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Insulin resistance mechanisms, the brain, and insulin resistance in youth and in the polycystic ovary syndrome

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This is the fourth of four articles summarizing presentations at the seventh World Congress on the Insulin Resistance Syndrome, held in San Francisco, California, on 5–7 November 2009. This installment pertains to insulin resistance (IR) mechanisms, the brain, and IR in youth and in the polycystic ovary syndrome (PCOS).

Hyperinsulinemia and insulin secretion abnormalities

Hyperinsulinemia causing IR. Jesse Roth (New York, NY) suggested that, rather than IR, hyperinsulinemia should be considered the major mediator of adverse outcome, with hyperinsulinemia the underlying characteristic of all syndromes of IR (1). Recalling Edgar Allan Poe's story "The Purloined Letter," Roth argued that the mediator of IR is insulin, which is "hidden in plain sight," causing hormone-induced inhibition of hormone action. Similar phenomena are seen in choriocarcinoma, in which enormous amounts of human chorionic gonadotropin have no biological effect, in the divergence between the effect of gonadotropin-releasing hormone, which enhances fertility when given in a pulsatile fashion, while when administered continuously, it halts precocious puberty, or between the effect of parathormone given continuously, causing bone resorption, while bolus administration increases bone formation. High levels of insulin similarly decrease the effectiveness of insulin, and mice overexpressing the insulin gene, with doubling and quadrupling insulin levels, fail to show change in weight or fasting glucose, while developing IR, postprandial hyperglycemia, and decreased insulin receptor binding. Similar effects of hyperinsulinemia may be demonstrated in normal rats that are given increasing daily doses of insulin or that have hypothalamic damage, whereas *ob/ob* mice that are given alloxan or streptozotocin show improvement in insulin sensitivity. In humans, the Somogyi effect is of decreasing insulin doses improving glycemia, whereas patients with insulinoma develop IR, and pulsatile administration in a manner mimicking its physiologic release appears to have greater biologic effect than that of continuous infusion of a considerably greater amount of insulin (2). Basal insulin levels are twice as great in type 2 diabetic as in normal persons, despite fairly marked fasting hyperglycemia, so that although postload insulin levels are decreased, Roth argued that IR, rather than deficiency, mediates the hyperglycemia of type 2 diabetes, with IR potentially mediating defects in insulin secretion, as insulin receptor activation appears to be required for β-cell glucose recognition. Presumably, Roth argued, other insulin responsive tissues such as the brain and the macrophage also develop IR as a function of hyperinsulinemia, leading to "unbalanced" effects from one tissue to the next. A wide variety of treatments including exercise, diet, metformin, acarbose, and thiazolidinediones reduce basal insulin levels and are associated with improvement in metabolic profile, whereas, at >20-year follow-up, basal hyperinsulinemia is the best predictor of subsequent diabetes (3), taking into account measures of obesity and glycemia. Diabetes is not a simple disease, and its complications are complex, but while microvascular disease is demonstrably related to glucose concentrations, Roth termed the link of glycemia to macrovascular disease difficult to demonstrate and "really marginal," so that earlier treatment initiation may delay the disease process. Furthermore, given the rather rapid shift that occurs from normal to high levels of glucose (and insulin), Roth suggested that the rapidity of change in these measures be taken into account in determining which patients with early disease require treatment and argued somewhat against the use of insulin in early diabetes treatment, endeavoring instead to "get at this much earlier" to reduce adverse outcome.

Insulin secretory dysfunction and IR

Kristina Utzschneider (Seattle, WA) discussed the role of β-cell dysfunction in glucose metabolism, pointing out that in type 2 diabetes IR is accompanied by β-cell dysfunction with β-cell apoptosis and subsequent loss of compensation (4). It has long been recognized that β-cell mass is decreased in type 2 diabetes (5), while obesity increases β-cell volume (6). Both impaired fasting glucose and type 2 diabetes are associated with normal β-cell replication rates but increased apoptosis. Reduction in β-cell mass is not, however, sufficient to explain the insulin secretory defect in type 2 diabetes, with evidence as well of a β-cell functional defect in the loss of acute insulin response (AIR) to intravenous glucose beginning at fasting glucose levels around 115 mg/dl (7), with the insulin response to oral glucose dependent on insulin sensitivity (8). If type 2 diabetes is, then, characterized by both IR and β-cell dysfunction, the latter may be relevant to identifying patients at risk and to evaluating the effects of interventions.

