

University of Miami

Theme: Sex and gender influences on addiction and health: a developmental perspective

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Abstract

This proposal seeks to establish a Specialized Center of Interdisciplinary Research (SCOR) on the overarching theme of sex and gender factors affecting addiction and health. The Center's mission is to address the health concerns of women and their developing offspring affected by drug abuse by providing the optimal environment to encourage and facilitate clinical and translational research. The approach will be to use interdisciplinary translational and clinical studies to assess sex/gender-specific differences in vulnerability to drug-taking and drug effects across development in adolescent and adult females and males with and without prenatal exposure to cocaine and other drugs. Project #1 (PI: Dow-Edwards), "Sex Differences in Drug Effects: The Prenatal Trajectory", is a series of preclinical translational studies using an established rat model of prenatal drug exposure. This project will examine the roles of prenatal cocaine exposure, postnatal environment, and polydrug exposure (cocaine with nicotine, THC, and alcohol) in the development of drug-taking behavior in male and female adolescent rats, emphasizing sex differences in conditioned place preference for cocaine and elucidating the potential biologic basis for sex differences by functional imaging and neurochemical assessments. Project #2 (PI: Izenwasser), "Sex Differences in Drug Effects: The Adolescent Trajectory" is a series of preclinical translational studies, the focus of which is to study the effects of nicotine, marijuana (A9-THC) and cocaine in male and female adolescent and adult rats on behavior and neurochemistry during adolescence and later during adulthood. Project #3 (PI: Bandstra), "Sex and Gender Influences on Adolescent Drug Involvement" is a clinical investigation of sex and gender differences affecting risk for drug abuse in adolescents (and

ultimately as adults) with and without prenatal exposure to cocaine and other drugs. Subjects were enrolled in the Miami Prenatal Cocaine Study (n=476); and assessed through early adolescence (retention 85%) for neuropsychological and other outcomes. In this proposal, subjects will be assessed at age 16 and 18 years by self-report and biomarkers for drug involvement, caregiver and self-report of psychosocial risk factors, and laboratory measures of stress reactivity, risk-taking, and decision-making. Analyses will include consideration of the influence of prenatal cocaine exposure on later drug involvement in the female and male adolescents. The Administrative Core will host a Scientific Steering Committee and Internal and External Advisory Committees of interdisciplinary investigators with relevant expertise. Enhanced understanding of the differential effects of drugs of abuse in females and males across development (from prenatal to postnatal exposures during adolescence and adulthood) should lead to improved sex-, gender-, and age-specific preventions and treatments for drug addiction and related conditions.

Project 1: Sex and Stress Mechanisms of Vulnerability to Addiction

Type: Basic

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Abstract

Human studies of children exposed to cocaine prenatally reveal a constellation of effects which include altered attention, affect, arousal regulation and cognitive function. While the effects often differ depending on the sex of the individual, no studies to date have investigated the effects of prenatal cocaine exposure on drug-taking behaviors in female and male offspring. Others have found that postnatal environment plays a role in the manifestation of the effects of many in utero exposures. Since animal studies can differentiate the biological effects of prenatal cocaine exposure from the effects of postnatal environment, we propose to examine the role of postnatal environment in the manifestation of prenatal cocaine effects in male and female offspring. Studies will parallel the clinical projects which are examining drug taking behavior in adolescent male and female subjects exposed to cocaine prenatally.

Aim 1: to determine the role of prenatal cocaine exposure in the function of reward circuits in female and male adolescent rats. Prenatally exposed male and female rats will be tested for conditioned place preference (CPP) as adolescents following rearing in an impoverished or a moderately enriched environment. Aim 2: to determine the role of prenatal poly-drug exposure along with cocaine in the development of the reward circuits in male and female rats. The effects of prenatal nicotine, THC and alcohol along with cocaine on CPP for cocaine will be determined

in female and male adolescents. Aim 3: to determine the biological basis for the sex differences in reward circuits using functional imaging techniques and neurochemical assessments. Studies will be carried out in subjects treated as in Aims 1 & 2 which show the greatest effects of prenatal cocaine in female and male adolescents undergoing CPP. Following CPP training with a dose of cocaine found to differentiate the prenatal cocaine subjects from the controls, functional imaging studies will be carried out on the test day to visualize the circuits activated by the drug cue. Other rats at 50 days of age will be sacrificed without undergoing CPP and the brains sent to U. Miami for neurochemical assessments.

