

Treatment Issues in Type 2 Diabetes

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This is the fifth in a series of reports on the American Diabetes Association (ADA) 61st Scientific Sessions held in Philadelphia, PA, in June 2001. It covers topics related to the treatment of type 2 diabetes.

Postprandial physiology

Alan Cherrington, Nashville, TN, examined the effect of insulin to inhibit hepatic glucose production. Using a dog preparation with somatostatin to block insulin and glucagon production and administration of insulin and glucagon into the portal vein, decreasing portal insulin to levels similar to those in the arterial circulation immediately increased hepatic glucose production via glycogenolysis, which was sustained over a period of several hours, with consequent hyperglycemia. There is a steep inverse dose-response curve of hepatic glucose production versus hepatic sinusoidal insulin levels. Tripling insulin quickly turns off hepatic glucose production. Glucose utilization by the liver in response to increasing insulin levels has a longer time course, taking several hours to reach maximal levels. This response is much less sensitive to changes in insulin levels than hepatic glucose production, and normal basal hepatic glucose utilization is very low. Muscle is less sensitive on a molar basis than in the liver, so that a tripling of insulin levels causes only a 50% increase in glucose utilization, compared with the more than sixfold increase in glucose uptake under maximal stimulation.

Comparing the effects of first-phase and second-phase insulin release in response to glucagon, the former more potently inhibits glucose production. Insulin levels show similar first- and second-phase responses to a hyperglycemic

clamp, and elimination of the first-phase insulin response leads to much greater hepatic glucose production, although it has little effect on glucose utilization. A recent study with nateglinide similarly showed a rapid insulin response and marked lessening of postprandial hyperglycemia (1). When intraduodenal glucose is given with dogs having somatostatin and portal catheters, a first-phase insulin spike dramatically decreases the amount of subsequent hyperglycemia by increasing glucose uptake. Glucose uptake by the liver is a function of hepatic exposure to glucose, to insulin, and to the signal of glucose entering via the portal vein. When glucose is infused portally versus peripherally, the hepatic glucose load increases, leading to considerably greater hepatic glycogen formation with the former. The nature of the gut signal is not known. It is not glucagon-like peptide (GLP)-1 or acetylcholine, and it is eliminated by denervation, suggesting it to be neurally mediated.

Robert O'Doherty, Dallas, TX, discussed manipulation of hepatic glucose metabolism in vivo using recombinant adenoviruses. In the fed state, glucose uptake and glycogen and lipid synthesis occur, while in the fasted state hepatic glycogenolysis and gluconeogenesis are the major processes. "Engineering of hepatic glucose metabolism may at some point serve as a treatment for the metabolic abnormalities of diabetes," he suggested. Glucokinase, which forms glucose-6-phosphate from glucose, is responsible for a form of maturity-onset diabetes of the young (MODY) when defective. Using adenoviral vectors, which primarily deliver genes to the liver, the glucokinase gene, which acts as a glucose sensor and regulates hepatic glucose

uptake, markedly increases in the liver. Treated rats expressing high levels of glucokinase show marked hypoglycemia and hypoinsulinemia with high lactate, triglyceride, and free fatty acid (FFA) levels. Liver glycogen metabolism increases, with a 10-fold increase in hepatic glycogen levels. Hepatic glycogen and lactate increase, with an increase in glycogen synthase activity. Overexpression of glucokinases increases fatty acid synthase, pyruvate kinase, and glucose-6-phosphatase. Glucose-6-phosphatase catalyzes the reverse reaction. With overexpression of the catalytic subunit of this enzyme, there is mild hyperglycemia and hyperinsulinemia, a mild fall in triglyceride and FFA levels, mild glucose intolerance, and a decrease in hepatic glycogen. Overexpression of either gene does not change insulin sensitivity.

Protein targeted to glycogen (PTG), a scaffolding protein for formation of glycogen, can be overexpressed with little effect in either the fed or fasting state on hepatic metabolites, but with improved glucose tolerance, suggesting improved ability of the liver to clear glucose. There is a 50% increase in hepatic glycogen in the fed state in these animals, without effect in the fasting state. The modified cells can accumulate glycogen regardless of carbon source (e.g., from pyruvate and from the gluconeogenic amino acid glutamine). PTG overexpression activates glycogen synthase, while glycogen phosphorylase activity decreases, suggesting impaired ability to mobilize glucose from glycogen stores. The ability of c-AMP to decrease glycogen decreases. These studies suggest an important role of hepatic glycogen metabolism in regulating the disposal of glucose, as well as suggesting that the use of gene therapy to deliver metabolic genes to the liver may provide a novel strategy for the correction of the metabolic abnormalities in diabetes and obesity.

