Insulin Sensitivity and Antiandrogenic Therapy in Women With Polycystic Ovary Syndrome

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Polycystic ovary (PCO) syndrome is strongly associated with insulin resistance and the accompanying adverse metabolic profile. To distinguish the mechanisms of this association, we determined the interactions of PCO with obesity and the influence of ameliorating direct androgenic actions via short-term treatment with the antiandrogen flutamide. Insulin sensitivity was determined by the hyperinsulinemic euglycemic clamp in groups of lean and obese PCO women and weight-matched controls. Compared with control values, insulin-mediated glucose utilization in PCO women was significantly lower in lean (1.96 ± 0.17 *v* 1.24 ± 0.10, $P < .01$) and obese (1.23 ± 0.18 *v* 1.03 ± 0.09 mmol/m²/min, $P < .01$) subjects. ANOVA indicated that the effects of obesity and androgenicity are independent and additive. In both lean and obese PCO women, treatment with flutamide for 1 or 3 months markedly improved the clinical and biochemical androgenic features, but did not significantly influence the overall insulin sensitivity. A large disparity between individuals in the response to treatment correlated significantly with a simultaneous reduction in plasma levels of dehydroepiandrosterone sulfate (DHEA-S). Thus in women, PCO and obesity exert synergistic effects on insulin resistance. The decreased insulin sensitivity is mediated via indirect androgenic actions or nonandrogenic mechanisms. In some individuals, a direct effect of androgens might have been masked by a decrease in DHEA-S levels.

INSULIN RESISTANCE and the accompanying hyperinsulinemia are strong predictors of several metabolic disorders, including hypertension and non–insulin-dependent diabetes mellitus.[1] Several studies demonstrate that androgenicity may influence insulin levels and sensitivity. Men, particularly the obese, exhibit a higher prevalence of glucose intolerance, insulin resistance, and hyperinsulinemia than equally obese women.[2] Among healthy premenopausal women, increasing androgenic activity is associated with progressively decreasing insulin sensitivity and increasing plasma insulin levels.[3,4] A disorder of insulin action has also been recognized in hyperandrogenic women with polycystic ovary (PCO) syndrome or idiopathic hirsutism.[5-10] Impairment of insulin sensitivity in patients with congenital adrenal hyperplasia has also been reported.[11] Furthermore, Amiel et al[12] described a decline in insulin sensitivity occurring at the time of puberty both in normal children and in children with diabetes, suggesting that the pubertal secretion of male hormones may contribute to insulin resistance.

The mechanisms underlying the associations between androgenicity and insulin resistance are likely to be complex and involve both direct and indirect effects of androgens on insulin-responsive target tissues. Direct actions are supported by the observation that hepatic insulin dynamics are rapidly influenced by administration of androgens to prepubertal female rats.[13] Testosterone administration to ovariectomized female rats is also followed by a rapid deterioration of insulin sensitivity due to a reduction in insulin-mediated glycogen synthesis in skeletal muscle.[14] On the other hand, androgenic activity could influence the predominant site of body fat deposition and skeletal muscle morphology, which in turn could affect splanchnic insulin dynamics and skeletal muscle insulin sensitivity. A strong correlation has been observed between androgenic activity and the waist to hip ratio (WHR) in healthy nonhirsute women.[3] At the same level of obesity, hirsute women exhibit a higher WHR than the nonhirsute.[15] Testosterone has been shown to influence preadipocyte differentiation and regional growth potential.[16] Testosterone could also induce expression of β-adrenergic receptors and increase the activity of adenylate cyclase, which regulates lipolysis.[17] As a result of the preferential deposition of highly lipolytic adipocytes in the abdominal/visceral regions and consequently enhanced free fatty acid (FFA) flux to the liver, cell-surface insulin receptor number and splanchnic insulin catabolism could be reduced.[18,19] Furthermore, testosterone administration to female rats is known to induce significant changes in skeletal muscle morphology toward fewer red, insulin-sensitive type-1 fibers, along with lower capillary density per muscle fiber surface area.[20] These structural changes might lead to impaired insulin sensitivity in skeletal muscle.

