Northwestern University

Theme: Excess male hormones (androgens) as the key to explaining polycystic ovarian syndrome (PCOS)

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Center Abstract

The unifying hypothesis of the NU SCOR continues to be that genetic variation resulting in hyperandrogenemia causes many of the phenotypic features of PCOS by prenatal androgen programming as well as by continued androgen excess in the adult. The following exciting findings from the initial award period support this hypothesis: 1) a major PCOS susceptibility variant, allele 8 (A8) of D19S884, has been mapped to intron 55 of the fibrillin-3 gene, 2) a distinctive metabolic phenotype, hepatic insulin resistance, is associated with the A8 variant; 3) prenatal androgen excess causes LH secretory defect, insulin resistance and increased visceral adiposity, all features of PCOS, in animal models; 4) LH secretory changes result from decreased expression of hypothalamic potassium sensitive ATP (KATP) channels that modulate gonadotropin releasing hormone (GnRH) secretion. Prenatal androgen exposure induces resistance to estrogen-mediated increases in KATP channel expression that occur through induction of progesterone receptor expression. 5) Prenatal androgens also decrease expression of KATP channels in pancreatic /?- cells providing one potential mechanism for the metabolic phenotype. Project 1 will investigate the mechanisms of hepatic insulin resistance associated with the A8 genotype in women with PCOS including the role of androgens. Potential sex-specific effects will be investigated in male first degree relatives with A8 genotype. Project 2 will investigate the impact of variation in D19S884 on parameters of glycemic control and pregnancy outcome in mothers and their infants from a large multiethnic population, including the possible association of D19S884 allelic variation with androgen levels in this non-PCOS population. In addition, the potential role of fibrillin-3 itself in the pathogenesis of PCOS will be

investigated by examining the TGF/? signaling pathway, which is potentially modulated by this molecule. Project 3 is a new project that will investigate the cellular and molecular mechanisms of androgen action on pancreatic p-cells. Project 4 will pursue the mechanisms that may mediate androgen programming of the distinctive metabolic phenotype associated with A8, in particular, the hypothesis androgen exposure produces the metabolic defects of PCOS by programming resistance to estrogen's metabolic actions in the brain or periphery.

Project 1 Androgens, Genotype And Insulin Resistance in PCOS
Type: Clinical

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Abstract

We have extremely exciting evidence from the initial award period of Project 1 that hepatic insulin resistance is the major defect in glucose homeostasis associated with the PCOS susceptibility variant. This variant, allele 8 (A8) of the dinucleotide repeat D19S884, was mapped to intron 55 of the fibrillin-3 gene as part of Project 2 of this SCOR. Male first-degree relatives with the A8 variant have evidence for abnormalities in insulin secretion suggesting that the metabolic phenotypes associated with the A8 variant are sex-specific. The central hypothesis of the NU SCOR is that hyperandrogenemia resulting from variation in a gene(s) regulating steroidogenesis causes the PCOS metabolic phenotype by programming actions at critical periods of development as well as by ongoing actions in the adult. We will plan three Specific Aims: 1. To test the hypothesis that hepatic glucose homeostasis differs by A8 genotype in women with PCOS. Postabsorptive hepatic glucose homeostasis, including rates of gluconeogenesis and glycogenolysis, will be assessed with state-of-the-art stable isotope techniques. Responses to stimuli that modulate hepatic glucose production, such as glucagon, hypoglycemia and glucose per se, will be examined. 2. To test the hypothesis that androgens alter hepatic glucose homeostasis, directly or by antagonizing estrogen action, in women with PCOS and that this action differs by A8 genotype. The impact of blocking androgen action with the nonsteroidal receptor antagonist, flutamide, alone and during transdermal estradiol replacement, will be investigated. Endpoints will include hepatic and peripheral insulin action as well as any alterations in hepatic glucose homeostasis identified in Aim 1. 3. To test the hypothesis that metabolic phenotypes associated with A8 are sex-specific in the families of women with PCOS. The impact of A8 genotype on hepatic and peripheral insulin action and on insulin secretion will be examined in the brothers of women with PCOS and in age, weight and ethnicity comparable control men. Since hyperandrogenemia appears to be a final common path to the female reproductive phenotype, elucidating the mechanisms for its association with metabolic defects will be relevant to understanding diverse causes of PCOS as well as an important risk factor for type 2 diabetes.