Kurt Jungermann, Göttingen, Germany, discussed the role of liver-gut neural signaling in glucose metabolism. Hepatoenteral and enterohepatic sensor-effector nerves are muscarinic signals between the liver and gastrointestinal tract. Hepatic effector functions include storage and synthesis of glucose and lipid and protein synthesis. The liver also, Junger-

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Abbreviations: ADA, American Diabetes Association; BW, birth weight; DPP, dipeptidyl dipeptidase; FFA, free fatty acid; GIP, glucose-dependent insulinotropic polypeptide; GLP, glucagon-like peptide; IKK, I κ B kinase; NO, nitric oxide; NSAID, nonsteroidal antiinflammatory drug; PG, prostaglandin; PKA, protein kinase A; PTG, protein targeted to glycogen; SHIP, the Src homology 2 domain-containing inositol 5 phosphatase; SUR1, sulfonylurea receptor-1; TNF, tumor necrosis factor; UCP, uncoupling protein.

man said, "has an extraordinary position in the circulation . . . in series behind the intestine and the endocrine pancreas." The liver is supplied by sympathetic and parasympathetic nerves entering around the portal artery and vein. Using an isolated combined intestine plus liver perfusion system perfused via the celiac trunk and superior mesenteric artery, it is possible to place substrates, such as glucose, in the intestine and hormones, such as insulin, in the portal vein to study "cross talk" between the organs. He discussed the finding that intraportal insulin increased gut glucose and galactose but not fructose absorption, indication of action on a specific transport protein. The process involves a frequency-dependent neural effect. Administration of dibutyl cAMP increases glucose absorption in the same fashion, while a protein kinase A inhibitor, which antagonizes cAMP, inhibits the action of portal insulin. Jungerman suggested that portal insulin stimulates insulin glucose absorption via hepatoenteral muscarinic nerves with cAMP acting as the intracellular messenger. Because muscarinic receptors decrease cAMP, this must be an indirect process. Enteroglucagon and prostaglandin (PG)-E₂ appear to be involved and can mimic the effect in isolated enterocytes. Indeed, portal insulin administration increases gut venous PG-E₂ outflow. Thus insulin may act in the splanchnic bed to not only increase hepatic glucose uptake, but to also do so in a fashion matched to glucose absorption. Jungerman speculated that the feedback system may be abnormal with both alcoholic and diabetic neuropathy.

Kirkman et al. (152-OR) studied 215 patients with early type 2 diabetes, with fasting glucose <140 mg/dl and 2-h oral glucose tolerance test (OGTT) glucose \geq 200 mg/dl (abstract numbers refer to the Abstracts of the 61st Annual Meeting of the American Diabetes Association, *Diabetes* 50 [Suppl. 2]:1-A649). The peak plasma glucose after the first meal of the day showed weak but significant negative correlation of -0.35, with insulin secretion during the first 30 min after a hyperglycemic clamp, and positive correlation of +0.21, with a marker of insulin resistance, the product of fasting glucose and fasting insulin. They suggest that gastric emptying and other gut and hormonal factors may also be important in determining prandial glucose increments.

GLP-1 and glucose-dependent insulinotropic polypeptide: physiology, pathophysiology, and treatment

Timothy Kieffer, Edmonton, Canada, discussed the entero-insulin axis and incretin action. After administration of oral glucose in normal individuals and those with impaired glucose tolerance, plasma glucose and insulin levels increase. This is regulated by neural factors and gut hormones as well as by the pancreatic islet response to ingested nutrients. The "incretin concept" can be demonstrated by comparing the response to oral or intravenous glucose, as the former causes less marked hyperglycemia with potentiation of insulin secretion. This process decreases with the development of type 2 diabetes. Two hormones are involved. Glucose-dependent insulinotropic polypeptide (GIP) was isolated from mucosal extracts in the early 1970s because of its ability to inhibit gastric secretion (and hence the original name, gastric inhibitory polypeptide). GIP subsequently was shown to have a glucose-dependent insulinotropic effect that was not manifest at basal glucose levels. GIP-secreting "K-cells" are present at the highest concentration in the duodenum and jejunum. GIP is released early after food consumption, particularly after oral glucose, and perhaps also with protein and fat. The K-cells are directly sensitive to changes in ambient glucose levels. They contain glucokinase and presumably have glucose responsiveness similar to that of β -cells.