There is a hyperbolic relationship between the acute insulin secretory response to glucose and insulin sensitivity (9). Superimposed on this is a decline in β-cell function with increasing fasting glucose and worsening glucose tolerance levels (10)—a pattern also seen in persons at risk of type 2 diabetes, such as relatives

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of persons with type 2 diabetes, women with PCOS, women who have had gestational diabetes mellitus, and older individuals; an example of this is a study of Pima Indians over time, with persons deteriorating from normal to impaired glucose tolerance to type 2 diabetes having progressive decrease in the hyperbolic relationship between insulin secretion and insulin sensitivity (11). Utzschneider examined the differences in effect of different interventions, reviewing a 6-month program of exercise training that improved insulin sensitivity without improvement in β-cell function, the effect of troglitazone in improving both β-cell function and insulin sensitivity, and the effect of administration of nicotinic acid for 2 weeks in worsening β-cell function. Similar information, although with somewhat less precision, can be obtained from analysis of insulin and glucose patterns following oral glucose. Measuring the change from time 0 to 30 min in insulin versus glucose ($\Delta I/\Delta G30$), indicative of insulin secretion adjusted for blood glucose, and the reciprocal of the fasting insulin as a measure of IR, the relationship is again hyperbolic, with deterioration from normal to impaired glucose tolerance/impaired fasting glucose to type 2 diabetes (12). Utzschneider referred to the constant of the hyperbolic relationship, the product 1/[fasting insulin] multiplied by $\Delta I/\Delta G30$, as the oral disposition index. As the disposition index worsens the likelihood of diabetes increases, with receiver operating characteristic analysis suggesting this to be a better predictor than either 1/fasting insulin or $\Delta I/\Delta G30$ alone. A number of other studies have shown the usefulness of these approaches; the incidence of diabetes was related to 1/[fasting insulin] in an analysis of the Diabetes Prevention Program (13).

Is insulin secretion reduced in type 2 diabetes?

Gerald Reaven (Stanford, CA) discussed approaches to measurement of insulin secretory function in type 2 diabetes to support his concept that the β-cell plays a secondary role in the pathogenesis of type 2 diabetes, with the notion of its being similar in importance to IR based on incorrect assessment methodologies (14). The conventional wisdom, he opined, has been that type 2 diabetes is characterized by progressive and inexorable loss of β-cell function. If one measures glucose and insulin levels through the day in persons with varying levels of glycemia, he said, it is remarkable that "the β-cell is far from dead" even as diabetes advances, with insulin levels similar to those in euglycemic persons, particularly during the overnight period, although with glucose and free fatty acid levels considerably higher, confirming IR.

A number of methods have been used in assessing insulin secretion, such as homeostasis model assessment of β-cell function (HOMA-B) (fasting insulin × 20/[fasting glucose − 3.5]); AIR during the initial 5 min following a 20-g intravenous glucose load; an oral glucose tolerance test to define the changes in glucose and insulin at 30 min after 75-g oral glucose, typically calculated as $\Delta I/\Delta G_{30\text{-}min}$; the hyperglycemic clamp, measuring the insulin secretory response to a given fixed level of glycemia; and the meal tolerance test, measuring glucose and insulin in responses to mixed meal. Reaven discussed four confounding issues: glucose toxicity, the effect of hyperglycemia on the β-cell, the effect of varying glucose loads (whether coexisting plasma glucose and insulin concentrations are constant in their relationship and physiologically meaningful), and the reliance on fasting glucose and insulin levels.