The present study was undertaken to determine the interactions of PCO and obesity on insulin sensitivity. We also examined the effects of ameliorating the direct actions of androgens via short-term treatment with the androgenic antagonist flutamide.

SUBJECTS AND METHODS

Subjects

Eighteen PCO and 13 control white women were recruited for the study. The diagnosis of PCO was made when increases in two or more plasma androgen levels (total testosterone, free testosterone, androstenedione, 3α-androstanediol glucuronide, and dehydroepi-

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androsterone sulfate [DHEA-S]) were associated with two or more clinical symptoms such as hirsutism, acne, or menstrual disturbances. Ultrasonographic findings (thickened stroma and multiple subcapsular cysts) were used to confirm the diagnosis of PCO. Subjects with a history of diabetes, adrenal disorders, hyperprolactinemia, or other endocrine disorders were excluded. Control subjects were selected to be healthy, with no history of hirsutism or major gynecologic disorders. Subjects had no clinical evidence of hypertension or heart disease. These disorders were excluded by a report from the subject's personal physician and confirmed by thorough physical examination and routine laboratory studies. Subjects were aged 17 to 43 years and in good health, and were not taking any drugs known to affect gonadal function or carbohydrate metabolism. Body weight was stable for at least 2 months before the study. Subjects participating in dietary or exercise programs for weight reduction were excluded.

Control and PCO subjects were further subdivided into lean and obese groups. Obesity level was determined from body mass index (BMI). Subjects with BMI less than 25 kg/m^2 were considered lean, and those with BMI greater than 26 kg/m^2 were considered obese. Body fat distribution was assessed by measurement of WHR as described previously.[21] Subjects were counseled to maintain a constant weight and activity level. No significant weight loss or change in body fat distribution was observed during the study period.

Antiandrogen Therapy

Treatment with flutamide (Flucinom; Schering-Plough, Kenilworth, NJ) was initiated on the first day of the menstrual cycle in menstruating women. Five women were amenorrheic and were given progestin for 5 to 7 days. In these women, flutamide therapy was initiated on the first day of progestin-induced menses. Studies were conducted in all subjects during the first 10 days from the onset of menstrual flow. Flutamide is a nonsteroidal antiandrogenic drug devoid of hormonal agonist activity. In contrast to other antiandrogens, flutamide does not affect 5α-reductase activity, and therefore it should not affect dihydrotestosterone (DHT) production. It acts through its major metabolite, 2-hydroxyflutamide, by blocking androgen binding to its nuclear receptors in target tissues.[22] Testosterone and DHT share a common receptor site in target tissues; flutamide competes with DHT for binding to this site. Subjects received 250 mg orally twice daily. This dose has previously been shown to induce a marked decrease in the hirsutism score in similar groups of subjects.[23] Subjects were checked monthly for 3 months, and hirsutism was assessed according to the Ferriman-Gallwey index.[24] No side effects were reported during the study period.

Experimental Protocol

The protocol was approved by the Institutional Review Committee, and informed written consent was obtained from each subject. Control subjects were studied only once, whereas PCO women were studied before, after 1 month, and after 3 months of flutamide therapy. Three separate blood samples were taken between 8 and 10 AM for determination of sex hormone levels. Equal aliquots from each sample were pooled to reduce the effects of short-term episodic hormonal changes. Insulin sensitivity was assessed using the hyperinsulinemic euglycemic clamp procedure as described previously.[25] In our hands, repeated clamps have variance of less than 10%. After an overnight fast, an intravenous polyethylene catheter was inserted retrogradely into a dorsal hand vein and kept warm at 65°C via a heated box for sampling of arterialized venous blood. A second catheter was inserted into an antecubital vein for infusions. After a stabilization period of 30 to 45 minutes, during which three plasma samples were taken every 10 minutes, a primed-continuous infusion of crystalline human insulin was initiated at a rate of 287 pmol (40 mU)/m^2/min for 180 minutes to increase plasma insulin level to approximately 500 pmol/L (~75 μU/mL) while maintaining plasma glucose at the basal level. We previously demonstrated in similar groups of normal and hirsute hyperandrogenic women that hepatic glucose production is suppressed by 90% at an insulin concentration of approximately 300 pmol/L and that the degree of suppression is comparable in both groups.[10] Peripheral glucose metabolism should therefore be equal to the rate of glucose infused to maintain euglycemia. Plasma glucose is maintained at euglycemia (5 mmol/L) by determining the plasma concentration every 5 minutes and periodically adjusting a variable infusion of glucose. The computation for periodic adjustment of the glucose infusion rate was based on the negative-feedback principle.[25]

