The 6th Annual World Congress on the Insulin Resistance Syndrome

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This is the first of a series of articles based on presentations at the 6th Annual World Congress on the Insulin Resistance Syndrome held 25–27 September 2008 in Los Angeles, California.

Yehuda Handelsman (Tarzana, CA), the organizer and prime mover of the International Committee for Insulin Resistance, discussed clinical implications of insulin resistance, touching on its relationship to sleep disorders, and the cytokines produced by adipocytes. Reducing adiposity appears to be an optimal approach to treatment of insulin resistance, with excess adipose tissue playing roles in genesis of nonalcoholic steatohepatitis (NASH), hyperuricemia, the polycystic ovary syndrome, atherosclerosis, and diabetes. There are ~57 million people in the U.S. and 314 million overall in the world with pre-diabetes, with conversion to diabetes directly related to insulin resistance, particularly in the setting of decreased insulin secretion. "Treating diabetes works," he commented, noting the recent UKPDS (United Kingdom Prospective Diabetes Study) follow-up study, and asked whether one should therefore treat pre-diabetes, given the strong similarities in risk for diabetes and cardiovascular disease (CVD), further suggesting that metabolic syndrome should be considered a pre-diabetes equivalent. Treatment of pre-diabetes may benefit from lifestyle intervention, with consideration of pharmacological treatment in high-risk patients, including thiazolidinediones, metformin, and α-glucosidase inhibitors; such patients should have aggressive efforts directed to CVD prevention with blood pressure and LDL cholesterol goals of <130/80 mmHg and <100 mg/dl, respectively.

Cellular mechanisms of insulin resistance

Ira Goldfine (San Francisco, CA) discussed the importance of plasma cell membrane glycoprotein-1 (PC-1), also termed ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1), in insulin resistance. PC-1 is an integral membrane protein that plays an enzymatic role in pyrophosphate and bone metabolism and, separately, contains a domain that binds to the insulin receptor. PC-1 overexpression decreases insulin action in tissue culture, and measurement of PC-1 content in fibroblasts from insulin-sensitive and -resistant individuals shows the latter to have either elevated levels of PC-1 or the Q-allele of PC-1, which is associated with greater binding affinity. PC-1 content of adipose tissue and of skeletal muscle similarly inversely correlates with insulin sensitivity. PC-1 inhibits the insulin receptor by blocking the connecting domain in the receptor's α-subunit, which transmits insulin-induced conformational change. When insulin attaches to its receptor, the conformational change brings the receptor's β-subunits together and leads to their transphosphorylation, initiating insulin action (1). PC-1 blocks the movement of the β-subunits, blocking then both the insulin receptor substrate and SHC/SOS/MAPK systems; PC-1 is specific for insulin action and does not inhibit IGF-1 signaling. In transgenic mice overexpressing PC-1, with activity at a level comparable with that in humans with insulin resistance, hyperglycemia and hyperinsulinemia occur, with decreased insulin-mediated glucose uptake in muscle and brain, perhaps explaining certain features of insulin-resistant states. PC-1 is increased in muscle of obese humans, correlating with BMI, and in animal models of obesity.

The Q-allele of the K121Q polymorphism of the glycoprotein PC-1 gene has a lysine-to-glutamate substitution, exhibiting two- to threefold greater binding to the insulin receptor and thus decreasing insulin receptor function for a given level of PC-1 expression. PC-1 Q-allele frequency is increased in some (2) but not all (3) insulin-resistant individuals, as well as in those with type 2 diabetes, obesity, polycystic ovary syndrome, and CVD, with evidence that diabetes risk doubles in subjects with two Q-alleles. PC-1 can be measured in circulating monocytes, lymphocytes, and plasma, appearing to be shed from cells and not interacting with the insulin receptor. Therapies may be developed to lower PC-1, and studies of monoclonal antibodies, antisense oligomers, and siRNA are ongoing. Monoclonal antibody treatment reduces elevated PC-1 in tissue culture and increases insulin but not IGF-1 receptor autophosphorylation. Goldfine discussed an activator of the β-subunit of the insulin receptor, which may be developed for oral administration, acting to recruit insulin receptors to the cell surface and in tissue culture increasing insulin sensitivity in hepatocytes overexpressing PC-1.