Glucose toxicity is an important consideration in the argument against the concept that type 2 diabetes per se is associated with insulin deficiency. AIR to glucose is essentially absent in persons with fasting plasma glucose (FPG) >115 mg/dl and is decreased markedly with FPG >100 mg/dl (15). Furthermore, when FPG is >126 mg/dl, AIR is no longer related to FPG and drops nearly to 0 (16), leading Reaven to state that "AIR has limited ability to quantify β-cell function at hyperglycemic states." Given the decreased insulin response to hyperglycemia with oral glucose, Reaven asked whether this is reflected in the insulin secretory response to meals and showed data suggesting that this is not the case, although he recognized that one could argue "insulin levels should be much higher" because of hyperglycemia.

The confounding effect of glucose load is an interesting subtlety which Reaven noted, pointing out that the amount of glucose that must be infused to reach a given level of hyperglycemia varies with baseline glucose and with insulin sensitivity. To compare β-cell function, one must then assume that differences in absolute glucose load have no effect on the amount of insulin secreted. In animal models, however, Reaven showed evidence that this is not the case, with greater and lesser glucose infusions achieving similar plasma glucose levels leaving to higher and lower insulin levels, respectively. [Note: This consideration may also be relevant to the classic studies of the "incretin effect," as the glucose load given orally exceeds that given intravenously to achieve similar blood glucose levels, and increasing insulin secretory responses can be demonstrated with similar plasma glucose levels in response to increasing oral glucose loads (17).]

Reaven also discussed issues pertaining to the notion of $\Delta I/\Delta G$, pointing out that this ratio assumes that the insulin response is a linear function of the plasma glucose and also that the plasma glucose is the sole determinant of the plasma insulin response, which is certainly not the case, as has been demonstrated in studies of the incretin effect showing that oral nutrient increases the insulin response to a given plasma glucose. Reaven reviewed a study of healthy volunteers who were given 20 or 40 g glucose/m^2 body surface area, with glucose levels similar but insulin responses quite different. Furthermore, $\Delta I/\Delta G$ may vary considerably when successive glucose tolerance tests are performed. Assumptions about the linear response of insulin to glucose may explain the much lower level of HOMA-B in type 2 diabetes than in persons with normal glucose tolerance, as the insulin levels of the former are not particularly low and the differences are driven by differing fasting glucose levels.

How inexorable, Reaven asked, is the loss of insulin secretion in type 2 diabetes? He discussed a study of a very low-calorie diet, during which day-long glycemia improved and β-cell function normalized. Another study of long-standing type 2 diabetic Pima Indians showed that 4 weeks of intensive dietary treatment to achieve euglycemia led to improved β-cell function (18). Similarly, a study comparing persons with normal versus impaired glucose tolerance showed that insulin sensitivity was lower in the latter, fasting glucose higher, fasting insulin higher, and HOMA-B lower, but total insulin secretion after a test meal was higher, which Reaven described as a "total disconnect" of HOMA-B from other measures of insulin secretion. Indeed, HOMA-B decreased with but total prandial insulin secretion increased with increasing FPG. If one compares the lower, middle, and higher tertile of FPG, fasting insulin and insulin secretion during the

meal increased, but HOMA-B decreased. Although the steady-state plasma glucose (SSPG), a measure of IR, correlated both with HOMA-B and with meal-related insulin secretion, the latter relationship was much stronger, suggesting that with decreased insulin sensitivity the β-cell does behave appropriately. Reaven concluded that insulin secretion estimates vary with the method used and that it is not clear that β-cell function progressively fails with the development of type 2 diabetes.

IR in brain aging and dementia

Suzanne Craft (Seattle, WA) discussed the role of IR in brain aging and dementia. Insulin is a feeding and satiety signal, involved in normal brain function and cognition, with dysregulation of insulin (both IR and hyperinsulinemia) increasing the risk for cognitive impairment, Alzheimer's disease (AD), and other neurodegenerative diseases. The insulin receptor is present in neuronal elements of the hippocampus and entorhinal and frontal cortex, and insulin crosses the blood brain barrier at physiologic levels via a transport system, with controversy as to whether insulin is also synthesized in areas of the brain. Insulin increases levels of neurotransmitters such as acetyl choline and norepinephrine and modulates glucose metabolism in the hippocampus, increasing neuronal firing, which enhances memory at optimal doses.

