Project III: Role of 17β-hydroxysteroid dehydrogenase in the hypertension of PCOS.
Specific Aims

Polycystic Ovary Syndrome (PCOS) is characterized by increases in plasma androgens and/or hirsutism, irregular menstrual periods, ovarian cystic morphology and infertility. Although the etiology of PCOS is unknown, one theory is that PCOS may be developmentally programmed due to exposure to prenatal androgens. PCOS is one of the most common female endocrine disorders, affecting 5 to 26% of women of reproductive age depending on ethnicity and lifestyle. Recent attention has focused on several metabolic derangements in women with PCOS in the US, such as obesity, insulin resistance and hypertension. In the US the prevalence of obesity in PCOS women is up to 80%. Obesity plays a major role in the clinical manifestations of the syndrome, since weight loss is associated with improved fertility and reductions in metabolic derangements in PCOS patients. Several lines of evidence indicate that there is a positive relationship between circulating levels of androgens, obesity, insulin resistance and blood pressure (BP) in women with PCOS. Whether and how increases in circulating androgens cause obesity, insulin resistance and hypertension in PCOS women remains poorly understood and is the main focus of this proposal.

We have established an animal model of PCOS in female rats that mimics many of the metabolic and cardiovascular abnormalities of women with PCOS. Implantation of dihydrotestosterone (DHT) pellets in female rats causes an increase in food intake, subcutaneous adipose tissue, insulin resistance, obesity, and elevated BP, as observed in PCOS women. Since adipose tissue can produce androgens via the 17β-hydroxysteroid dehydrogenase (17β-HSD) type 5, we hypothesize that *the increase in DHT activates the androgen receptor and leads to an increase in adipose androgen production via activation of 17β-HSD type 5, setting up a vicious cycle.*

Hypertension in PCOS is mediated by activation of the renin-angiotensin system (RAS). We also have preliminary data in the PCOS model that enalapril, an angiotensin converting enzyme inhibitor (ACEI), abolishes the increase in BP. We hypothesize that *androgens upregulate the androgen receptor in subcutaneous adipose tissue leading to release of androgens from the adipose, causing activation of the intrarenal RAS.*

Based on our exciting preliminary data, we will test the hypothesis (**Figure 1**) that *in PCOS, increased plasma androgens via the androgen receptor cause an increase in food intake leading to obesity that includes an increase in subcutaneous adipose tissue, and insulin resistance. The combination of increased circulating androgens, obesity and insulin resistance activate adipose 17β-HSD type 5, resulting in increased adipose androgen synthesis that further increases circulating androgen levels setting up a vicious cycle. Increased circulating androgens lead to subsequent activation of the <u>intrarenal</u> renin angiotensin system and elevated blood pressure.* This hypothesis will be tested using an integrative physiological approach utilizing whole animal, cellular, molecular and imaging methods in the following Specific Aims:

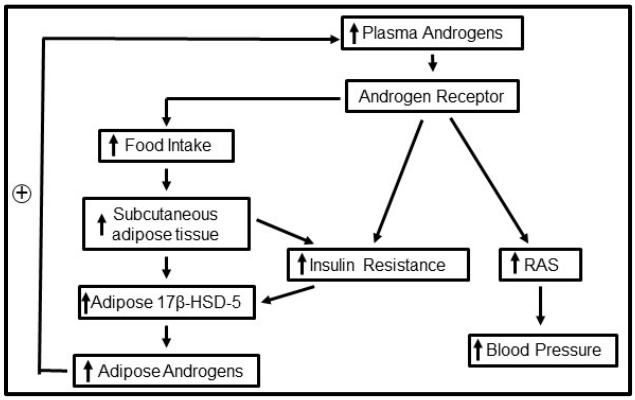

Figure 1. Working hypothesis.

Aim 1: To test the hypothesis that increased circulating androgens via activation of the androgen receptor promotes obesity with an increase in subcutaneous adipose tissue and insulin resistance in PCOS.

Aim 2: To test the hypothesis that increases in subcutaneous adipose tissue and insulin resistance lead to activation of 17β-HSD type 5 in the subcutaneous adipose tissue, thus further increasing circulating levels of androgens in PCOS.

Aim 3: To test the hypothesis that increased <u>circulating</u> androgens activate the <u>intrarenal</u> renin-angiotensin system (RAS), shifting the pressure-natriuresis curve to the right, leading to increases in blood pressure in PCOS.

Aim 4: To test the hypothesis that elevated circulating androgens via androgen receptor leads to insulin resistance and increases in BP in PCOS independent of obesity.

This is a significant, novel and clinically relevant proposal that will elucidate the mechanisms by which androgens regulate blood pressure, promote obesity and insulin resistance in women with PCOS, determine the pathophysiological interactions between these cardiovascular risk factors and will pave the way to identify novel and improved therapeutic tools to treat the clinical manifestations associated with hyperandrogenism in PCOS women.