Gerald Shulman (New Haven, CT) discussed cellular mechanisms of insulin resistance and pointed out that in 2030, 366 million people worldwide will have diabetes, with projected doubling of prevalence in Asia. Understanding cellular mechanisms will allow development of new targets for treatment. There is evidence of decreased hepatic glucose uptake, for which potential rate-controlling steps are GLUT4, hexokinase, and glycogen synthase, the former appearing to be rate controlling, which led Shulman to think that glycogen synthase activators are unlikely to improve flux into glycogen in skeletal muscle. He showed the effects of increased free fatty acids (FFAs) reducing muscle glucose uptake. The Randle hypothesis posits that this is due to accumulation of glucose-6-posphate in the myocyte because of competition for its metabolism, but Shulman noted studies of effects of increased FFA with intracellular glucose-6-posphate levels and intracellular glucose decreasing, suggesting interference with GLUT4 in muscle and

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liver. Increased FFAs appear to increase intracellular diacylglycerol (DAG), acting via protein kinase C (PKC)-θ to increase insulin receptor substrate-1 serine phosphorylation and to decrease tyrosine phosphorylation, reducing insulin action. Acetyl-CoA carboxylase appears to be involved in this process, leading to reduced mitochondrial oxidation, with FFA-induced insulin resistance in muscle also involving DAG acting via PKCε. Shulman suggested that this pathway is involved in hepatic steatosis, with weight loss presumably reducing intracellular DAG; cytokine abnormalities did not appear to be major mediators in his studies. Insulin sensitivity measurements in ~200 young adults with normal weight and glycemia showed that insulin-resistant offspring of diabetic parents had reduced muscle non–oxidative glucose disposal, reflecting increased intramuscular cytoplasmic lipid, presumably with increased DAG (4). Shulman hypothesized this to be due to mitochondrial abnormalities, given that ATP synthesis was reduced, and there was evidence of decreased mitochondrial density in these individuals (5). Insulin resistance, then, has "many different ways to get there" including diet/lack of activity–related obesity, genetic abnormalities, age, and inherited defects in mitochondrial metabolism—all of which may be associated with intracellular fat accumulation in liver and muscle leading to insulin resistance. The metabolic syndrome studies, which Shulman discussed, show decreased muscle glycogen synthesis, decreased peripheral glucose uptake, and increased liver triglyceride content with doubling of de novo hepatic lipogenesis that leads to atherogenic dyslipidemia, suggesting similarity to diabetes.

Adipocyte and insulin resistance

Gerald Reaven (Stanford, CA) reviewed aspects of the relationship between obesity and insulin sensitivity. Using the steady-state plasma glucose (SSPG) after infusion of somatostatin, insulin, and glucose as a measure of insulin resistance, there is a sixfold variation from the most insulin-sensitive to the most insulin-resistant decile in the apparently healthy nondiabetic population. He mentioned a study of ~300 people in whom the correlation coefficient of BMI versus SSPG was 0.46, which he interpreted as indicative of "enormous variability at any level of BMI." Obesity is associated with sedentary lifestyle, and he then mentioned another study with a somewhat stronger correlation of 0.63 between clamp insulin sensitivity and Vo_{2max} during exercise.