IR, hyperinsulinemia, and impaired glucose tolerance and type 2 diabetes are associated with increased AD risk and memory impairment in epidemiologic studies, with possible mechanisms including impaired cerebral glucose metabolism, disrupted β-amyloid (Aβ) trafficking and clearance and abnormal regulation of other key proteins, impaired synaptic maintenance, increased inflammation, impaired vascular function, and prolonged hyperinsulinemia reducing brain insulin transport, decreasing brain insulin uptake and signaling. AD is the most common form of dementia, affecting six million people in the U.S., with exponential increase in prevalence with age, defined by deficits in memory as well as one or more other area of cognition. The first pathologic finding is loss of synapses, with subsequent loss of neurons leading to atrophy and cerebral volume loss. Histology shows neurofibrillary tangles of hyperphosphorylated tau and neuritic plaques composed of aggregated Aβ. Positron emission tomography shows abnormal brain glucose metabolism in nondemented adults with hyperglycemia. AD shows a pattern of hypometabolism in the frontal and temporoparietal cortex and the posterior cingulate area, a pattern also seen in persons with IR, implying that "IR creates a vulnerability in cerebral glucose metabolism that may increase the risk of developing AD over time." Aβ peptide oligomers may have neurotoxic and memory-inhibiting effects, even prior to its aggregation into plaques. Insulin regulates Aβ levels by promoting its intracellular release from neurons, and insulin-degrading enzyme degrades Aβ as well, further suggesting important interaction, whereby insulin and Aβ exert reciprocal effects in regulating each others' metabolism, with Aβ potentially worsening brain IR, while, conversely, insulin can protect Aβ-induced toxic effects on synapses, although in animal models peripheral IR increases brain Aβ burden and impairs memory. In a hyperinsulinemic-euglycemic clamp human study, there was an age-related increase in spinal fluid Aβ, with insulin infusion also increasing spinal fluid interleukin (IL)-1b, IL-6, and tumor necrosis factor-α, as well as increasing F2-isoprostane, a marker of lipid peroxidation and inflammation and oxidative stress. Lipid infusion caused IR with increased spinal fluid Aβ, further implying a reciprocal relationship between insulin and Aβ, with such changes in Aβ associated with markers of inflammation and oxidative stress.

Another important component of AD is reduced brain insulin uptake and signaling, with low levels of spinal fluid and brain insulin. Insulin treatment reduces brain atrophy in AD models, although raising peripheral insulin levels would not be expected to benefit. Craft's group has studied intranasal insulin administration, as this route bypasses the blood brain barrier by following the olefactory and trigeminal nerves to rapidly reach the brain (19). Intranasal insulin in humans appears to improve memory in early AD. In the Study of Nasal Insulin to Fight Forgetfulness (SNIFF), intranasal insulin (20 units twice daily) improved memory, although it did not change fasting or postprandial glucose or insulin; a larger clinical trial is underway. Insulin sensitization may also be beneficial, with both pioglitazone and rosiglitazone suggesting benefit, and a 6-month intensive aerobic (versus stretching) exercise intervention enhanced cognition. Caloric restriction in primates beginning in midlife improved insulin sensitivity, cognition, and overall health (with lessening of gray hair, leading to great enthusiasm in the audience!) (20).

Not all dementia in older individuals with diabetes reflects AD. An autopsy study comparing people with and without diabetes and with and without AD showed highest Aβ in people with dementia who did not have diabetes, perhaps from diabetic patients with dementia having greater risk of cerebrovascular disease. There was also an association of microvascular lesions with dementia in the diabetic group, perhaps as markers of vascular pathology or by a direct role, with such findings and lower levels of amyloid plaques particularly in demented diabetic patients who were treated with insulin.

