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Center Overview

PCOS is among the most common disorders of adolescent and premenopausal women, affecting approximately 710% of this population. It is a high priority and overarching women's health problem with substantial reproductive and metabolic morbidities throughout the lifespan. Dunaif's recent studies on the mechanisms of insulin resistance in PCOS have revealed the surprising finding that defects in skeletal muscle insulin action are acquired secondary to a factor (or factors) in the in vivo environment (Project 1). Dunaif and colleagues' family studies have shown that hyperandrogenemia is the major reproductive phenotype in PCOS kindreds (Figure 3). Urbanek and colleagues have compelling evidence that this phenotype is linked with a marker, D19S884, on chromosome 19p in the region of the insulin receptor gene (Project 2). This marker is also associated with a metabolic phenotype in PCOS women as well as in their brothers characterized by decreased insulin secretion, particularly in response to sulfonylurea (Project 1). Abbott and colleagues have shown that many of the phenotypic features of PCOS, such as ovarian hyperandrogenism, polycystic ovaries, increased LH levels, anovulation, central adiposity and decreased insulin secretion can be produced in rhesus monkeys by intrauterine testosterone exposure (Project 3). Levine has obtained evidence that one mechanism for some of these androgen actions is decreased function of ATP-sensitive potassium channels (K⁺ATP channel) in gonadotropin releasing hormone (GnRH) containing neurons and in pancreatic islet P-cells (Project 4). Sulfonylureas stimulate insulin secretion through activation of one of these channels, known as the sulfonylurea receptor, and the same channel complex appears to function in GnRH neurons. These observations have led to a paradigm shift in our concept of the pathogenesis of PCOS. Exposure of the fetus to androgens could result in the reproductive phenotype and the pancreatic P-cell dysfunction characteristic of PCOS. We propose to test the hypothesis that hyperandrogenemia resulting from variation in a gene in linkage disequilibrium with D I 9S884 causes many of the phenotypic features of PCOS by prenatal androgen programming. This hypothesis will be directly tested in two animal models and in translational human studies. The metabolic phenotype associated with the chromosome 19p PCOS susceptibility gene will be defined and this susceptibility gene will be identified. These studies will elucidate the pathogenesis of PCOS and provide the potential for molecular diagnosis of the syndrome. These objectives will be accomplished in four highly synergistic and interactive research projects.

Principal Investigator: Andrea Dunaif, M.D.

Project 1: Gene, Intrauterine Environment and PCOS

Polycystic ovary syndrome (PCOS) is among the most common endocrine disorders in premenopausal women. Women with PCOS have profound insulin resistance as well as pancreatic beta-cell dysfunction, independent of obesity and glucose intolerance. However, skeletal muscle insulin resistance reverse in cultured myotubes suggesting that insulin resistance in this tissue is induced by factors in the in vivo environment. We have recently shown that hyperandrogenemia is the reproductive phenotype in males as well as female relatives of PCOS women. Moreover, Urbanek and colleagues have shown (Project 2) that this phenotype appears to have a genetic basis in PCOS families and shows significant linkage and association with a marker locus on chromosome 19P in the region of the insulin receptor (allele 8 of D19S884). We now have extremely existing evidence that this allele is also associated with a metabolic phenotype in PCOS probands and their brothers: increased post-challenge glucose levels, apparent defects in insulin secretion, especially in response to sulfonylurea, and accelerated weight gain with age. Abbott (Project 3) has shown that in utero testosterone excess can reproduce many features of the PCOS reproductive and metabolic phenotype in female rhesus monkeys, including decreased insulin secretion and increased LH levels. Levine (Project 4) has shown that one mechanism for these changes is androgen-mediated sulfonylurea-stimulated insulin secretion by the pancreatic beta cells. Taken together, these observations have led to a new hypothesis for the etiology of PCOS: genetic variation resulting in hyperandrogenemia results in many of the reproductive and metabolic features of PCOS by fetal androgen programming. In this Project, we will test two components of the hypothesis. First, is the metabolic phenotype that is associated with the marker locus decreased insulin secretion, consistent with androgen-mediated suppression of K^+ /ATP channels? Second, is there in utero androgen excess, decreased fetal insulin secretion and/or intrauterine growth retardation (IUGR) in the female offspring of PCOS women, and does the marker allele identify a subpopulation of offspring with these findings?

Principal Investigator: Margrit Urbanek, Ph.D.