In Pima and Caucasian subjects, obesity showed a negative relationship with insulin action up to 28% body fat, with further degrees of obesity not significantly changing insulin sensitivity (6). In both groups, Vo_{2max} was linearly related to insulin action, independently of the degree of obesity, with the two factors together accounting for approximately half the variation in insulin sensitivity. Reaven suggested that the other half must be genetic. Family studies of Pima Indians, for example, show a strong inherited component. Similar effects have been reported in a number of ethnic groups, with a very high degree of insulin resistance among Asian Indians. It is the insulin resistance that appears to convey abnormalities rather than obesity per se; with comparison of nonobese hyperinsulinemic with normoinsulinemic individuals and obese hyperinsulinemic with normoinsulinemic individuals with similar levels of activity, high triglyceride and low HDL cholesterol levels are seen in both insulin-resistant groups. Comparing insulin sensitivity tertiles, the upper tertile has much greater levels of hypertension and new CVD. In studies of CVD risk factors among obese subjects according to SSPG tertile, all risk factors (including C-reactive protein) other than LDL cholesterol are affected by insulin resistance. Weight is associated with higher LDL cholesterol levels, not related to insulin sensitivity, whereas for triglyceride and HDL cholesterol and for glycemia, both insulin resistance and BMI interact in effect. Reaven pointed out that obesity also reduces insulin clearance, further increasing the insulin response. A U.S. population epidemiological database analysis of age- and sex-standardized prevalence of cardiometabolic abnormalities by body size and race/ethnicity showed that a substantial number of normal-weight individuals exhibit the abnormalities of insulin resistance, while a substantial number of obese subjects have normal cardiometabolic parameters (7). Addressing the use of waist circumference or BMI, there is, of course, a strong correlation between the two measures (8), and changes in either lead to change in SSPG; however, among subjects with either normal waist or increased waist circumference, the degree of insulin resistance progressively increases with increasing BMI. A recent study of 168,000 subjects in 63 countries showed that for 1-SD increase in waist circumference and BMI, the prevalence of CVD increased by 36 and 32%, respectively, with similar effects on diabetes (9), suggesting that either can be used and that both are important although similar measures, with the two "highly correlated and provid[ing] essentially the same information concerning insulin sensitivity and CVD risk factors." Reaven expressed a degree of caution about the concept of a "metabolic syndrome," showing evidence from the Framingham study that having two rather than three of the five diagnostic abnormalities led to a similar degree of increase in cardiovascular risk (10). Of the five National Cholesterol Education Program Adult Treatment Panel III diagnostic criteria, however, the only one not independently related to stroke or coronary disease risk is waist circumference (11), and Reaven pointed out that the pronounced ethnic variability in normal waist circumference makes it a less sturdy measure; one-third of a group of subjects in Singapore with metabolic syndrome, for example, had normal waist circumference. This has led some to recommend a change in the criteria for the syndrome (12), although Reaven commented that this does not seem to be securely based on clinical studies.

Richard Bergman (Los Angeles, CA) discussed the pathological basis of and potential therapies for the insulin resistance syndrome. There is a strong relationship between insulin sensitivity and central adiposity (13), more than for other fat depots, which has not been fully elucidated yet. Furthermore, Bergman noted that it also has not been fully clarified why insulin resistance causes hyperinsulinemia because "we do not really know how the β-cell upregulates its function." He defined the metabolic syndrome, from a pathophysiological perspective, as visceral and subcutaneous adiposity associated with hepatic and peripheral insulin resistance, with elevated FFA, adipokines, and hyperinsulinemia.

Bergman pointed out that the pattern of obesity in dogs is similar to that in humans, with most fat in the trunk, so that magnetic resonance imaging allows accurate visceral and subcutaneous fat measurement, and portal venous sampling and infusions can be readily carried out. With high-fat diet leading to modest weight gain but doubling of both subcutaneous and omental fat, the two compartments are similar in size (in contrast to the ratio in humans), although the degree of weight gain and the ratio of omen-

tal to subcutaneous fat varies from animal to animal. After the high-fat diet, hepatic fat increases and small adipocytes are seen, particularly in omental fat. Isoproterenol-stimulated lipolysis is considerably greater in omental than in subcutaneous fat, suggesting greater sensitivity to sympathetic nervous system (SNS) adrenergic stimulation. Genes responsible for release of fatty acids from the visceral depot, for hepatic gluconeogenesis, and for fat handling are upregulated by overfeeding (14). Release of fatty acids from the visceral fat depot is cyclic with a period of 11 min in dogs, as in humans, with the oscillations suppressed by β_3 blockade, implying a role of the SNS (15). Pulsatile FFA release causes hepatic insulin resistance, a mechanism by which the SNS controls insulin sensitivity, and Bergman suggested that FFAs rather than adipokines are the major adipocyte-derived cause of insulin resistance.