A GIP-like peptide in the proglucagon sequence was identified ~10 years after GIP. GLP-1 was shown to be a potent insulinotropic hormone. Its action is also glucose-dependent. GLP-1 cells are located in highest concentration in the "L-cells" of the distal gut, including ileum, colon, and rectum. GLP-1 levels increase rapidly after glucose ingestion to approximately twice the basal level, at a magnitude approximately one-tenth of GIP. The autonomic nervous system plays a role in secretion of both GLP-1 and GIP, and there may be a direct stimulatory effect of GIP on GLP-1 release.

GIP and GLP-1 both bind specifically to pancreatic β -cells, activating adenylate cyclase and increasing cAMP levels. When antibody to GIP is infused, the glucose response to oral glucose increases while the insulin response decreases. With GLP-1, the 9-39 fragment of ex-

endin-4, the natural GLP-1 analog from the venom of the Gila monster, acts as an antagonist, similarly leading to impaired glucose tolerance. Basal GLP-1 may be involved in suppressing glucagon release, and administration of exendin-4 (9-39) also increases the glycemic response to parenteral glucose. In animal or human type 2 diabetes, GLP-1 increases insulin response to glucose, but the response to GIP is diminished, with evidence of defective GIP receptors on β -cells. Other biological effects of GLP-1 are pancreatic islet β -cell proliferation and inhibition of gastric acid secretion, satiety, and peripheral insulin-like actions. However, a protease, dipeptidyl dipeptidase (DPP) IV, quickly cleaves GLP-1 (7-36) to GLP-1 (9-36), which is not insulinotropic. Thiazolidide compounds can inhibit DPP-IV, increase GLP-1 (7-36), and improve glucose tolerance, even in normal animals. DPP-IV has many other peptide substrates, and it remains to be determined whether there are adverse effects of inhibition of this enzyme.

Daniel Drucker, Toronto, Canada, discussed GLPs as regulators of energy absorption and disposal. GLP-1 has a number of non-incretin effects, including regulation of gastric emptying, effects on appetite, resetting the β -cell response to other secretagogues, and effects on β -cell mass and glucose sensing. Effects of GLP-1 on food intake and satiety have been shown in animal and human studies, with abundant GLP-1 binding sites in the hypothalamus, although GLP-1 knockout mice are resistant to development of obesity; therefore, this does not appear to be a dominant regulator of food intake. The most striking finding is the CNS response to stress, including glucocorticoid secretion, with the GLP-1 effect duplicating stress responses, suggesting it to act as a nonspecific noxious stimulus. Intriguingly, diabetes is a metabolic stress, conceivably mediated in part by the GLP-1 receptor signaling system. Even small amounts of GLP-1 in the portal vein appear to have greater effect than similar amounts administered systemically. When GLP-1 receptor signaling is eliminated acutely with exendin-4 (9-39) or chronically in a knockout mouse model, the enhanced insulin secretion with intraportal glucose is abolished, suggesting that GLP-1 has effects beyond its incretin actions. GLP-1 may become a

treatment for type 2 diabetes, preventing the progressive decline in β -cell function.

GLP-2 is another portion of the preproglucagon molecule. It is also secreted by L-cells, and it stimulates an increase in intestinal mucosal mass by stimulating proliferation and inhibiting cell death of enterocytes and crypt cells. It has been shown to be protective in models of ulcerative colitis and nonsteroidal antiinflammatory drug (NSAID) enterocolitis, with a marked decrease in apoptosis. This may be particularly useful in chemotherapy-induced gastrointestinal tract damage. GLP-2 acts at a specific receptor expressed in the gastrointestinal tract, particularly on gut endocrine cells, with the mechanism of its proliferative effect on the gut mucosa not yet known. GLP-2 also acts in the brain, with intracerebroventricular administration inhibiting food intake similarly to GLP-1. Thus, both GLP-1 and GLP-2 may be involved in nutrient sensing and disposition in an interrelated fashion.