Analytical Procedures

Duplicate plasma samples were analyzed using commercial radioimmunoassay kits to determine levels of total testosterone, free testosterone, androstenedione, 3α-androstanediol glucuronide, and DHEA-S. Within- and between-assay coefficients of variation were 5 to 7% and 8 to 11%, respectively. A solid-phase ^{125}I-radioimmunoassay was used for quantitative measurement of serum insulin levels as described previously.[26]

Plasma glucose was determined using a Beckman Glucose Analyzer (Palo Alto, CA), which uses the glucose oxidase method.

Statistical Analysis

All results are reported as the mean ± SEM. A one-way ANOVA with Sheffé's post hoc test was used to compare age, weight, BMI, and WHR between the four groups. Two-way ANOVA was performed to examine the interaction between obesity and androgenicity (PCO) on basal insulin levels and insulin-mediated glucose utilization. Two-group repeated-measures ANOVA was used to compare baseline measurements with those obtained after 1 and 3 months of treatment with flutamide. A correlation matrix was constructed to examine the relationship between plasma hormone levels and insulin sensitivity measures before treatment, as well as the relationship between changes in hormone levels and insulin sensitivity after flutamide treatment.

RESULTS

Clinical characteristics of the study groups are listed in Table 1. Lean and obese PCO groups were matched to their respective controls with regard to body weight and BMI. The mean WHR was also similar in the two lean groups and averaged 0.77 ± 0.02 and 0.79 ± 0.03 for controls and PCO women, respectively. Similarly, obese groups were matched with respect to WHR, which averaged 0.85 ± 0.02 in controls and 0.90 ± 0.03 in PCO women. Lean and obese

Table 1. Clinical Characteristics of the Subject Groups

Experimental Group	Age (yr)	Weight (kg)	BMI	WHR
Lean PCO (n = 8)	22 ± 1.4	57 ± 3.2	21.5 ± 0.9	0.79 ± 0.03
Lean controls (n = 8)	33 ± 2.8	63 ± 3.7	23.1 ± 0.5	0.77 ± 0.02
Obese PCO (n = 10)	22 ± 1.2	84 ± 4.2	31.5 ± 1.1	0.94 ± 0.03
Obese controls (n = 5)	41 ± 2.0*	99 ± 7.7	37.1 ± 2.2	0.85 ± 0.02

*Significantly different from obese PCO ($P < .05$).

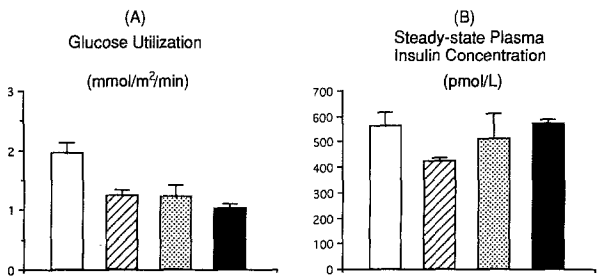

Fig 1. Insulin-mediated glucose utilization (A) and steady-state plasma insulin concentration (B) in lean and obese PCO women and controls. Data are the mean ± SEM. Lean controls (□), lean PCO (▨), obese controls (▩), and obese PCO (■).

