University of Chicago
Theme: Sex steroids, sleep, and metabolic dysfunction in women

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The prevalence of obesity and chronic sleep loss are at record levels among Americans and evidence continues to emerge to support a causal link between the two conditions. Metabolic and cardiovascular abnormalities related to sleep disruption are particularly evident in individuals with obstructive sleep apnea (OSA), a disorder traditionally associated with male gender. While more prevalent in men, OSA is under recognized in women in part because its clinical and polysomnographic features differ from those of men. Women with polycystic ovary syndrome (PCOS) are particularly susceptible to OSA with at least a 5- fold higher risk for its development compared to obese women without PCOS. The overarching aim of this SCOR application is to therefore establish the basis for the apparent gender difference in prevalence of OSA by focusing on the mechanistic role of sex steroids in the pathogenesis of the disorder as well as its metabolic complications. Four Projects sharing integrated hypotheses, aims, and methods, plus an Administrative Core are proposed. In Project 1 (Van Cauter. PI) and Project 2 (Ehrmann. PI) subjects with and without OSA will have detailed assessments of sleep, metabolic, and cardiovascular function; studies will be conducted in serum and urine for metabolomics and in fat biopsies for adipocyte function. Obese men and women with and without OSA will participate in Project 1: those with OSA will be treated with continuous positive airway pressure (CPAP) and its impact on baseline measures will be assessed. Project 2 will enroll obese women with PCOS, with and without OSA. Those with OSA will receive CPAP or will be randomized to receive depot leuprolide to suppress ovarian steroid output over 12 weeks, reassessed at 6 weeks, and then randomized (double-blind, placebo controlled) to 6 weeks of either micronized estrogen + placebo or micronized progestin + placebo. The independent effects of androgen, estrogen, and progesterone on OSA and metabolic function will be assessed. Project 3 (Mittendorfer, PI) will focus on mechanisms responsible for increased plasma triglyceride (TG) concentration, a finding common to both OSA and PCOS. Studies of VLDL-TG kinetics will be undertaken before and after modulation of plasma glucocorticoid, progesterone, and testosterone concentrations. In Project 4 (Brady. PI) primary human adipocytes will be prepared from fat biopsies obtained in Projects 1 - 2. Insulin sensitivity will be determined by phospho-specific immunoblotting in conjunction with glucose uptake and anti-lipolysis assays. In parallel, adipocytes from these subjects will be cultured for 1-5 days prior to metabolic assays to ascertain if removal of from circulating factors will improve insulin signaling, or if insulin resistance persists in vitro. Finally, the Administrative Core will have oversight of all Project functions; interface with the Metabolomics Laboratory at Duke University (C. Newgard, Lab Director); and coordinate meetings of the External Advisory Committee.

Project 1: Sleep and Metabolism in Obesity: Impact of Gender
Type: Clinical

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Obesity is a major risk factor for obstructive sleep apnea (OSA), a condition characterized by repetitive respiratory disturbances, intermittent hypoxia, sleep fragmentation by frequent microarousals and low amounts of deep slow wave sleep [SWS]). Today, more than 10 million American women suffer from OSA. OSA has been identified as an independent risk factor for the metabolic syndrome. Because OSA is more prevalent in men than in women, a disproportionate number of studies of OSA and its consequences have been conducted in men. Thus, OSA has been characterized as a disorder associated with gender-based health care inequity. Recent evidence, including data from our group, suggests that reduced amounts and intensity of SWS (i.e. slow-wave activity [SWA]) may play a pivotal role in the development of metabolic and cardiovascular disturbances in obese men and women, particularly those with OSA. The present project will focus on sex differences in SWA and their relationship with daytime sleepiness and metabolic vulnerability in obese men and women with and without OSA. We propose to simultaneously characterize: 1. sleep-wake regulation; 2. measures of diabetes risk 3. measures of cardiovascular risk and 4. profiles of sex steroids, cortisol and adipokines in a. obese men without OSA, b. obese men with OSA before and after treatment with continuous positive airway pressure (CPAP), c. obese pre-menopausal women without OSA, and d. obese pre-menopausal women with OSA before and after CPAP treatment. The completion of these interdisciplinary studies will provide a unique data set contrasting in obese women versus obese men the relationships between sleep and the metabolic syndrome, OSA and the metabolic syndrome and the impact of CPAP treatment on the metabolic syndrome. The proposed work will provide important insights regarding the pathophysiology of OSA and its adverse consequences in obese men and women, and the basis for the development of effective sex-specific prevention and treatment strategies.