Given the much greater effect of mesenteric than subcutaneous fat on insulin sensitivity, as demonstrated by the marked improvement with omentectomy in his studies, and the hypothesis that FFA determines insulin sensitivity, he studied nocturnal FFA release in the canine model, as particularly seen on a high-fat diet, measuring arterial-portal venous FFA differences. These further suggest a relationship of visceral adiposity to the pathogenesis of insulin resistance. He showed evidence of prevention of fat accumulation and insulin resistance with the cannabinoid-1 antagonist rimonabant, with restoration of the initial fat deposition pattern, prevention of hepatic fat accumulation, and elevations in adiponectin levels, not accounted for by changes in food intake, suggesting a peripheral effect.

Samuel Cushman (Bethesda, MD) discussed evidence that dysfunctional adipogenesis plays a role in the development of insulin resistance, with similar consequences of excess adipose tissue in the context of limited expansibility and lipoatrophy. Adipose tissue acts as a site of energy storage, for energy production, and in secretion of circulating factors such as leptin, resistin, interleukin 6, tumor necrosis factor-α, and adiponectin. Models with adipocyte-selective deletion of GLUT4 expression have impaired insulin action in skeletal muscle as a consequence both of increased levels of adipocytokines and of ectopic fat within muscle, associated with decreased phosphatidylinositol 3-kinase activity.

Adipose tissue develops in a complex fashion from stem cells that differentiate into chondroblasts, osteoblasts, myoblasts, or preadipocytes, with subsequent peroxisome proliferator–activated receptor (PPAR)γ-mediated differentiation into adipocytes. Adipocyte cell size histogram analysis reveals a substantial subset of smaller and larger adipocytes, with the former possibly representing preadipocytes or other cell types. Compared with subjects with elevated BMI who are insulin sensitive, those who are insulin resistant have smaller adipocytes with reduced expression of sterol regulatory element–binding protein-1c and PPARγ, compatible with lack of expansibility, and a lesser capacity to store fat (16). In an obesity-prone rat strain, loss of large fat cells develops over a 12-week period on a high-fat diet, with the greater fat mass comprised of larger numbers of smaller adipocytes. In a 12-week human study of obese insulin-resistant nondiabetic subjects receiving pioglitazone, weight increased; however, there was a significant decrease in visceral fat. Adipocyte size histograms showed an increase in large and decrease in small cells—the ratio correlating with the degree of improvement in insulin action.

Tracy McLaughlin (Stanford, CA) continued the discussion with a presentation of the clinical relationships between obesity and insulin resistance. Eighty-five percent of glucose disposal occurs in skeletal muscle; as BMI increases, the insulin sensitivity decreases, although with a great degree of variability, so that among people with BMI 30–34.9 kg/m^2, ~55% are in the most insulin-resistant and 12% in the most insulin-sensitive tertile, while among those with BMI 25–29.9 kg/m^2, 44% are in the most insulin-resistant and 25% in the most insulin-sensitive tertile. Reduction in body weight improves insulin sensitivity (17), and this appears to be sustained and even to improve over a 3-year period, with attendant improvement in dyslipidemia (18). Insulin sensitivity improves with dietary weight loss in insulin-resistant but not insulin-sensitive women (19).

A number of theories have been proposed that explain the relationship of excess adipose tissue to insulin resistance, suggesting it to be mediated by changes in distribution of fat, adipocytokines, and inflammation or by the development of ectopic fat stores. Upper body fat contributes 70% of circulating FFA (20). Basal lipolysis is greater in subcutaneous than in omental tissue and is proportional to fat cell size (21). Catecholamines have greater effect in stimulating lipolysis, and insulin has a lesser effect in suppressing lipolysis, in omental than in subcutaneous fat. The visceral adiposity portal concept is that direct FFA delivery to the liver increases production of VLDL and glucose and decreases insulin clearance, whereas elevation in systemic FFA levels decreases skeletal muscle glucose uptake and stimulates hepatic inflammation. Only 15% of FFA comes from visceral fat, however, and increased hepatic glucose and VLDL production are likely consequences rather than causes of insulin resistance. Visceral fat does not, according to McLaughlin, show clear correlation with insulin sensitivity, and interventions that improve insulin sensitivity do not consistently decrease circulating FFA and typically decrease both visceral and subcutaneous fat. Although adiponectin levels are on average higher in insulin-sensitive than in insulin-resistant individuals, again there is a great deal of variability (22), and although adiponectin is increased by thiazolidinediones, McLaughlin stated that her studies have not clearly shown increases with weight loss.