PCO women were matched for age, as were the two control groups. However, PCO women were younger than control women.

Effects of Obesity and PCO on Insulin Sensitivity

Fasting plasma glucose concentrations were comparable in all groups and averaged 5.22 ± 0.03 in lean controls, 5.39 ± 0.06 in lean PCO, 5.28 ± 0.03 in obese controls, and 5.56 ± 0.07 mmol/L in obese PCO. Mean fasting plasma insulin levels were 32 ± 4 and 50 ± 4 pmol/L in lean controls and PCO women and 106 ± 14 and 192 ± 24 pmol/L in obese controls and PCO women, respectively. ANOVA indicated that both obesity and androgenicity significantly increased basal insulin levels ($P < .0001$ and $< .05$ for obesity and androgenicity, respectively). There was no interaction between the effects of obesity and the effects of androgenicity on basal insulin levels ($P = .26$).

During the hyperinsulinemic euglycemic clamp, euglycemia was attained approximately 2 hours after starting the infusion. The coefficient of variation in steady-state plasma glucose was less than 4% in all four groups. Figure 1 shows steady-state plasma insulin levels and mean glucose utilization rates attained during the clamp period. Mean steady-state plasma insulin levels did not differ significantly in the four groups (580 ± 50, 427 ± 12, 510 ± 100, and 570 ± 20 pmol/L in lean controls, lean PCO, obese controls, and obese PCO, respectively). When expressed per square meter of body surface area, mean glucose utilization rates were significantly lower in both PCO groups as compared with their respective controls. In the lean groups, glucose utilization rates averaged 1.24 ± 0.1 and 1.96 ± 0.17 mmol/m²/min in PCO and control women, respectively. In the obese groups, glucose utilization rates averaged 1.03 ± 0.09 in PCO women and 1.23 ± 0.18 in controls. In both obese groups, glucose utilization rates were significantly lower as compared with the rates in respective lean groups. The lowest value was observed in obese PCO women. ANOVA showed that for the effect of obesity, the F value was 13.47 and P was less than .001, and for the effect of androgenicity (PCO), F was 9.46 and P was less than .005. No significant interaction between the effects of obesity and androgenicity was found ($F = 2.59$, $P < .12$). These results support the conclusion that the effects of obesity and androgenicity on insulin-mediated glucose utilization are independent and additive. Since the insulin effects on glucose metabolism were assessed at one level of insulin, these results cannot distinguish whether the defect in insulin action is due to diminished sensitivity or decreased maximum responsiveness.

Effects of Treatment With Flutamide on Androgenicity and Insulin Sensitivity

Treatment with flutamide ameliorated the clinical symptoms and signs of hyperandrogenemia in women with PCO. Despite the short period of treatment, hirsutism improved dramatically. The Ferriman-Gallwey index decreased from 14.5 ± 0.76 to 9.5 ± 0.66 after treatment with flutamide. Acne, seborrhea, and skin oiliness also showed remarkable improvements shortly after flutamide therapy.

Effects of the androgen receptor blocker on serum androgens and their metabolites are listed in Table 2. Total testosterone and free testosterone did not change. Their metabolite at the hair follicle level, 3α-androstanediol glucuronide, was significantly reduced from a basal value of 18.70 ± 2.63 to 15.05 ± 2.05 nmol/L after 1 month of flutamide treatment, and this decline was maintained through 3 months of treatment. Plasma androstenedione and DHEA-S levels were also significantly reduced after 3 months of flutamide therapy. There were no significant correlations between plasma sex hormones and insulin sensitivity before flutamide therapy.