Project 2: PCOS, Sleep Apnea, and Metabolic Risk in Women
Type: Clinical

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Obstructive sleep apnea (OSA) appears to be an under recognized, yet significant factor in the pathogenesis of metabolic derangements in polycystic ovary syndrome (PCOS). Recent findings suggest that there may be two "subtypes" of PCOS, i.e. with or without OSA, and these two subtypes may be associated with distinct metabolic and endocrine alterations. PCOS women with OSA may be at much higher risk for diabetes and cardiovascular disease than PCOS women without OSA and may benefit from therapeutic interventions targeted to decrease the severity of OSA. Thus, a major goal of the present project is to contrast the metabolic and hormonal features of these two subtypes of PCOS, explore causative mechanisms for the high prevalence of OSA in PCOS, and test the hypothesis that continuous positive airway pressure (CPAP) treatment may decrease the risk of diabetes and other cardiovascular and metabolic abnormalities in PCOS women with OSA. In Specific Aim 1 we will determine if women with PCOS who have OSA differ from those without OSA as a consequence of differences in circulating concentrations estrogen and progesterone. We will further test our hypothesis by comparing stimulated steroid levels in response to a single dose of the GnRH agonist leuprolide in PCOS women with and those without OSA. In Specific Aim 2. we will determine if OSA improves in women with PCOS treated with estrogen or, progesterone. For these studies, we will enroll women with PCOS who have OSA. Subjects will have a detailed baseline metabolic and metabolomic profile together with a baseline polysomnogram. Subjects will then receive a single dose of depot-leuprolide in order to suppress ovarian production of estrogen, progestin, and androgen over a period of 3 months. Six weeks after administration of depot-leuprolide, subjects will have repeated assessment of metabolic, metabolomic, and sleep measures to determine if these outcomes are altered by the combined suppression of ovarian sex steroids. Subsequently, subjects will be randomized in a double-blind placebo controlled fashion to one of two treatment arms for a period of six weeks. Treatment arms are: estrogen plus placebo or progesterone plus placebo. At the end of this second six weeks, subjects will have metabolic, metabolomic, and sleep measures repeated. Primary outcome measures will be compared both within and between treatment arms. In Specific Aim 3. we will determine if metabolic disturbances present in PCOS women with OSA are ameliorated by the treatment of OSA with continuous positive airway pressure (CPAP). Results of our preliminary studies indicate that CPAP treatment of OSA results in attenuation of cortisol levels not only during sleep, but throughout waking hours as well. This aim will serve to test the hypothesis that correction of OSA in PCOS will lead to improved metabolic function which can be attributed, at least in part, to a reduction in circulating levels of cortisol.

Project 3: Sex steroids, Sleep, Body Fat, and Plasma Triglycerides in Women
Type: Basic