Inflammatory markers are increased in proportion to obesity, and there is some evidence of improvement in insulin sensitivity with anti-inflammatory agents. When equally obese insulin-sensitive and -resistant individuals are compared before and after weight loss, the former have lower C-reactive protein levels that do not change, whereas levels are higher in the latter group and decrease with weight loss, although not to the level in the insulin-sensitive individuals (23). Adipose tissue macrophage numbers increase with increasing BMI (24), with some suggestion that adipocyte apoptosis causes inflammation (25). In periumbilical subcutaneous fat biopsy of moderately obese subjects, there was significant increase in inflammatory gene expression, but macrophage infiltration did not show strong association with insulin resistance, so the role of inflammation remains to be elucidated (26).

An interesting question is whether fat storage capacity (either by hypertrophy or hyperplasia) determines whether ectopic fat develops. Adipocyte enlargement is limited; an overfeeding study in Pima Indians showed 3-kg weight gain but a re-

duction in mean adipose cell size, with a 50–100% increase in the number of small cells (27). McLaughlin found that peak adipocyte diameter increases as BMI increases from 30 to 35 kg/m^2, without subsequent change as weight increases further, with the ratio of small to large cells appearing more strongly associated with weight gain, suggesting failure of expansion of adipocyte reserves. In this view, increase in caloric load necessitates increased fat storage with adipocytes unable to enlarge indefinitely, with overfeeding causing recruitment of small cells and thiazolidinediones appearing to act by increasing adipocyte mass. Although insulin resistance is associated with small adipocytes, there is evidence that pioglitazone increases the number of small adipocytes, suggesting multiple possible mechanisms of the relationship between adipocytes and insulin sensitivity.

Antonio Vidal-Puig (Cambridge, U.K.) discussed adipose tissue expandability, lipotoxicity, and pharmacological targets based on these concepts. Adipose tissue should be considered as part of an integrated system designed to prevent negative energy balance, in which decreased food intake is associated with decreased energy expenditure to avoid weight loss, while energy expenditure may increase in the setting of adipose tissue expansion. There is epidemiological evidence of a strong link between obesity and diabetes (28), and an individual person's insulin sensitivity decreases as fat mass increases. Obesity leads, of course, to a variety of mechanical and psychological issues but should be considered in essence a mismatch between energy availability and storage capacity leading to lipotoxicity with the metabolic syndrome of fatty liver, diabetes, heart failure, hypertension, dyslipidemia, and a variety of other consequences. Lipotoxicity may, then, be considered a state of inappropriate lipid storage in nonadipose tissues, thus causing insulin resistance. This formulation suggests that improving lipid storage in adipose tissue will be protective, whereas in the event of lipid not being appropriately stored in adipose tissue, activation of mitochondrial fatty acid oxidation will have a protective effect. The adipose tissue expandability hypothesis suggests that there are limits to the capacity to expand fat mass to store lipid and that at the point of maximal expansion lipotoxicity ensues (29). Adipose tissue expandability is genetically determined by the number of preadipocytes, dipogenesis, vasculogenesis, and dysfunction of other cellular components in adipose tissue. There may be a relatively fixed number of adipocytes, perhaps genetically determined (30). This concept is illustrated by rodent lipodystrophy models that show the extreme of impaired adipose tissue expandability. Another example, based on studies by Vidal-Puig, is of mice with dominant negative PPARγ mutation that unexpectedly show normal amounts of adipose tissue and are insulin sensitive. When these mice lack leptin, however, although they are less obese than *ob/ob* animals, they are more insulin resistant (31). The adipose tissue expandability hypothesis suggests conversely that it should be possible to have extreme degrees of obesity without metabolic complications—a finding exhibited in *ob/ob* mice with increased expression of adiponectin (32). Such concepts have human relevance, in subjects with lipodystrophy (33) but also in subjects with severe obesity but without metabolic syndrome (34).