Table 3 lists the effects of flutamide on steady-state plasma insulin levels and insulin-mediated glucose utilization during the clamp procedure. After 1 or 3 months of treatment, steady-state plasma insulin levels attained during clamping were similar to those attained during the basal pretreatment phase. Despite significant amelioration of the clinical and biochemical androgenic manifestations, there was no significant improvement in insulin sensitivity. The insulin-stimulated glucose utilization rate after flutamide treatment for 1 or 3 months was not significantly different from the baseline value in either lean or obese PCO women. There were also no significant differences in the response to treatment between lean and obese groups. However, a wide range of individual variability in the

Table 2. Effects of Flutamide Treatment on Serum Sex Hormone Concentrations

Hormone	Before Treatment	After Treatment	
		1 Month	3 Months
Total testosterone (nmol/L)	3.26 ± 0.59	3.54 ± 0.55	3.36 ± 0.55
Free testosterone (pmol/L)	14.41 ± 1.56	16.28 ± 2.48	13.27 ± 1.82
3α-Androstanediol glucuronide (nmol/L)	18.70 ± 2.63	15.05 ± 2.05*	15.13 ± 2.20*
DHEA-S (μmol/L)	10.98 ± 1.67	6.93 ± 1.10*	7.28 ± 1.02*
Androstenedione (nmol/L)	15.42 ± 2.29	12.69 ± 1.54	9.71 ± 0.79*

NOTE. Values are the mean ± SEM.
*Signficantly different from pretreatment value ($P < .05$).

Table 3. Effects of Flutamide Treatment on Insulin Sensitivity in PCO Women

	Before Treatment		After Treatment			
			1 Month		3 Months	
Experimental Group	Glucose Utilization (mmol/m²/min)	Insulin Levels (pmol/L)	Glucose Utilization (mmol/m²/min)	Insulin Level (pmol/L)	Glucose Utilization (mmol/m²/min)	Insulin Level (pmol/L)
Lean PCO subjects	1.31 ± 0.11	388 ± 21	1.30 ± 0.11	428 ± 32	1.50 ± 0.16	450 ± 41
Obese PCO subjects	1.03 ± 0.09	569 ± 19	1.24 ± 0.15	538 ± 42	1.21 ± 0.13	636 ± 68

response to treatment was observed. After 3 months of treatment, changes in glucose utilization during the clamp ranged from −0.5 to +1 mmol/m²/min. These changes correlated significantly and positively with changes in plasma levels of androstenedione ($r = .548, P = .017$) and DHEA-S ($r = .563, P = .021$) (Fig 2).

Treatment with flutamide did not significantly change body fat topography. In lean PCO women, WHR averaged 0.80 ± 0.03 and 0.82 ± 0.02 before and after 3 months of flutamide treatment, respectively. Similarly, in the obese group, WHR averaged 0.88 ± 0.02 and 0.90 ± 0.02 before and after treatment, respectively.

DISCUSSION

This study suggests that obesity and PCO influence insulin sensitivity via independent and additive mechanisms. In addition, we demonstrated that although short-term treatment of PCO women with the antiandrogen flutamide significantly ameliorated the clinical manifestations and reduced metabolite levels of androgen, it did not significantly improve insulin sensitivity. These results suggest that the effects of PCO on insulin sensitivity are likely mediated by indirect androgenic or nonandrogenic mechanisms. The wide range of individual variability in response to treatment and its correlation with changes in plasma DHEA-S levels suggest that in some PCO women, there might also be direct effects that were masked by the decrease in DHEA-S.