Project 2 Genetic Analysis Of PCOS/Diabetes Susceptibility Genes
Type: Clinical

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Abstract

PCOS is a common endocrine disorder characterized by hyperandrogenemia and oligomenorrhea/ amenorrhea. In addition to these reproductive features, PCOS is also associated with significant metabolic abnormalities including an increased incidence of obesity and insulin resistance and a 7x increased risk of developing type 2 diabetes mellitus (DM2). Genetic factors, lifestyle, and the prenatal environment are believed to contribute to the etiology of PCOS. Using family-based genetic studies, we have identified a PCOS susceptibility locus, D19S88, within intron 55 of FBN3, the gene encoding the extracellular matrix protein, fibrillin-3. In addition to their structural properties, members of the fibrillin gene family are also important in regulating the TGF/? signaling cascade. Furthermore, the D19S884 disease-associated allele, A8, is associated with both the reproductive and metabolic features of PCOS in PCOS families. Based on these findings we hypothesize that variation in D19S884 alters FBN3 function and/or expression leading to perturbation in TGF/? signaling and that this perturbation is important the development of insulin resistant states such as PCOS, DM2, and gestational diabetes (GDM). In this application, we address the role of variation at D19S884 and the TGF/? signaling pathway in insulin resistant phenotypes with three specific aims. Aim 1 asks whether D19S884 is a susceptibility locus specifically for PCOS in women of European ancestry or whether it also contributes to other insulin resistant states (i.e. pregnancy), is this effect the same in multiple ethnicities, and does D19S884 variation impact pregnancy outcome and fetal growth? These questions will be addressed with D19S884 association studies in the HAPO Study cohort, a multi-ethnic epidemiological study of 25,000 women and their babies collected to address glycemic control during pregnancy and its impact on pregnancy outcome. The second aim asks whether D19S884 allele status correlates with androgen levels in serum of pregnant mothers and/or neonates from the HAPO study. The third aim asks whether TGF/? signaling is altered in PCOS. We will compare expression levels of ~60 genes in the TGF/? signaling pathway in skin, muscle and fat tissues from women with PCOS and controls. These studies will result in a more global understanding of the role of D19S884 variation and TGF/? signaling in PCOS, insulin resistance, and fetal growth - phenotypes that are of significant medical importance.

Project 3. Role Of Androgen Excess In Provoking Ox I Dative Stress In Females
Type: Basic

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Abstract

The polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age in the U.S. The PCOS present with hyperandrogenism accompanied by chronic inflammation, insulin resistance and type 2 diabetes (T2DM). Evidence presented in this proposal suggests that in women and mice, excess testosterone production generates inflammation which alters fat biology and insulin production, thus contributing to insulin resistance, the metabolic syndrome and T2DM. Despite these observations, the evidence that testosterone directly alters insulin secretion from pancreatic p-cells is lacking and the role of testosterone in disrupting fat biology, thus provoking insulin resistance, has not been investigated. The goal of this application is to demonstrate that excess testosterone in females predisposes to the metabolic syndrome and T2DM by acting on AR and provoking oxidative stress in pancreatic p-cells and in fat-cells. The specific aims of this application are: To demonstrate, through use of the p-cell AR knockout mouse (PARKO) that in females, excess testosterone activation of AR in p-cells provokes insulin-deficient diabetes. We will test the hypothesis that excess testosterone activation of AR in p-cells provokes oxidative stress. We will use a fat-cell AR knockout mouse (FARKO) to establish that, in females, excess testosterone activation of AR in adipocytes alters adipocytokines secretion and provokes systemic inflammation and insulin resistance. Finally, we will test the hypothesis using FARKO female mice and adipocytes that excess testosterone action on AR in adipocytes provokes oxidative stress and disrupts adipocytokines production. Successful completion of these studies will help define the AR as a target in hyperandrogenic women. This will help this center program in achieving its goal of supporting research to improve women's health.