Vidal-Puig noted that abnormal production of adipocytokines with increases in adipose tissue inflammation remains possible with the adipose tissue expandability hypothesis and that as 70% of fat delivered to the liver is not viscerally derived. Failure of subcutaneous adipose tissue to expand would also be predicted to lead to insulin resistance. Adipose tissue expandability implies the existence of metabolic set points. Once individuals reach their maximal adipose tissue mass, metabolic complications ensue, suggesting that pharmacological agents increasing adipose tissue expandability would be beneficial, allowing treatment of NASH, diabetes, and dyslipidemia. Identification of organ-specific lipid networks may provide key information for specific treatments, and specific lipotoxicity patterns may be useful as biomarkers of CVD and metabolic risk.

Gut hormones, β-cells, and insulin resistance

Vivian Fonseca (New Orleans, LA) discussed the need for basic research to better understand the mechanisms of glucagon-like peptide-1 (GLP-1) effect and noted that the peptide may directly suppress FFAs. He also pointed out that GLP-1(9–36) amide, the production of which is decreased by dipeptidyl peptidase-4 inhibitors, does not affect glucose metabolism but may have vascular effects and that glucose-dependent insulinotropic peptide has not yet been well studied for vascular actions. The possibility that GLP-1 may improve insulin sensitivity is difficult to assess, given the weight loss associated with the agent. Glucagon suppression, which occurs in the postprandial state, clearly improves insulin action. The dipeptidyl peptidase-4 inhibitor vildagliptin appears to reduce fat mobilization, suggesting decreased ectopic fat, which also might be expected to improve insulin sensitivity, and there is evidence that the agent also reduces postprandial triglyceride, with particular effect on chylomicrons (35), potentially improving endothelial function. A 6-week GLP-1 infusion in type 2 diabetic patients reduced food intake (36), and GLP-1 analogs act similarly, as shown in studies of the extended release form of exenatide (37). A 3-year follow-up of exenatide showed weight loss, increased HDL and decreased LDL cholesterol levels, and decreased blood pressure, with a dose-response relationship between weight loss and the reduction in triglyceride and increase in HDL cholesterol. Another GLP-1 receptor activator, liraglutide, decreased weight in a dose-dependent fashion, with particular reduction in visceral rather than subcutaneous fat. Over 14 weeks, weight decreased by 3 kg, with reduction in blood pressure by 3–5 mmHg and in triglyceride and cytokine levels. GLP-1 improves left ventricular function and systolic wall motion abnormalities following acute myocardial infarction and angioplasty in diabetic and also in nondiabetic patients (38).

There is fascinating information on vascular effects of GLP-1. GLP-1 is cardioprotective in an ischemia-reperfusion model (39). Fonseca cited a study showing that human coronary artery endothelial cells express the GLP-1 receptor and reviewed evidence that glyburide, but not glimepiride, reduces a beneficial effect of GLP-1 on endothelial function (40). Both GLP-1(7–36) and (9–36) improved left ventricular function in a cardiomyopathy model (41), and there is evidence that both increase nitric oxide synthase activity, with the (9–36) peptide possibly not acting via the GLP-1 receptor and with exenatide not showing such effect (42). In a Zucker fatty rat model of intimal hyperplasia following balloon catheter carotid artery injury, the degree of intimal hyperplasia with insulin resistance and early diabetes was markedly re-

duced by exenatide, in a fashion similar to the effects of thiazolidinediones and statins.