Antipsychotic drugs and IR

Sun Kim (Stanford, CA) discussed effects of antipsychotic medications on IR and on insulin secretion. She noted that lipid-lowering medication is the first, proton pump inhibitors are the second, and antipsychotic medication is the third in ranking by dollar volume of drugs sold in the U.S., implying very wide use of the latter, not only for schizophrenia but also for bipolar states, dementia, psychotic depression, autism, developmental disorders, and adolescent conduct disorders. Individuals with mental health disorders have a two- to threefold increase in risk for diabetes, cardiovascular (CV) disease, and death, leading to concern as to whether the obesity- and diabetes-causing effects of antipsychotic agents may be mediators. Mental illness is itself associated with obesity, with mediators including increased caloric intake, decreased activity, "stress," and genetic predisposition, but the weight-increasing effect of medications as well. Prior to the widespread use of second-generation antipsychotics, the weight of persons with schizophrenia was somewhat greater than that in the reference population. The U.S. is, Kim stated, the most obese country in the world, with 30% of the population having BMI >30 kg/m^2, but 47% of people with schizophrenia have BMI above this level, and similar associations of schizophrenia with obesity are seen in other countries. The prevalence of metabolic syndrome among people with schizophrenia was 36.6% in men and 54.2% in women (21), far above the levels of 25.1% and 19.7%, respectively, in the overall U.S. population.

Olanzapine and clozapine are associated with the greatest degree of weight gain, risperidone and quetiapine are intermediate, and aripiprazole and ziprasidone lead to the lowest amounts; a recent study showed similar effects of these agents on weight gain in children and adolescents (22). Olanzapine may also cause a greater degree of IR than that attributable to the weight gain alone (23). Kim reviewed a study that compared 54 subjects treated with olanzapine, risperidone, or aripiprazole with a control population and showed that one-quarter of the variance in IR was explained by the degree of obesity in both groups, suggesting overall similarity of these agents, although there was a trend to a greater reduction in insulin sensitivity for a given BMI among subjects receiving olanzapine.

The question also has been raised as to whether there are direct effects of second generation antipsychotics on insulin secretion. In animal models, there is some such evidence, but Kim suggested that little supporting evidence of decreased insulin secretion can be demonstrated in human studies; her study of olanzapine, risperidone, and aripiprazole during a graded increasing glucose infusion over 4 h showed the highest glucose-stimulated insulin secretion rate with olanzapine, a similar level with aripiprazole, and a lower level with risperidone, with glucose-stimulated insulin secretion corrected for SSPG similar with the three drugs, suggesting that the weight-increasing effect of the drugs is responsible for their metabolic effects. Most studies show the second-generation antipsychotics to have greater diabetes-causing effect than first-generation agents such as chlorpromazine and haloperidol (24). American Diabetes Association (ADA) guidelines suggest regularly checking weight, lipids, and blood glucose in patients receiving these medications (25), although adherence to such screening has been limited, with only approximately one-quarter of patients having glucose and one-tenth lipid measurements, which Kim considered rather worrisome (26).

Initial approaches to treatment are, Kim suggested, lifestyle modification, metformin, perhaps pioglitazone, and lipid and blood pressure treatment. Kim reviewed a pilot study her group had undertaken, in which 15 persons who had gained >10 kg on prior antipsychotic treatment were given aripiprazole (27). Of the group, five could not tolerate the agent, three lost some weight (but showed little change in insulin sensitivity), and the remainder showed little change in either parameter. A recent study of 173 persons randomized to continuing olanzapine or changing to aripiprazole showed that 26 vs. 36% dropped out, suggesting the former to be better psychiatrically, although weight and triglycerides levels did improve (28). Clearly, this is a complex topic, and the treating physician needs to weight risks and benefits of the various agents.

IR in adolescence

Alan Sinaiko (Minneapolis, MN) discussed the role of IR in development of CV risk in adolescents. He pointed out that insulin sensitivity measures based on fasting insulin and glucose such as HOMA-IR (fasting insulin × fasting glucose/22.5) are driven more by the nearly 100-fold range of fasting insulin (from 1.5 to 79.6 pmol/l) than by the 2-fold nondiabetic range of fasting glucose (from 3.5 to 6.5 mM/l), explaining the close correlation between fasting insulin and HOMA-IR in nondiabetic children. The correlations of fasting insulin or of HOMA-IR with IR as measured from euglycemic-hyperinsulinemic clamps are low, with Pearson correlation coefficient ~0.4 (29), and the correlation is even worse in lean children, leading to Sinaiko to suggest that the usefulness of the insulin level in distinguishing the degree of insulin sensitivity in an individual child is limited. He reviewed the patterns of worsening insulin sensitivity leading to increases in blood pressure and worse lipid levels during adolescence in boys, whereas all parameters tend to improve in girls, with discordance in consequent CV risk. IR at age 13 years predicts blood pressure and triglyceride abnormalities at age 19 years (30). Fasting insulin levels, however, become similar during adolescence in the two sexes, and body fat increases in girls and decreases in boys, further suggesting this not to be particularly useful in assessing insulin sensitivity (31). Obesity appears to be the factor that best predicts which children will develop into adults with coronary artery disease (CAD) risk and subsequent CAD events. The presence of IR adds significantly to CV risk in obese but not in lean adolescents, and metabolic syndrome appears to be a good predictor of future CV risk.