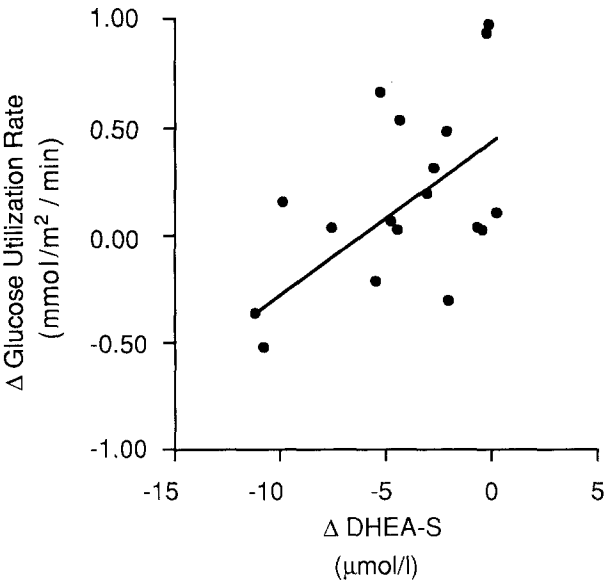

Fig 2. Correlation between changes in insulin-mediated glucose utilization and changes in plasma DHEA-S levels after 3 months of flutamide therapy ($r = .563, P = .021$).

It has been claimed that insulin resistance in PCO women is secondary to obesity, since most hyperandrogenized women are obese.[27,28] Also, in a study reported by Pasquali et al,[29] weight reduction in obese PCO women resulted in improvement of insulin sensitivity, with no changes in gonadotropin or sex steroid levels. However, this notion has been disputed, since lean PCO women are also insulin-resistant.[8] Indeed, several lines of evidence support a strong causal relationship between hyperandrogenicity and insulin resistance, irrespective of obesity.[5,9] The present study indicates that in women, both obesity and PCO affect insulin sensitivity independently and the effects of the two are additive. This is in agreement with the studies reported by Dunaif et al,[30] which demonstrated significant reductions in insulin-stimulated glucose utilization in both lean and obese PCO women. Thus, women with PCO have a disorder of insulin action that is independent of and additive to that due to obesity.

Animal models of obesity demonstrate synergistic interactions between androgenicity and obesity. In the SHR/N-Mcc-*cp* rat, obese males but not females become insulin-resistant and overtly diabetic by 16 weeks of age. In situ liver-perfusion studies demonstrate a reduction in the insulin clearance rate in obese animals as compared with lean controls. The clearance rate is also lower in males than in their female littermates. ANOVA demonstrates that the effects of obesity and male gender on hepatic insulin dynamics are independent and additive.[31] A similar mechanism may be involved in producing the synergistic effects of obesity and PCO on insulin sensitivity and peripheral plasma insulin levels.

The present study suggests that androgens may precipitate insulin resistance via a mechanism independent from the direct effects on insulin-responsive cascades. One possible mechanism could be by influencing body fat distribution. The relationship between androgenicity and body fat topography has long been recognized.[32] In premenopausal women with PCO or idiopathic hirsutism, increased testosterone levels were accompanied by upper-body fat predominance, independent of obesity level. A strong positive correlation exists between plasma testosterone and WHR.[3] In addition, women with PCO, when compared with normal women matched for body weight, had larger abdominal fat cells.[33] Abdominal/visceral fat is metabolically more active than femoral fat.[34] This fat depot is highly lipolytic, releasing large amounts of FFA into the portal circulation

and hence enhancing FFA flux to the liver. In vitro and in situ perfusion studies[18,19] indicate that FFA could alter hepatic insulin catabolism, resulting in increased posthepatic delivery of insulin and peripheral hyperinsulinemia. Studies in premenopausal women indicate that the decline in hepatic insulin extraction accompanying abdominal obesity is correlated with the increase in androgenic activity.[4] In the present study, short-term treatment with flutamide did not alter body fat topography, since there was no significant change in WHR. Whether longer periods of treatment will result in changes in WHR and improvement of the insulin-resistant state remains to be assessed.

Muscle is one of the primary sites of insulin-mediated glucose disposal.[35] It is therefore possible that elevated androgen levels, by influencing muscle fiber composition, could result in insulin resistance and compensatory hyperinsulinemia. Another effect of androgens on skeletal muscle is the decline in capillary density per muscle fiber surface area following long-term administration.[36] The first step in insulin action is the translocation of the hormone from the intravascular to the extravascular compartment prior to its cellular interactions. Capillary rarefaction has been observed and is correlated with decreased insulin sensitivity in some human[37] and animal[38] models of obesity. These changes may require a longer treatment time with antiandrogens.