Peter Butler (Los Angeles, CA) discussed β-cell adaptation or maladaptation to obesity and its reversal by gastric bypass surgery. Approximately 80% of subjects with morbid obesity have a fivefold or greater increase in insulin secretion to maintain normoglycemia despite severe insulin resistance. Some type 2 diabetic patients with morbid obesity have much more rapid resolution of diabetes after bariatric surgery than can be explained by early weight loss, and some individuals develop severe postprandial hypoglycemia after the procedure, both suggesting improvement in insulin secretion. In an autopsy study, nondiabetic subjects have a 50% increase in β-cells with obesity with increased β-cell number rather than size (43). Interestingly, this is much more exaggerated in rodents who have a 10-fold increase in β-cell mass with obesity, suggesting this not to be an ideal model for human β-cell abnormalities. Pancreas fat volume can be measured using computed tomography scan, with similar relationship to BMI in diabetic and nondiabetic subjects, with no evidence that excess pancreatic fat is the cause of β-cell dysfunction in type 2 diabetes (44). There are fewer β-cells in the pancreas of people with type 2 diabetes, and there is increased pancreatic amylin, with pathology similar to that in the brain, leading Butler to question whether this is a consequence of diabetes or a cause. In autopsy studies, obese nondiabetic subjects show a wide range of β-cell volume, ranging from 1 to 8% of pancreatic mass, with β-cell mass reduced by 50% on average in subjects who had impaired fasting glucose and reduced by 65% on average in those who had type 2 diabetes on no treatment, suggesting that reduction in β-cell mass by half "is an important breakpoint" for development of diabetes. Although there is no consensus on the mechanism of β-cell loss in type 2 diabetes, amyloid appears to be an important mediator, perhaps causing the increased β-cell apoptosis in type 2 diabetic patients. Butler pointed out that β-cells produce insulin at an extremely high rate, perhaps leading to amyloid oligomer formation, which causes apoptosis via endoplasmic reticulum stress in a fashion similar to that in Alzheimer's disease, involving the unfolded protein response transcription factor CCAAT/enhancer-binding protein/homologous protein.

Butler made several controversial assertions at the conclusion of his lecture. Addressing the question of a change in β-cell mass after gastric bypass surgery, he criticized the study suggesting that some cases of bariatric surgery are complicated by nesidioblastosis, causing postprandial hypoglycemia (45). He stated that the study was not properly carried out to give a real measurement of β-cell mass, reanalyzed the pathology of the pancreases from these patients compared with 16 lean and 31 obese nondiabetic control subjects, and found no difference in β-cell mass or in insulin-positive cells in or around pancreatic ducts, suggesting that postprandial hypoglycemia after gastric bypass surgery is due to inappropriate insulin secretion rather than increased β-cell number, perhaps related to abnormal regulation of the β-cells of some individuals who had sustained hyperinsulinemia for the many years during which they were obese. He presented results of a study showing that β-cell mass increases from ~0.2 to 0.8 g from birth to age 5 years, with average β-cell mass subsequently stable for the remainder of life, although with fairly marked variability (46). He pointed out that studies showing that GLP-1 increases β-cell mass were carried out in neonatal mice and stated that his group showed that the peptide does not affect β-cell mass subsequently, although this is certainly a topic about which there is disagreement.

Dan Porte (Seattle, WA) discussed central control of body weight. In a study carried out more than 3 decades ago, of groups of rats after periods of over- and underfeeding, resulting in greater or lesser weight gain in comparison with ad libitum fed animals, the overfed rats lost and the lean rats gained weight to a degree directly proportional to basal insulin levels, with all groups eventuating at the same weight, suggesting that body weight is regulated by insulin levels (47). Intracerebroventribular insulin infusion lowered weight in baboons, with subsequent regain, while animals not expressing insulin receptors in the brain develop obesity (48), supporting this hypothesis (49). Leptin acts in a similar fashion (50), suggesting a complementary set of signals giving extended time scale controls of body weight. The two signals, leptin and insulin, act by increasing proopiomelanocortin and decreasing agouti-related peptide (AgRP)/neuropeptide Y (NPY) neuronal activity. Endothelial cell insulin and leptin receptors in localized areas of the blood brain barrier allow these peptides to be taken up to regulate caloric balance. A separate gut peptide–based system acts on day-to-day and meal-to-meal control of caloric balance, with receptors on the vagus for cholecystokinin, bombesin, neuromedin B, GLP-1, peptide YY (PYY), amylin, glucagon, apolipoprotein A-IV, enterostatin, and somatostatin—all of which reduce food intake. Ghrelin, in contrast, increases food intake (51).