Project 4. Fetal Androgen Induces Ovarian, LH and B-Cell Defects
Type: Basic

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Abstract

Polycystic ovarian syndrome (PCOS) is a reproductive and metabolic disorder that occurs in 5-10% of premenopausal women, often producing infertility and increased risk of metabolic and cardiovascular disease. The combined evidence obtained by our SCOR investigators strongly supports our central hypothesis that PCOS has a genetic basis linked to excess androgen production, and that the androgen excess in the intrauterine environment programs the pathogenesis of the disorder. Our animal studies have provided further support for this hypothesis, showing that prenatal androgen exposure can program the development of PCOS-like phenotypic traits in rats and mice. The proposed experiments are designed to determine the mechanisms by which prenatal androgen exposure may program two of the most clinically important of these pathophysiological traits: hepatic insulin resistance and visceral adiposity. We have determined that prenatal androgenization (PNA) produces reproductive dysfunction in adulthood by programming resistance to several classic actions of estrogen (E2) in the brain. Estrogen was also found to induce expression of ATP sensitive potassium channel (KATp) subunit genes in hypothalamus; these channels have been shown to be critically important in the neural control of hepatic insulin sensitivity. Estrogen has also been shown to promote subcutaneous vs. visceral fat deposition by a hypothalamic action. We have therefore proposed the novel hypothesis that PNA programs development of hepatic insulin resistance and visceral adiposity by altering functional development of hypothalamic-autonomic control circuitries, rendering them resistant to regulation by E2, and hence depleted of KATp channels and compromised in their ability to regulate hepatic insulin sensitivity. To test this hypothesis, we will first determine if PNA programs reduced hypothalamic KATP channel expression and reduced hepatic responsiveness to hypothalamic KATP channel activation (Aim 1). We will then assess whether PNA programs impaired responsiveness of hypothalamic neurons to metabolic (Aim 2) and endocrine (Aim 3) signals that regulate hepatic insulin sensitivity. The ability of E2 to regulate hepatic insulin sensitivity and visceral adiposity by a hypothalamic action will then be assessed (Aim 4), using local infusions of E2 in the brain as well as a novel neuron-specific estrogen receptor-a knockout (NERKO) mouse to differentiate hypothalamic versus peripheral actions of E2. Finally, we will test whether PNA blocks E2 effects on these metabolic parameters in adulthood. These studies will provide important new information on mechanisms by which intrauterine androgen exposure programs metabolic pathophysiologies in adulthood, and may thus provide major new insights into the pathogenesis of metabolic dysfunction in PCOS women.

CORES

CORE A. Administrative Core

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Abstract

The NU SCOR brings together leading investigators in the field from a variety of disciplines and specialties to address a major women's health problem, PCOS. The SCOR includes investigators from the Departments of Medicine, Surgery, Cell and Molecular Biology and the Center for Genetic Medicine at the Feinberg College of Medicine and from the Department of Neurobiology and Physiology at the Weinberg College of Arts and Sciences at Northwestern University. It includes faculty based at Northwestern Memorial Hospital and Evanston Hospital. The Administrative Core will continue to be headed by the Director, Dr. Andrea Dunaif, assisted by the Associate Director, Dr. Jon Levine. The Administrative Core provides leadership, coordination of activities, and exchange of information, ideas and common resources for Northwestern University's four SCOR projects. The Administrative Core coordinates educational, training and outreach activities related to the SCOR as well as joint initiatives with the Northwestern University Center for Reproductive Sciences and the NICHD Specialized Cooperative Centers Program Reproductive Research (SCCPRR) Center at Northwestern University. Through these activities, the Administrative Core advances research on sex and gender differences. The primary functions of the Administrative Core are to:

- Provide overall oversight of the Center, including strategic planning and coordination of the research projects;

- Support common activities of the projects, including meetings of the External and Internal advisory committees, the Midwest Interdisciplinary PCOS Study Group and Speaker Series, and any other joint meetings of the project leaders and investigators;
- Coordinate the SCOR Scholar and Fellowship for advanced training in reproductive endocrinology and women's health. Liaise with training grant and career development programs at NU to provide mentoring and career development opportunities related to NU SCOR;
- Coordinate educational training and outreach activities related to the SCOR as well as joint initiatives with the Northwestern University Center for Reproductive Sciences and the NICHD Specialized Cooperative Centers Program Reproductive Research (SCCPRR) Center at Northwestern University;
- Build and enhance intra- and inter-institutional relationships;
- Ensure that NIH management and reporting requirements for all projects are met;
- Manage purchasing, budgeting and fiscal management, and personnel matters for the Center;
- Provide support in the dissemination of findings, including the preparation of reports and manuscripts; and
- Maintain the NU SCOR website, which contains information on the SCOR scientific projects as well as information for the public on PCOS. The website also has links for individuals interested in participating in the Project 1 SCOR research as well as links to other organizations such as the Hormone Foundation of the Endocrine Society, PCOSupport and the PCOSA E-Bulletin. Thus, the website promotes research and public information on sex and gender differences.