Julia Steinberger (Minneapolis, MN) discussed the development of IR in survivors of childhood cancer. The mortality of childhood cancers has decreased over the past 3–4 decades, with estimated cure rates now more than 85%, although the incidence of childhood cancers has increased. Currently 1 of every 900 young adults is a survivor of a childhood cancer, with myriad consequences affecting the endocrine, cardiac, pulmonary, renal/urologic, gastrointestinal/hepatic, and neurologic/psychiatric systems, as well as increased likelihood of a second malignancy. Chemotherapy, radiation, and surgery all have the potential to produce vascular, musculoskeletal, and nerve damage. Growth issues often are caused by radiotherapy directed to the brain or spinal cord, leading to hypothalamic/pituitary damage. Myocardial infarction and stroke appear to increase in limited studies, with a 10-fold increase in late mortality, caused by cancer relapse, most commonly from subsequent malignancy, but with cardiac disease the next most likely cause (32). Hypercholesterolemia, hypertension, obesity, and hyperinsulinemia are seen with increased prevalence. In Steinberger's study of survivors of bone marrow transplantation, there were 3.7- and 2.1-fold increases in rates of diabetes and hypertension, respectively, with 3.5-fold increase in stroke risk and 1.2-fold increase in myocardial infarction, not associated with obesity. High triglyceride, low HDL, and IR were found, and one-third of trial participants had evidence of growth hormone (GH) deficiency, not only related to radiation treatment. The group was shorter, with lower IGF-1, greater adiposity, and higher triglyceride levels, although no differences were found in blood pressure, HDL cholesterol, or fasting glucose levels. GH therapy appeared to somewhat ameliorate the abnormalities, and the degree of metabolic abnormality appeared to be proportionate to the degree of reduction in GH secretion, so that consideration is being given to a study of GH replacement, but a number of oncologists have raised the concern that this could cause development of second malignancies.

PCOS

John Nestler (Richmond, VA) discussed the role of IR in PCOS, and the rationale for use of insulin sensitizers in women with PCOS who have normal insulin sensitivity. PCOS is a disorder defined by having at least two of chronic oligo/anovulation and/or hyperandrogenism and/or PCO on ultrasound (with exclusion of congenital adrenal hyperplasia,

adrenal androgen-producing tumors, and a variety of other causes of hyperandrogenism), affecting 6–10% of women of childbearing age. Hyperinsulinemic IR appears to be a characteristic of women with PCOS when compared with similar weight women who have normal ovulation; an obese woman with PCOS has a degree of IR similar to one with type 2 diabetes (33).

In opposite-sex twin pairs, intrauterine exposure to androgens may contribute to development of PCOS, and studies of androgen administration in utero to female rhesus monkeys, particularly early in pregnancy, show subsequent development of a PCOS phenotype. Nestler, however, presented data from a Netherlands registry of 1,325 monozygotic and 1,191 dizygotic twins, with 711 female subjects from same-sex and 480 female subjects from opposite-sex twin pairs, not showing such an association (34). It may be, then, that androgens do not act directly in the fetus, but rather that metabolic disturbances induced by androgens in the mother program the developing fetus for PCOS. In a study of 30 prepubertal and 69 pubertal girls born to women with PCOS, compared with 20 and 64, respectively, born to normal women and with similar age and BMI, insulin, glucose, lipid, luteinizing hormone, 17-hydroxyprogesterone, and testosterone were higher in Tanner stages IV and V PCOS daughters, but ovarian volume and the 2-h insulin were higher in PCOS daughters through all puberty stages (35), implying that PCOS daughters show features of the syndrome and hyperinsulinemia prior to the development of androgen abnormalities. PCOS penetrance was high, 45 and 60% at Tanner stages IV and V, respectively.