George Holz, West Falmouth, MA, discussed the signaling transduction properties of GLP-1 in controlling insulin secretion. GLP-1 interacts with heterotrimeric proteins to stimulate adenylate cyclase to increase cAMP, acting via protein kinase A (PKA), but with additional signaling. β -cell insulin secretion involves increasing cytoplasmic calcium from the endoplasmic reticulum and increasing calcium entry from extracellular compartments, both of which increase with GLP-1 action, which has sulfonylurea-mimetic effects that close the K_{ATP} channel. GLP-1 also affects phosphatidylinositol 3-OH kinase and protein kinase B and increases pancreatic duodenal homeobox-1 activity. The cAMP-binding proteins and the cAMP-regulated cyclic nucleotide guanylyl exchange factors may further mediate GLP-1 actions. GLP-1 also affects β -cell hormone-sensitive lipase and may activate the atypical protein kinase $C\zeta$, which may be involved in β -cell proliferation.

The β -cell triggering mechanism via the K_{ATP} channel may be sensitized by GLP-1. This may involve a G-protein attaching to the channel and influencing its sensitivity to ATP, or may involve facilitation of ATP production. GLP-1 also may have a PKA-mediated effect on the voltage-dependent Ca^{2+} channels, influencing their opening by closing the K^+ channel. There is also a partially K_{ATP} -independent mechanism of insulin secre-

tion, with cAMP increasing Ca^{2+} -dependent insulin exocytosis of β -cell insulin granules. Both mobilization of Ca^{2+} stores from intracellular endoplasmic reticulum stores and Ca^{2+} entry may be affected by GLP-1 signaling via cAMP, modulating insulin secretion. Cyclic AMP antagonists block GLP-1 action. The cAMP binding proteins are expressed in β -cells and can interact with the exocytotic secretion complex and with ion channels, potentially acting in the Ca^{2+} entry-induced insulin secretion. Mitochondrial ATP production may itself be very sensitive to intracellular Ca^{2+} levels, and GLP-1 may also act by mitochondrial effects of cAMP, perhaps acting on mitochondrial PKA. These factors may cause long-term effects on mitochondrial ATP production, changing the response of the β -cell to glucose.

Michael Nauck, Bochum, Germany, presented concepts of GLP-1 and GIP as therapeutic agents. Current evidence is that the GIP response is increased in type 2 diabetes. GIP is not the hormone of choice in view of the resistance to its action in type 2 diabetes. When glucose levels are clamped at a hyperglycemic level and GIP is infused in normal control subjects, first-degree relatives of patients with type 2 diabetes, and patients with type 2 diabetes, there is an increment in insulin in the normal subjects that is not seen in the patients or in the relatives, suggesting this to be an early defect. GIP, which induces lipoprotein lipase, increases triglyceride clearance after chylomicron infusion, a response that is diminished in type 2 diabetes.

Active GLP-1 (7-36) levels are decreased in type 2 diabetes. GLP-1, administered to patients with type 2 diabetes, has glucose-lowering actions, by both stimulating insulin and reducing glucagon concentrations, which occurs to an increasing degree at higher blood glucose levels. This suggests that when used therapeutically, the agent is less likely than existing insulin secretagogues to produce hypoglycemia. A problem is the inactivation of GLP-1 (7-36) by DPP IV, so that subcutaneous injection only gives brief periods of elevation in active GLP-1. Inhibition of DPP-IV leads to much greater GLP-1 action, so that all—rather than 25%—of circulating GLP-1 is active. Exendin 4 or the analog NN2211 may be effective. Toxicology studies are necessary with all of these agents.

Nauk discussed the study of Zander et al. (124-OR), in which administration of GLP-1 versus placebo using continuous subcutaneous infusion was studied for 6 weeks in 20 patients with type 2 diabetes. Fasting and 8-h mean glucose decreased from 14.4 to 10.1 and from 15.8 to 10.3 mmol/l. HbA_{1c} decreased from 9.2 to 7.9%, insulin sensitivity increased, and body weight decreased from 106 to 104 kg. Nauk pointed out that this represents “the longest [study of] continuous infusion” of GLP-1 to date. Patients reported reduced appetite, which may explain the observed weight loss. GLP-1 could have a role during in producing perfect metabolic control in a variety of settings. GLP-1 treatment is associated with intact counterregulatory response to hypoglycemia, is active in patients with varying degrees of hyperglycemia, and may increase β -cell mass.