Project 2: Identification of Chromosome 19 PCOS Susceptibility Gene

Polycystic ovary syndrome (PCOS) is a common form of anovulatory infertility in women affecting 4-10% of reproductive age women. It is associated with obesity, insulin resistance, and Type 2 diabetes mellitus. Both environmental and genetic factors are believed to play a role in the pathogenesis of the syndrome. Multiple studies have shown evidence of familial clustering of PCOS indicating that there is a genetic component to the etiology of PCOS. However, the mode of inheritance of PCOS remains unclear, and to date no susceptibility genes for PCOS have been identified. From a series of linkage and association studies we have accumulated strong evidence for a susceptibility gene that maps near D19S884, an anonymous dinucleotide repeat marked, on Chr19p13.3. Forty putative genes map to within 250 kb of D19S884 including 13 confirmed genes, 16 mRNAs or spliced ESTs, and 11 predicted genes. The goal of this project is to identify the gene(s) and its variant(s) that maps to this region and characterize the role that the protein product of the gene plays in the etiology of PCOS. Our approach to identifying the PCOS susceptibility gene mapping in this region consists of three research aims; 1) to identify sequence variants in genes mapping near D19S884 in PCOS patients, 2) to differentiate between common polymorphism found in the general population and variants relevant to the etiology of PCOS, and 3) evaluate the functional consequences of variants identified in Aims 1 and 2. The identification of a PCOS susceptibility gene will shed light onto the etiology of a chronic disorder that affects literally millions of women in the United States and is expected to result in improved treatment and diagnosis for both PCOS and related phenotypes including type 2 diabetes mellitus, obesity, and cardiovascular disease.

Principal Investigator: David H. Abbott, Ph.D.

Project 3: Fetal Androgen Induces Ovarian, LH and B-Cell Defects

Polycystic ovarian syndrome (PCOS) affects approximately 5-10% of reproductive aged women and is characterized by hyperandrogenic anovulation, early-onset type II diabetes mellitus, obesity, atherosclerosis and endometrial cancer. Hyperinsulinemia plays a key role in the mechanism of hyperandrogenic anovulation. The etiology of PCOS in women, however, is unknown. Prenatal androgen excess in female rhesus monkeys results in ovarian, endocrinological and metabolic features in adulthood that closely resemble those found in women with PCOS. In Project #3 of this SCOR application, we propose to employ a unique non-human primate model of PCOS to define a fetal origin for the syndrome. We propose that hyperandrogenism, the core functional disorder in women with PCOS, reprograms multiple fetal organ systems in females resulting in the phenotypic expression of the syndrome. Recent findings of prevalent PCOS in women exposed to in utero androgen excess strongly support this hypothesis. Our preliminary results suggest that early exposure to androgen excess during gestation produces ovarian hyperandrogenism, LH hypersecretion and impaired pancreatic insulin secretion in adult animals. This project will [1] demonstrated increased fetal and neonatal LH hypersecretion in female rhesus monkeys following prenatal androgenization on Days 40-80 of gestation (LH defect), [2] establish ovarian hyperandrogenism in fetal and neonatal PA female rhesus monkeys [ovarian defect], [3] characterize the neonatal ovaries removed from PA female rhesus monkeys for morphological abnormalities and changed mRNA expression indicative of hyperandrogenic phenotype [ovarian defect], [4] determine whether in utero testosterone (T) excess during Days 40-80 of gestation induces impaired fetal and neonatal pancreatic insulin secretion in female rhesus monkeys [beta-cell defect], [5] assess impairments in fetal and neonatal physical development induced by prenatal androgen excess. The project will also provide a complementary and experimental study to that in PCOS pregnancies in [Project #1] and will produce hypothalamic and pancreatic tissue to determine whether prenatal androgen excess in female rhesus monkeys results in profound suppression of KATP channel subunit expression [Project #4].

Principal Investigator: Jon E. Levine, Ph.D.

Project 4: Neuroendocrine Actions of Androgens in Females

Hyperandrogenemia, LH excess, hyperinsulinemia, and impaired pancreatic beta cell function are core features of the polycystic ovarian disease (PCOS) that can be experimentally induced in female rhesus monkeys by prenatal androgenization. We will thus use the prenatally androgenized female monkey to study the pathogenesis of these PCOS symptoms. We hypothesize that prenatal androgenization "programs" subsequent 1) hyperactivity of the "hypothalamic" GnRH pulse generator", leading to LH excess, and 2) hypersecretion of insulin and impaired insulin secretory responses to glucose. In Aim 1 of the proposed studies, GnRH release will be monitored in adult, prenatally androgenized monkeys to determine if these animals exhibit hyperactivity of the GnRH pulse generator. A series of studies will then be performed to test the idea that the effects of androgens are mediated by modulation of ATP-sensitive potassium channels (KATP channels). The KATP channels appear to regulate secretion in both GnRH neurons and pancreatic beta cells, and we have obtained evidence that androgens suppress KATP channel expression. We will therefore test the idea that the effects of prenatal androgen exposure on LH and insulin secretions are mediated by suppression of KATP channel expression and/or activity. It will specifically be determined whether KATP channel subunits are expressed in GnRH neurons in the female rhesus monkey (Aim 2), and if prenatal androgenization leads to suppression of KATP channel expression in both hypothalamus and pancreas (Aim 3). We will then determine if modulation of KATP channel activity in vivo is functionally linked to GnRH pulsatility, and whether prenatal androgenization reduces the activity of these channels (Aim 4). In Aim 5 a transgenic mouse will be developed in which dominant negative KATP channels will be targeted to GnRH neurons, to determine if the experimental suppression of KATP channel activity in GnRH neurons results in LH excess. These experiments will provide the first direct assessment of the neuroendocrine consequences of prenatal and androgenization, and will establish the hypothesis that the ability of prenatal androgenization to induce PCOS symptoms is mediated by a suppression of KATP channel activity. A clearer understanding of the pathogenesis of PCOS symptoms will hopefully prompt exploration of new therapies for this common, yet perplexing reproductive and metabolic disorder.