Nestler pointed out that most women with PCOS are obese and hence will be certain to have IR and that there is no simple method to determine insulin sensitivity in an office setting, so that he felt the correct question is whether any variable predicts whether a woman will or will not respond to insulin sensitizer treatment. In a study of 128 nonobese women with PCOS, with fasting insulin <15 μIU/ml, metformin did induce ovulation although requiring ~6 months to show effect (36). Nestler suggested that the finding could be interpreted to show that these women did actually have IR, or that metformin directly inhibited ovarian androgen biosynthesis, or, perhaps, that PCOS is characterized in some women by ovarian hypersensitivity to insulin, implying that a threshold may exist, varying from woman to woman based on IR (whether intrinsic or related to obesity) and ovarian sensitivity to insulin, so that women with a low such threshold could exhibit a PCOS phenotype.

David Abbott (Madison, WI) gave a different view of the developmental origins of IR and β-cell defects based on a nonhuman primate model for PCOS (37). His group hypothesized that the PCOS ovary develops as an overproducer of androgens regulating ovarian follicle development and steroid synthesis, with consequent effect on genes regulating insulin secretion and action and adipocyte differentiation. In their study, pregnant nonobese rhesus monkey females were administered testosterone from days 40 to 80 of the typical 170-day gestation, with testosterone levels increasing from 0.03 to 0.3–0.4 ng/ml. The adult female offspring had oligomenorrhea, an increased testosterone response to human chorionic gonadotropin, and 40% had polycystic ovaries. They had increased abdominal fat with no difference in total body fat mass, and free fatty acid levels were higher during an intravenous glucose tolerance test (38). Insulin sensitivity and disposition index were lower; pancreatic islet histology showed decreased insulin staining, suggesting decreased β-cell mass; and 27.3% developed type 2 diabetes, compared with no controls. In the neonate, there was androgenization of external genitalia. Abbott pointed out that the model was imperfect, as there was greater maternal weight gain and glucose intolerance during pregnancy after testosterone administration. Furthermore, fetal glucose at gestational day 80 correlated negatively with serum glucose immediately after birth suggesting maternal hyperinsulinism, and there was somewhat increased weight of treated infants after birth, with a 75% increase in insulin staining in islets of the offspring of testosterone-treated mothers. One cannot, then, clearly distinguish exogenous androgen-induced mild-moderate maternal glucose intolerance causing hyperglycemia that increases fetal growth from fetal androgen excess as the cause of the PCOS phenotype—showing the complexity of the relationship between IR and abnormal androgen status.

David Ehrmann (Chicago, IL) discussed a potential effect of sleep apnea as a contributory factor to PCOS. Given the high prevalence of obstructive sleep apnea (OSA) in people with obesity, hyperinsulinemia, and, perhaps, hyperandrogenemia, it is reasonable to assume that PCOS would be associated with this condition. OSA is characterized by frequent microarousals and reductions in slow-wave sleep and is associated with glucose intolerance and IR. In a study of three nights of sleep disruption during stage 3–4 sleep in normal-weight men and women, glucose tolerance and insulin sensitivity decreased (39). OSA can cause sympathetic nervous system overactivity, hypertension, glucose intolerance, and dyslipidemia. Overnight polysomnography of 18 obese women with PCOS and age/weight-matched control subjects showed OSA in 44 and 5%, respectively (40). Ehrmann's study showed OSA to be 7.1-fold more common in women with PCOS than in control subjects, and the severity of OSA correlated with fasting insulin and fasting and 2-h glucose levels. Although androgen levels did not correlate with the degree of OSA, low estrogen and progesterone were not excluded as contributory factors (41). Continuous positive airway pressure treatment improves sympathetic hyperactivity and insulin sensitivity both in lean and in obese women.

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