Vilshøll et al. (43-OR), noting that GLP-1 is strongly insulinotropic in type 2 diabetic patients, whereas GIP has little or no effect, infused GLP-1, GIP, or neither to eight patients with type 2 diabetes during a 2-h 15 mmol/l hyperglycemic clamp. Insulin secretion from 0 to 20 min was similar with all infusions, while insulin secretion from 20 to 120 min increased 6-fold after GLP-1, but only 1.4-fold after GIP, suggesting a defect in response to GIP but intact response to GLP-1 in type 2 diabetes. Wang and Brubaker (123-OR) administered the GLP-1 agonist exendin-4 to *db/db* mice before onset of diabetes, showing improved glucose tolerance though no change in insulin sensitivity. Pancreatic insulin content increased with a 1.4-fold greater β -cell mass. Bregenholt et al. (125-OR) reported that both GLP-1 and its long-acting derivative NN2211 inhibit interferon- γ , tumor necrosis factor (TNF)- α , and interleukin-1-induced islet cell apoptosis in a dose-dependent fashion. Preincubation of islets with a PKA or phosphatidylinositol 3-kinase inhibitor prior to exposure to GLP-1 with the cytokines blocked the antiapoptotic effect, suggesting dependence on these pathways. Rømer et al. (1296-P) administered NN2211 to 60% pancreatectomized rats, showing 21% lower glucose response to oral glucose. There was doubling of β -cell mass without increased islet proliferation, suggesting the importance of the antiapoptotic effect. Juhl et al. (473-P) treated 11 patients with type 2 diabetes with

NN2211 10 $\mu\text{g}/\text{kg}$ administered at bedtime, showing fasting glucose of 6.9 vs. 8.1 mmol/l, and 23% decrease in the glycemic response to a meal with increased insulin and decreased glucagon secretion, and delay in gastric emptying. Jakobsen et al. (472-P) reported a half-life of 12 h with maximal absorption of NN2211 at 11 h after subcutaneous injection, with dose-related nausea and vomiting observed.

Xu et al. (127-OR) reported decreased GLP-1 receptor mRNA and protein in islets from rats that were made hyperglycemic with 90% pancreatectomy, with normalization by administration of phloridzin to lower glucose levels, suggesting downregulation of GLP-1 receptor by hyperglycemia contributing to the decreased insulin secretion of diabetes. In a study of STZ-diabetic rats, Xu et al. (1290-P) showed that exendin-4 improved glucose tolerance with evidence of increased β -cell mass. In a human pancreatic duct-derived cell line, PDX-1, which is involved in development of the endocrine pancreas, showed increased protein levels, although no change in mRNA, after administration of exendin-4. Dupre et al. (442-P) administered exendin-4 to eight insulin-deficient diabetic patients, showing glucose responses to a standardized breakfast of 53, 36, and 30% of that seen without treatment at doses of 0.02, 0.04, and 0.08 $\mu\text{g}/\text{kg}$ exendin-4, respectively, without anorexic effects. The agent may delay gastric emptying, potentially giving it a role in the treatment of type 1 diabetes.

Ahrén et al. (416-P) administered NVP DPP728, a selective, orally active inhibitor of DPP IV, which slows degradation of GLP-1, to 93 patients with type 2 diabetes for 4 weeks. Fasting glucose decreased from 8.5 to 7.7 mmol/l, with decrease in prandial excursion from 4.0 to 2.8 mmol/l, and decrease in 24-h mean glucose from 8.9 to 7.8 mmol/l, without change in a placebo group.

Lynn et al. (312-PP) reported an animal model of insulin-resistant type 2 diabetes in which β -cell GIP receptors and GIP signaling were decreased. However, in mice that did not express the GIP receptor, Miyawak et al. (335-PP) reported that the degree of obesity caused by a high-fat diet was lessened, with less insulin resistance and lower glucose levels than in normal rats fed the same diet, suggesting a role of GIP as a “thrifty gene,”

with either the hormone or its receptor as potential therapeutic targets for obesity.