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Increased plasma triglyceride (TG) concentration is a common feature of the metabolic abnormalities associated with obesity and a major risk factor for cardiovascular disease. Obesity is a major risk factor for two conditions that appear to be increasing in prevalence in women: the polycystic ovary syndrome (PCOS) and sleep disordered breathing. PCOS affects 5-8% of women. Sleep disordered breathing affects up to 10% of women. Obstructive sleep apnea (OSA) is the most common cause for sleep disordered breathing and particularly prevalent in obese women with PCOS (~50%). Both PCOS and OSA augment the increase in plasma TG concentration associated with obesity, and the effects of PCOS and OSA on plasma TG concentration appear to be additive. The mechanisms responsible for the adverse effects of PCOS and OSA on plasma TG metabolism are not known. The primary goal of this project, therefore, is to determine the mechanisms responsible for the increase in plasma TG concentration in obese women with PCOS and OSA. It is our general hypothesis that alterations in the hormonal milieu that are characteristic of PCOS (hyperandrogenemia and progesterone deficiency) and OSA (hypercortisolemia) are, at least in part, responsible for the increase in plasma TG concentration in obese women with PCOS and OSA. Furthermore, we hypothesize that the hormonal aberrations, characteristic of PCOS and OSA, are particularly harmful to obese, compared with lean, women. To test our hypotheses, we will measure the rates of hepatic VLDL-TG and VLDL-apoB-100 secretion, VLDL-TG plasma clearance rate, and factors that may affect VLDL-TG plasma clearance (i.e., the concentrations of VLDL-apoC-ll, VLDL-apoC-lll, VLDLapoE) in four groups of subjects: i) obese women with OSA (but not PCOS); ii) obese women with PCOS (but not OSA); iii) obese women without PCOS or OSA; and iv) lean women without PCOS or OSA, both before and after interventions that will alter plasma testosterone, progesterone, and glucocorticoid availability. A better understanding of the mechanisms responsible for plasma TG homeostasis could lead to more effective treatment strategies for women with OSA and PCOS.

Project 4: Assessment of Adipocyte Function in Women with PCOS
Type: Basic

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Abstract

Polycystic ovary syndrome (PCOS) affects up to 10% of women of reproductive age, and is characterized by elevation in circulating androgen levels, insulin resistance, dyslipidemia and obesity. However, the molecular mechanisms that underlie the development of the metabolic syndrome in PCOS remain unclear. The interplay between PCOS and obstructive sleep apnea (OSA) in women may play a critical but under appreciated role in these pathologies. Despite the recent linkage between OSA and insulin resistance, and the finding that obese women with PCOS are up to 30 times more likely to develop OSA as weight matched women without PCOS, most of the studies on OSA and metabolism have been conducted in men. The central hypothesis of this application is that OSA is a novel risk factor for the development of insulin resistance in adipose tissue in women with PCOS. We will test this hypothesis by measuring insulin sensitivity in primary adipocytes from obese PCOS women with OSA, before and after therapeutic intervention for the OSA. Insulin signal transduction and regulation of lipid metabolism will be assayed in vitro and compared to values obtained in vivo. Additionally, we will determine the role alterations in circulating glucocorticoids and the localized activation of glucocorticoids in adipocytes by the enzyme 110- HSD1 on adipocytic insulin action. Finally, the effects of modulating reducing endogenous ovarian androgen production on insulin signaling in adipocytes from obese PCOS women with OSA will be determined, as will the effects of giving exogenous estrogen or progesterone to patients. Together, these studies will comprise an integral part of a larger SCOR application that will undertake a comprehensive examination of the role of OSA and circulating androgen on the development on insulin resistance, obesity and the metabolic syndrome in women with PCOS.

Relevance: Women with PCOS suffer from obesity, metabolic syndrome, dysregulation of sex steroid synthesis and obstructive sleep apnea. However, the inter connections between these various disorders is not well understood. As part of an integrative collaborative project, this application will directly investigate the effects of OSA and androgens on insulin sensitivity in adipocyte biopsies from PCOS patients before and after therapeutic interventions.

CORES

Administrative Core

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Abstract

The Administrative core provides the overall logistic and financial coordination to the SCOR, facilitates the scientific and administrative interactions between the various Projects and ensures that the proposed studies are completed in a cost effective manner. Specifically, the Core performs all bookkeeping and accounting tasks, maintains personnel employment records, orders supplies and coordinates inter-institutional relationships, prepares all required narrative and fiscal reports, organizes all meetings related to the SCOR. The Administrative Core is run by the Principal Investigator (David A. Ehrmann) with the assistance of the Advisory Committee, which serves to evaluate the integration and progress of research efforts. The various functions performed by the Administrative Core greatly enhances the efficiency and integration of the research efforts of the Individual Projects.