In monkeys and humans, glucose tolerance was not altered by either androgen administration or suppression.[38,39] In another study, total gonadal steroid production was suppressed for 12 weeks, using an analog of gonadotropin-releasing hormone in PCO women. Despite a significant reduction in androgen levels, there were no significant changes in insulin-mediated glucose disposal.[40] In the present study, flutamide was used for selectively amelioration of the androgenic effects while maintaining physiologic levels of female hormones.[41] Previous studies showed that flutamide has no effect on sex hormone production or plasma levels. Preliminary studies from our group indicate that although flutamide affects basal levels of follicle-stimulating hormone and luteinizing hormone in anovulatory women with PCO, it has no effect on levels of these hormones in women with regular menses. In addition, after gonadotropin-releasing hormone stimulation, gonadotropin levels remained unchanged in both groups. However, the decrease in DHEA-S observed after flutamide treatment was previously reported and is attributed to a decrease in the cortisol clearance induced by the drug.[42] The physiologic role of this hormone in regulating tissue sensitivity to insulin has been recently suggested. Administration of an analog of DHEA (16α-fluoro-5-androsten-17-one) to mice markedly improved insulin sensitivity.[43] In human studies, the ratio of DHEA to testosterone proved to be an important modulator of insulin sensitivity in hyperandrogenic women.[44] However, in young men tissue sensitivity to insulin was unaffected after 4 weeks of treatment with DHEA.[45] In the present study, we observed a significant positive correlation between the decrease in DHEA-S and the change in glucose utilization rates after 3 months of flutamide therapy. It is therefore possible that in some PCO women the persistence of insulin resistance following flutamide treatment might be due to simultaneous reductions in DHEA-S levels.

An alternative explanation for the lack of effect by flutamide is that in PCO women insulin resistance is the cause and not the result of increased androgenic activity. Chronic hyperinsulinemia has been demonstrated to exacerbate hyperandrogenicity. Recent studies indicate that hyperinsulinemia can stimulate ovarian production of androgens either directly[46] or by cross-reaction with insulin-like growth factor-I receptors.[47] In addition, in vitro[48] and in vivo[49] studies indicate that insulin suppresses production of sex hormone binding globulin by cultured hepatoma cells, and that hyperinsulinemia can reduce serum sex hormone binding globulin in obese women with PCO independently of its effect on androgen production. The hyperinsulinemia of PCO could therefore be responsible for the hyperandrogenism.[50]

A third explanation for the lack of a flutamide effect is that the androgen interaction with insulin target tissues could be mediated via nonreceptor mechanisms. Androgen receptor-independent induction of a kidney protein[51] and an increase in hepatic cytoplasmic protein[52] have been described in a testicular feminized strain of mice. It is therefore tempting to speculate that androgen or one of its metabolites may interact with proteins involved in regulating insulin action and homeostasis independently of its receptor. Since flutamide acts by blocking androgen receptor-mediated processes, it would then be ineffective in reversing the insulin insensitivity.

Like any pharmacologic intervention, flutamide could have a direct adverse effect on insulin sensitivity. Indeed, flutamide is known to have hepatotoxic effects. To our knowledge, there are no studies that examine the possibility of a direct effect of flutamide on hepatic or peripheral insulin sensitivity. Furthermore, key enzymes of glucose metabolism in epididymis and prostate tissues of rats are not affected by the addition of flutamide to the incubation medium.[53]

Finally, insulin resistance in PCO women could be the result of a specific gene defect(s) in insulin action that is linked to candidate genes for the reproductive disorders in this syndrome. In adipocytes from PCO women, insulin resistance is independent of obesity, body fat distribution, and sex hormone levels, suggesting a primary genetic abnormality.[54] Recent studies also demonstrate decreased expression of GLUT-4 glucose transporters associated with the disturbed insulin responsiveness in adipocytes.[55] Other genetic abnormalities might also be involved.

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