inter-SCOR collaborations on common stress mechanisms to study similarities and differences in biological and social factors that contribute to stress-related disorders affecting women's health.

Project 1: Sex and Stress Mechanisms of Vulnerability to Addiction
Type: Basic

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Sex and stress are known vulnerability factors for addiction, with females and stress-experienced individuals being more sensitive to the reinforcing effects of drugs. Stress also increases recidivism by exacerbating both physiological and psychological symptoms. We hypothesize that sex, stress and cocaine converge within the ventral tegmental area (VTA) having similar, and potentially additive, effects on dopamine (DA) signaling. Ultimately, this leads to altered signal transduction within cortico-limbic-striatal regions. Our preliminary data demonstrate a role for the stress hormone, corticotropin-releasing factor (CRF), in the behavioral, neurochemical and molecular responses to cocaine. We have found that VTA CRF regulates behavioral responses to cocaine; it increases the release of CRF into the VTA and this release sensitizes with repeated cocaine administration. VTA CRF antagonism also blocks cocaine self-administration and cocaine-induced locomotor sensitization. Here we will characterize vulnerability factors associated with addiction using well-established tasks that measure critical processes that contribute to addictive behavior - acquisition, binge, reinstatement - to determine the role for CRF receptor subtypes (CRFR1 or CRFR2) and sex in these effects. Our goal is to establish the mechanism by which VTA CRF contributes to cocaineinduced changes in DA signaling and molecular neuroadaptations within the nucleus accumbens, prefrontal cortex and amygdala using in vivo microdialysis, Western blot analysis of downstream molecular markers (e.g., GluR1, AFosB, CDK5) and proteomics. Aim 1 will determine whether VTA CRF signaling is more sensitive in females compared to males following acquisition of and relapse to cocaine self-administration. We will examine how sensitivity is related to estrus cycle and

determine the role of estrogen and progesterone on cocaine-induced VTA CRF responses. Both cue- and stress-induced relapse will be investigated. We will also use a transgenic line of mice in which gonadal sex and chromosomal sex are independent to test the hypothesis that components of addiction are differentially mediated by sex chromosomes and gonadal hormones. Our preliminary data show independent contributions of chromosomal sex and gonadal sex in habit formation and cocaine-induced locomotor sensitization. Aim 2 will examine whether prior stress experience sensitizes cocaine-induced CRF responses and intracellular signaling in the VTA to test the hypothesis that these effects are more pronounced in females. Aim 3 will use CRF receptor deficient mice to establish whether CRF receptors are necessary for cocaine self-administration. Acquisition of and relapse to cocaine self-administration (cue and stress) and VTA CRF responses in males and females will be assessed after prior chronic stress. Together our studies will clarify the relationship and potential converging effects of sex and stress on VTA functioning in vulnerability to addiction.

Project 2: Sex Differences in Stress Arousal in Cocaine Exposed Youth at Risk for Addiction
Type: Clinical

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Abstract

Adolescence is a critical period in the maturation of a subcortical-prefrental neural system central to stress regulation and the regulation of hedonically-driven behaviors such as drug use and abuse. Emerging preclinical data support the observation that prenatal and early life stressors constitute an important vulnerability factor associated with dysregulated stress response mechanisms in adolescence and young adulthood. That is, a key mechanism for the initiation of drug use and abuse in adolescence may be a dysregulated balance between reward and stress response systems. Further, there is evidence of a significant association between early trauma history before age 18, recent adverse life events, laboratory induced acute stress/drug cue reactivity and drug use relapse in addicted women, as compared to men. These findings suggest that the proposed dysfunctional stress-regulation system as one mechanism for initiation of drug use and then abuse in adolescence may be differentially more active in girls compared to boys. We propose to study adolescent response to stressors and gender differences in that response in a well characterized cohort of adolescent males and females beginning at age 14 who have been studied since birth and who were exposed or non-exposed to cocaine and other drugs prenatally. Both exposed and nonexposed adolescents have grown up in psychosocial adversity with one

group also exposed to the early stressors of a drug-using environment. This cohort provides a unique opportunity to examine the relation between early experience and functioning assessed prospective^ and stress response and drug use in adolescence. Two hundred adolescent girls and boys will participate in laboratory based stress-induction sessions with detailed assessments of their behavioral and physiological response. Adolescents will then be followed with biyearly assessments of drug use and other risk taking behaviors. Specifically we aim to examine sex differences in adolescents as well as the impact of early life stressors, especially prenatal exposure to drugs of abuse, in measures of emotion state, HPA activation, physiological arousal and urinary catecholamine response to both a social stress and to stress, appetitive and neutral imagery; to examine the interaction between early life stressors and current adverse life events on adolescent response to social stress and stress imagery and to examine the relation between stress response as measured physiologically and behaviorally and initiation of drug use in a one to four year follow-up period. Understanding possible mechanisms for the initiation of drug use and early abuse, and how these mechanisms work differentially in females and males will inform the development of more effective and targeted interventions in adolescents at risk.