Insulin secretion

Glyburide interacts with two different binding sites on sulfonylurea receptor-1 (SUR1), termed the “sulfonylurea” and “benzamido” sites, with nateglinide appearing to have structural similarity to the sulfonylurea and repaglinide having similarity to the benzamido portion of glyburide. Hansen et al. (35-OR) showed that a point mutation of the human SUR1 markedly decreased the abilities of tolbutamide and nateglinide, and partially that of glyburide, to close the K_{ATP} channel, while not affecting that of repaglinide. This finding supports the concept that these agents act differently on SUR1. Leech and Habener (37-OR) showed evidence that amino acids are ligands of the β -cell receptor that senses extracellular Ca^{2+} . This may activate nonselective cation channels, potentiating glucose-induced depolarization via closure of the K_{ATP} channel. Smukler et al. (38-OR) showed that nitric oxide (NO) stimulates β -cell insulin exocytosis via the guanylate cyclase/cGMP pathway, suggesting a role of NO in insulin secretion and a potential role in treatment of type 2 diabetes. Perret et al. (41-OR) suggested that uncoupling protein (UCP)-2, by decreasing ATP synthesis in β -cells, could inhibit insulin secretion, and showed that a mouse model not expressing UCP-2 had increased basal and glucose-induced insulin secretion, suggesting a target for treatment of type 2 diabetes. Ahrén and Holst (42-OR) showed that the ganglionic blocking agent, trimetaphane, which decreases both parasympathetic and sympathetic neurotransmission, decreased the cephalic phase insulin response to a standard meal by 73%, with elevation of blood glucose from 25 to 60 min after meal ingestion. This exceeded the effect of atropine, which decreased insulin 20%, suggesting both cholinergic and noncholinergic mediators of this component of insulin release. There was no change in GIP or GIP-1 levels.

Low birth weight (BW) may be associated with an increased risk of type 2 diabetes. Comparing 20 19-year-old men who had low BW (mean 2.7 kg) to control subjects who had normal BW (mean 3.8 kg), Jensen et al. (330-PP) reported that the former group had increased fasting and 2-h glucose levels and decreased in-

ulin secretion in response to oral glucose, while actually showing greater suppression of plasma glycerol and hepatic glucose production during an insulin clamp. These results suggest that insulin deficiency, rather than insulin resistance, mediates the development of diabetes in this group.

Secretagogues

Noting that islets express a variety of imidazoline-binding proteins involved in insulin secretion, Morgan et al. (320-PP) reported that a low molecular weight GTP-binding protein, similar to the one expressed in the brain, may be a potential target for the imidazoline compounds that regulate insulin secretion. Khan et al. (321-PP) found that insulin itself opens K_{ATP} channels, resulting in hyperpolarization, an effect reversed by both tolbutamide and wortmannin, which inactivates PI 3-kinase, a key enzyme in insulin signaling. This may be the biochemical explanation of the physiological negative feedback of insulin on subsequent further insulin secretion, which was shown in vivo many years ago.

Wallace et al. (411-P) used annual $\text{HbA}_{1\text{c}}$ data from 191 patients in the U.K. Prospective Diabetes Study cohort treated for at least 3 years, showing similar rates of failure with metformin and chlorpropamide, but a failure rate 52% greater with glyburide, which was due to a more rapid decline in β -cell function rather than a worsening of insulin sensitivity. Gerstein et al. (454-P) compared 93 patients (42% or whom received metformin) treated with repaglinide to achieve glucose 4–7 mmol/l before meals with 83 patients (31% of whom received metformin) given a 1-h postprandial target of 5–11 mmol/l. Repaglinide was started at a dose of 0.5 mg before each meal and doubled weekly to achieve target glucose levels over 6 weeks. Treatment continued for 12 weeks, most typically at a repaglinide dose of 2 mg before meals. $\text{HbA}_{1\text{c}}$ decreased similarly from 8.4 to 7.3% and from 8.5 to 7.2% in the two groups, suggesting that approaches using preprandial targets are similarly effective to those using postprandial targets. Hasslacher et al. (463-P) administered repaglinide to 151 patients with creatinine clearance >80 ml/min (64 patients with clearance 60–80 ml/min, 44 with clearance 40–60 ml/min, 12 with clearance 30–40 ml/min, and 10 with clearance 20–30 ml/

min). The frequency of hypoglycemia was similar at all levels of renal function. Ishii et al. (471-P) reported similar evidence of safety in eight patients with creatinine clearance 22–72 ml/min treated with nateglinide 90 mg before each meal, without evidence of variation in nateglinide levels with the degree of renal insufficiency.