Together these studies will determine the influence of two major confounders in clinical studies (environment and polydrug use) on the effects of prenatal cocaine exposure emphasizing the differences/similarities of male and female subjects in drug taking behavior using an appropriate preclinical model.

Project 2: Sex Differences in Drug Effects: The Adolescent Trajectory

Type: Clinical

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Abstract

Epidemiological studies have suggested that exposure to drugs such as nicotine and marijuana during adolescence is correlated with a significantly higher incidence of subsequent use of other drugs such as cocaine. In addition, there are different responses between female and male adolescents in response to drug use. Animal laboratory studies have shown that female and male rats respond differently to drugs and that the neurochemical adaptations that occur also differ. Studies have shown that drug administration during adolescence leads to differential neurochemical and behavioral effects than drug administration during adulthood. In addition, many of the effects of drugs during this critical developmental period have longlasting effects that persist into adulthood. In general, the studies suggest that there may be an increased vulnerability to the effects of drugs during adolescence and that the effects differ across both sex and age. The main hypothesis of this proposal is that females and males will respond differently to drugs during different stages of development and that it may therefore be necessary to develop sex- and age-specific treatments for drug addiction. The focus of this proposal is to study the effects of nicotine, marijuana (A9- THC) and cocaine in female and male adolescent and adult rats on behavior and neurochemistry during adolescence and later during adulthood. In addition, the effects of environment on the changes produced by these drugs will be examined. An understanding of the differential effects of drugs in females and males during adolescence, and

of how these changes use impact drug effects in adults may lead to sex- and age specific treatments for drug addiction.

Project 3: Sex and Gender Influences on Adolescent Drug Involvement

Type: Clinical

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Abstract

SCOR Project #3 (Bandstra) relates to the overall Center and the preclinical projects in that it examines an important women's health problem (addiction and related disorders) from an interdisciplinary approach over the lifespan from gestation through adolescence, and ultimately, adulthood. The study seeks to answer important questions about previously understudied hypothesized sex and gender differences in drug involvement through late adolescence as well as the outcomes of female (versus male) offspring exposed to drugs in utero. The project emanates from a well-established research program on perinatal substance abuse. Participants (low SES, inner-city African American infants and their mothers) were enrolled at delivery (n=476) and have been assessed for developmental, neuropsychological, educational, and social environmental outcomes through early adolescence (retention 85%). Within a developmental model allowing for multiple determinants of behavior and health, this project seeks to estimate male-female differences in progression through levels of adolescent drug involvement, with examination of hypothesized mediators and correlates including stress/coping, internalizing/externalizing behaviors, impulsivity and risk-taking propensity. The influence of in utero cocaine exposure on observed male-female differences will be assessed. Subjects will be tested at ages 16 and 18 by self-report and biomarkers for drug involvement, caregiver and self-report of psychosocial risk factors, and measures of stress reactivity (with salivary cortisol), risk-taking, and decision-making. Benefiting from data from a related K01, the study will have 4 waves of data on drug involvement from ages 12-18 years for analyses with a sex/gender focus and linkage to earlier data on in utero and longitudinal measurements (e.g., neuropsychological functioning, internalizing and externalizing behaviors). Findings should undergird future planned serial assessments of drug involvement into adulthood, when drug dependence among women during child-bearing years is anticipated to be more prominent, endangering their health and that of their offspring. The ultimate goal is enhanced understanding of the differential effects of drugs of abuse in females and males across development (from prenatal to postnatal exposures during adolescence and adulthood), resulting in improved sex-, gender-, and age-specific preventions and treatments for drug addiction and related conditions.

CORES

Administrative Core

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Abstract

This application details a plan to establish a Specialized Center of Interdisciplinary Research (SCOR) entitled "Sex and Gender Influences on Addiction and Health: A Developmental Perspective" with 3 Project Components and this Administrative Core with the overall goal of expediting development and application of new knowledge of specific importance to women's health on the Center theme as described in the Overall Research Plan, Leadership and Resources.

The Administrative Core is responsible for the management and overall direction of the Center, relating to the University, the funding agency, the Center's External and Internal Advisory Boards and Scientific Steering Committee.

The goals of the Administrative Core are as follows:

- 1) Provide leadership to the research enterprise, including overall research management, organization, and direction; oversight and quality control of research data collection, laboratory assays
- 2) Promote the highest standards of human subjects protection, animal care and use, and ethical conduct of research
- 3) Provide administrative and fiscal management and oversight of the studies within the Center
- 4) Foster research education and training

5) Seek additional support for Center expansion through NIH and other governmental research, service, and educational funding agencies and private foundations