These systems may be perturbed in obesity. Leptin resistance has been demonstrated to occur with obesity. Although intranasal insulin, which may be transported via olfactory neurons, reduces body fat when administered over a period of months (52), there is central insulin resistance in obesity, so it would not appear to be effective given alone as an obesity treatment. Interestingly, although subthreshold leptin had no effect alone, when administered with exendin-4 there appeared to be additive effect (53). As weight gain occurs, then, the gut peptide signal may become more important, and there is a similar study showing a subtherapeutic dose of insulin to produce satiety when administered with cholecystokinin (54).

David Heber (Los Angeles, CA) discussed obesity, insulin, and the gut-brain axis and addressed effects of insulin and leptin resistance. There have been a number of important discoveries over the past 15 years, including those of the adipocyte hormones leptin and adiponectin, the gastrointestinal hormones ghrelin and GLP-1, and many brain hormones and transmitters, including NPY, AgRP, melanin-concentrating hormone, endocannabinoids, α-melanocyte–stimulating hormone, cocaine- and amphetamine-regulated transcript, corticotrophin-releasing hormone, thyrotropin-releasing hormone, and serotonin. Multiple brain areas involved in food intake, with the hypothalamus best studied, and concepts of reward signaling and non–homeostatic food intake with its relationship to emotional eating are being studied. There are two long-term satiety signals indicating nutrient availability, leptin and insulin, while short-term satiety signals principally arise from the gastrointestinal tract, including PYY, cholecystokinin, and GLP-1, with brain-gut messaging principally occurring via the SNS. Thermogenesis regulation by brown adipose tissue may also play a role in energy balance.

Human obesity is resistant to the effect of leptin. Leptin appears to play its major role in signaling and survival in times of food deprivation, and the principal effect of leptin appears to be an increase in food intake occurring when leptin levels fall—one of many hypothalamic circuits related to food intake. An individual who was previously obese, then, has a lower metabolic rate than the never-obese person in part mediated by reduction in leptin levels. Leptin resistance may have teleological benefits in preventing inappropriate reduction in food intake, although being counterproductive in the current environment. Visceral fat, a combination of omental and mesenteric adipose tissue, comprises 20% of fat in men and 5–8% in women. High body fat levels may be seen in normal-weight individuals, and approximately one-third of normal-weight subjects have low muscle and high fat mass. Insulin resistance produced by excess abdominal fat may in part represent activation of the innate immune system to prevent weight loss–related infection. Advantages of insulin resistance include the maintenance of glucose levels between meals allowing adaptation to malnutrition, while not impeding lipogenesis in fat cells, so that fat storage can occur.

Cholecystokinin inhibits food intake with maximal effect within 30 min, while GLP-1—the most potent incretin—also inhibits food intake, although it is not clear whether this occurs at physiological levels. Ghrelin, identified in 1999, is synthesized by gastric epithelium and increases food intake when administered either peripherally or centrally, acting to signal premeal hunger, with levels tending to be low in obesity. PYY(3–36) inhibits food intake markedly, but daily fluctuations in endogenous PYY do not appear to be related to changes in appetite. The effect of bariatric surgery may involve reduction in ghrelin or increases in PYY levels. Central regulation of food intake occurs to a large extent in the arcuate nucleus of the hypothalamus, which also regulates reproductive function. The paraventricular nucleus, releasing corticotrophin-releasing hormone and thyrotropin-releasing hormone, is another site of food intake regulation. NPY stimulates appetite, with central administration causing sustained hyperphagia, and also appears to increase calmness, with antagonists causing anxiety/stress symptoms. AgRP increases food intake through antagonism of the melanocortin-3 and -4 receptors, blocking inhibition of food intake caused by α-melanocyte–stimulating hormone, which is derived from brain proopiomelanocortin. PYY(3–36) acts directly to inhibit orexigenic NPY neurons. Thus, low leptin, insulin, and PYY(3–36) and high ghrelin appear to be physiological factors increasing food intake. Emotional eating, learned and probably preprogrammed behaviors, and frontal cortex reward circuits are, according to Heber, "very hard circuits to unwire," with diet and physical exercise as "the difficult but most effective means of working against" these biological systems.

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