De Kreutzenberg et al. (538-P) treated 19 individuals with type 2 diabetes and coronary insufficiency with glyburide versus insulin for 12-week periods in a crossover study. Glycemic control was similar. After dipyridamole-induced ischemia, with administration of glyburide, the peak left ventricular ejection fraction decreased to 37 from 43% and the wall motion score index increased to 1.98 from 1.4; with insulin, the ejection fraction was 45 and 46% and the wall motion index 1.6 and 1.4, suggesting greater ischemia-induced myocardial dysfunction with glyburide. Pogatsa et al. (513-P) analyzed ventricular ectopic beat frequency in 22 digoxin-treated patients receiving glimepiride and gliclazide in a crossover study, showing fewer arrhythmias during the glimepiride treatment period. Riddle et al. (518-P) compared the first-dose insulin secretory effect and hypoglycemic risk during a 10-h extension of overnight fasting after an initial dose of glimepiride 1 mg or glyburide 2.5 mg in 30 type 2 diabetic patients who were withdrawn from previous treatment for at least 2 weeks. The blood glucose decreased similarly from 182 to 156 mg/dl and from 181 to 152 mg/dl, but C-peptide levels increased 8 vs. 32%, and 2 vs. 10 patients had glucose levels <70 mg/dl, suggesting an advantage of glimepiride.

Type 2 diabetes and gonadal steroids

Kanaya et al. (11-LB) presented data on the glycemic effects of postmenopausal hormone therapy in the Heart and Estrogen/Progestin Replacement Study (HERS). Diabetes was present in 734 of the 2,763 participants. Fasting blood glucose was stable at 4 years with estrogen treatment while increasing with placebo. There was a 36% lower (5.6 vs. 8.8%) rate of development of new diabetes in women receiving estrogen. Oh et al. (302-PP) reported that among 294 men in the Rancho Bernardo study, those with total

testosterone in the lowest quartile in 1986 had higher fasting insulin levels and a 2.7-fold increase in the rate of developing diabetes over the next 8 years, while bioavailable testosterone, calculated from sex hormone binding globulin concentration, did not show a relationship to diabetes. Among 233 women, those with bioavailable testosterone in the highest quartile had higher fasting insulin levels and a 2.9-fold increase in the rate of developing diabetes. Total testosterone was not significantly associated with diabetes among women, and neither total nor bioavailable estradiol showed association with diabetes among either men or women.

New therapeutic targets

Mitchell A Lazar, Philadelphia, PA, recalled Ben Franklin's dictum, "To lengthen thy life, lessen thy meals." Noting that it is not yet known how obesity predisposes to insulin resistance, he suggested that fat cells may communicate with other tissues in an endocrine fashion. Potential mediators of insulin resistance are FFAs themselves, TNF- α , leptin, and adiponectin (although its levels are reduced in obesity, and it may lower glucose levels). Peroxisome proliferator-activated receptor (PPAR)- γ is preferentially expressed in white adipose tissue. Lazar showed evidence that adipocytes secrete a hormone, resistin, that was discovered by screening for proteins suppressed by thiazolidines (TZDs) in rats. Resistin increases insulin resistance in peripheral tissues. Other resistin-like proteins are expressed in adipose tissue and in colon, with function unknown. Neutralization of resistin improves glucose tolerance, and administration of resistin impairs it. Resistin markedly decreases insulin-stimulated glucose uptake in adipocytes and decreases basal and insulin-stimulated glucose uptake in cardiac myocytes. The closest related protein in human adipose tissue only has 50% homology with resistin and is expressed at much lower levels, so this protein may play a less important role in humans.