Project 3: Sex Differences in fMRI of Stress in Cocain-Exposed Youth at Risk for Addiction

Type: Clinical

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Abstract

Addictions constitute the most costly medical illnesses in society today. Onset of drug addiction often begins in adolescence and an improved understanding of the neural correlates of addiction vulnerability within this developmental period has significant implications for prevention and treatment interventions. Few prior investigations have followed at-risk cohorts from birth through adolescence, and many have focused on boys, generating a relative deficiency in our understanding of these processes in girls and in how boys and girls differ. No longitudinal studies to date have used brain imaging to identify how boys and girls at risk for addiction differ in brain function. Furthermore, although cocaine and other drug exposure in utero remains a significant public health problem, no studies to date have examined the influence of such exposure upon human adolescent brain function or addiction vulnerability. We propose examining 120 adolescent girls and boys 13-15 years of age who have been followed since birth, and were either prenatally cocaine-exposed to (PCE) or non-drug exposed in utero (NDE) and are matched on important sociodemographic features that categorize them as particularly vulnerable to the development of addiction. We propose using fMRI to investigate gender differences in the neural correlates of stress-responsiveness using an fMRI paradigm that our group has developed and used in prior SCOR-supported research. Our prior SCOR research

found that adult men and women differed in the neural responses to individualized stress, appetitive and neutral scripts within limbic or "emotion-related" brain regions including caudate, amygdala, hippocampus and anterior cingulate, and that these differences in activations were largely observed during the stress scripts. Furthermore, these responses were differentially altered by chronic cocaine abuse in men and women. We propose using this paradigm to examine: 1) sex differences in the neural correlates of stress-responses in these younger individuals at increased risk for addiction; 2) sex differences in neural activations related to inutero cocaine exposure; and, 3) the stress-related brain activity that is predictive of subsequent substance use behaviors in girls and boys and how they differ across sex group. Findings from this study will provide critical gender-specific data on brain correlates of stress responses in adolescent girls and boys and provide insights into the risk related neural pathways in adolescent addiction.

Project 4: Sex Differences in Progesterone Effects on Responses to Stress and Drug Cues
Type: Clinical

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Abstract

Stress, drug cue exposure and cocaine itself potently stimulate stress and reward systems in the brain and each increase drug craving, thereby increasing the susceptibility to relapse. Women, in particular, show a greater stress and negative affect related susceptibility to relapse. Previous SCOR-related research shows clear sex differences in stress responses, behavioral effects of cocaine and in negative affect and anxiety associated with cocaine craving and stress related relapse susceptibility. However, no previous research has examined the basis of sex differences in stress and cue induced craving and arousal, both of which are known to increase relapse susceptibility. Cumulating evidence suggest that gonadal hormones, estradiol (E) and progesterone (P), may contribute to these sex differences. While E enhances behavioral responses to cocaine, P attenuates subjective, behavioral and physiological responses to cocaine. Whether gonadal hormones such as progesterone affect stress and drug cue-induced craving, and mediate vulnerability to cocaine relapse, especially in women has been studied thus far. Our preliminary findings in cocaine dependent women suggested that high levels of luteal phase P was associated with decreases in stress and drug cue-induced drug seeking, anxiety and blood pressure responses. On the basis of these data, we hypothesize that progesterone treatment vs. placebo will decrease stress and drug cue-induced cocaine craving, negative affect and alter physiological and HPA responses to stress, and these changes will be greater in women than men. In a sample of 120 treatment-seeking cocaine dependent men and women (60 men and 60 women), the following specific aims are proposed: (1) to examine if progesterone alters stress

and cue-induced craving, anxiety and negative emotion responses in cocaine dependent men and women, with sex differences in these effects; (2) To assess progesterone's sex-specific effects on HPA axis measures (ACTH, cortisol and prolactin) during stress and drug cue exposure; (3) To examine progesterone's sex-specific effects on cardiovascular responses to stress and drug cue exposure and to assess its effects on plasma catecholamines; (4) To explore whether progesterone's effects on craving, HPA axis and sympathetic responses are associated with neuroactive steroids and whether these are differentially affected in men and women. Findings from this study will (A) provide a greater understanding of the effects of progesterone, a key gonadal hormone, and it's role in stress regulation, stress-related cocaine seeking and relapse vulnerability, and (B)contribute crucial information needed to develop progesterone as a potential pharmacotherapy to prevent stress-related cocaine relapse in women.

CORES

Core A. Administrative Core

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Abstract

The Scientific and Administrative Core will be the central organizing force for this research SCOR. It will provide scientific and administrative support to conduct translational and interdisciplinary studies to address the following three scientific goals: (1) to examine sex differences in the neural and psychobiological effects of prenatal cocaine exposure (PCE) on stress-related factors increasing risk of developing drug abuse; (2) to evaluate the effects of sex-specific factors in the association between stress, drug seeking and vulnerability to cocaine relapse; and (3) to build scientific collaborations through consultation and research support so as to increase the study of sex-specific effects on stress and drug abuse among investigators locally, regionally and nationally. It will provide Core resources and support to basic science and clinical studies conducted in animals and in humans across the lifespan. The aims of this Core will be the following: (1) To provide scientific planning, integration, synthesis and oversight of Center goals by the Principal Investigator, Co- Director and the Executive Committee, with consultation from the Scientific Advisory Board; (2) To provide fiscal and administrative oversight to the SCOR, its component and affiliated projects; (3) To provide scientific consultation and support to SCOR research collaborations with junior and senior investigators at Yale and at other research institutions to examine sex-specific hypotheses pertaining to stress and SUDs in the proposed specific aims of their respective research; (4) To coordinate human subject recruitment across SCOR projects by facilitating recruitment of subjects, especially women and minorities, to achieve the goals of the Center and its component and affiliated projects; (5) To assist

component and affiliated projects through coordinated data collection, data management and statistical analysis approaches and in core laboratory resources for processing sex and stress hormones; (6) To maximize the yield across individual studies by utilizing a core battery of methods and assessments and coordinating the training of assessments and methods centrally; and (7) To facilitate inter-SCOR collaborations on common stress mechanisms in order to study similarities and differences in biological and social factors affecting stress-related disorders in women's health.