Christophe Erneux, Brussels, Belgium, discussed the Src homology 2 (SH2) domain-containing inositol 5 phosphatase (SHIP) 2, which controls insulin sensitivity. SHIP2 is localized in muscle and liver, as well as in the fetal cerebral cortex, and interacts with the in-

ulin and epidermal growth factor (EGF) receptors, while the similar protein SHIP1 is present only in hematopoietic cells and is associated with the erythropoietin receptor. After EGF and insulin stimulation, SHIP2 relocates to the cell membrane from intracytoplasmic sites. Absence of SHIP2 results in increased insulin sensitivity with severe neonatal hypoglycemia (2), and adult heterozygotes show increased insulin sensitivity, suggesting that "SHIP2 acts as a break on the insulin cascade." Interestingly, absence of SHIP1 results in a myeloproliferative-like syndrome and pulmonary infiltrates with macrophage infiltration, suggesting that SHIP1 inhibits cell growth. Heterozygous SHIP2 deficiency does not cause abnormal cell growth.

Steven E. Shoelson, New Haven, CT, showed data that suppression of the activity of I κ B kinase (IKK)-mediated proinflammatory pathways reverses insulin resistance, suggesting that the IKK complex (which can be activated by fatty acids) is a mediator of insulin resistance in type 2 diabetes and a possible mechanism whereby FFAs cause insulin resistance. An effect of salicylates in treatment of diabetes has been known since the late 1800s, and has been documented in medical literature for more than four decades. In Zucker diabetic fatty rats and leptin-deficient mice, insulin levels fall with salicylate treatment, with falls in triglyceride and FFAs and improved insulin sensitivity. These models show improvement of insulin receptor and Akt phosphorylation. Shoelson et al. noted that low-dose aspirin acts on COX1, while higher doses act both on COX1 and -2, and very high doses affect nuclear factor (NF)- κ B and IKK, the latter effects not seen with NSAIDs. IKK is activated by protein kinase C (PKC) activators (including FFAs), hyperglycemia, and oxidative stress. IKK reduces TNF- α effects on insulin receptor substrate (IRS)-1. Overexpression of IKK β or its activators in animal models decreases tyrosine phosphorylation of the insulin receptor, while heterozygotes with decreased IKK β activity show decreased fasting and postoral glucose blood glucose and insulin levels. In obese patients with type 2 diabetes treated with aspirin in doses of 6–7 g daily, there is a fall in fasting glucose, cholesterol, triglyceride, and FFAs and lower glucose and FFA levels after a mixed meal. There is a 25% fall in hepatic glucose pro-

duction with a smaller decrease in peripheral glucose uptake. The aspirin effect may therefore not be mediated by action on COX in decreasing prostaglandin production, but may rather involve this newly described pathway.

Yuan et al. (232-OR) studied two mouse models of type 2 diabetes with heterozygous gene deletion of IKK β (homozygotes die in utero). Insulin sensitivity was greater in both models, with improved glucose tolerance and lower FFA levels in the *ob/ob* model. Hundal et al. (470-P) treated nine patients with type 2 diabetes with aspirin, 7 g daily for 2 weeks. Fasting hepatic glucose production, glucose, cholesterol, and triglyceride levels decreased 25, 25, 15, and 50%, respectively, with 21 and 56% lower increases in glucose and FFA levels following a mixed meal. Insulin-stimulated peripheral glucose uptake,

measuring during a hyperinsulinemic-euglycemic clamp, increased 19%.

Exercise

Boulé et al. (905-P) presented a meta-analysis of 14 trials with 528 individuals with type 2 diabetes having an exercise intervention. HbA_{1c} was 7.7% with exercise versus 8.5% in control subjects after a mean of 3 sessions/week for 23 weeks, while there was no significant difference in weight loss, suggesting direct benefit of this approach. Castaneda et al. (906-P) randomized 43 older Hispanic adults with type 2 diabetes to progressive resistance training or to not exercising, showing a 1.4% lower HbA_{1c} after 16 weeks, with decreases in waist circumference and fasting insulin levels. Hu et al. (826-P) followed 84,941 female nurses for 16 years from 1980, with 3,300 developing new diabetes. Nonsmokers with BMI <25 kg/m² who performed at least 30

min of daily moderate physical activity, maintained a high-fiber and polyunsaturated fat diet, and drank at least one-half of an alcoholic beverage daily had one-tenth the risk of diabetes of the remaining individuals.

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