Pharmacologic Treatment of Type 2 Diabetes

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Pharmacologic therapy for diabetes prevention

At a symposium on pharmacologic therapy for diabetes prevention, Saul Genuith (Cleveland, OH), chairperson, commented that there is now evidence that three different classes of pharmacologic treatment, biguanides, α-glucosidase inhibitors, and thiazolidinediones (TZDs), are effective in preventing diabetes. Steven Kahn (Seattle, WA) discussed data from the Diabetes Prevention Program (DPP), showing evidence for efficacy of metformin in persons over age 25 years whose BMI exceeded 24 kg/m² (22 in Asian Americans), with 2-h glucose between 140 and 199 and fasting plasma glucose (FPG) between 95 and 125 mg/dl. Those in the “intensive lifestyle” intervention group aimed to increase exercise by 150 min/week and to lose 7% of body weight, while those randomized to metformin received 850 mg twice daily; a third group received placebo. The average BMI was 34 kg/m² and the average FPG was 105 mg/dl. The diagnosis of the primary outcome, diabetes, was based either on a 75-g oral glucose tolerance test (OGTT) with FPG or 2-h glucose exceeding 125 or 199 mg/dl, respectively, or on 6-month FPG exceeding 125. In the placebo group, diabetes developed at a rate of 11%/year, while with metformin, a 31% reduction was seen, and with lifestyle, a 58% reduction was seen. Metformin had an effect similar to lifestyle among those under age 45 years, but was less effective among older subjects. Persons with BMI exceeding 35 kg/m² also showed efficacy of metformin similar to that of lifestyle, while neither sex nor ethnicity affected the efficacy of the agent. FPG increased slowly in the placebo group, while decreasing initially with subsequent increase to baseline at 3 years in the lifestyle and metformin groups. HbA₁c levels, however, increased with placebo, decreased with lifestyle, and then slowly increased, and showed a lesser decrease with metformin, suggesting that metformin may have had a greater effect on fasting than on postprandial glucose. In support of this interpretation, metformin was particularly effective in decreasing diabetes among individuals with FPG exceeding 110 mg/dl, while the lifestyle intervention was similarly effective in persons above and below this level. Both the lifestyle intervention and metformin had similar efficacy among subjects with higher and lower 2-h glucose levels.

The blood pressure decreased by 3 mmHg with lifestyle, but only by 1 mmHg with metformin, with insulin levels also showing greater decrease with lifestyle intervention. Triglyceride levels decreased 23 mg/dl with lifestyle, while showing a lesser decline with metformin; HDL increased 0.5 and 0.8 mg/dl with metformin and with lifestyle; and LDL cholesterol decreased 4 mg/dl with both metformin and lifestyle. Asked whether metformin prevents diabetes or merely shows a treatment effect, Kahn mentioned that after an 11-day washout, the effect of the agent was maintained, although there is as yet no data over longer periods of follow-up. Half of those treated with metformin experienced gastrointestinal side effects, and some reduced the dose to 850 mg once daily. There is no evidence as to whether combined lifestyle-metformin treatment would have an additive benefit.

Jean-Louis Chiasson (Montreal, Canada) discussed the use of the α-glucosidase inhibitor acarbose in diabetes prevention. The Study To Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) trial (1) was carried out in eight countries among 1,429 persons aged 40–70 years, averaging 54, with BMI 25–40 kg/m², averaging 31, and FPG exceeding 5.5 mmol/l with impaired glucose tolerance (IGT) and hyperinsulinemia. Acarbose 100 mg three times daily was compared with placebo, after preliminary studies showed no effect of placebo on postprandial plasma glucose or insulin, while acarbose decreased both parameters and showed evidence of improvement in insulin sensitivity, suggestive of an effect on glucose toxicity. The mean study duration was 3.3 years, with annual OGTT and 3-month follow-up; 211 vs. 130 patients discontinued prematurely, mainly because of gastrointestinal side effects during the first year of the study, leaving 683 vs. 686 persons for analysis. As with the DPP, the OGTT was more sensitive than FPG measurement in the diagnosis of diabetes. The relative risk of diabetes decreased by 25% with acarbose, a decrease in absolute risk of 9%, without effect of age, sex, or BMI. Requiring a second OGTT to confirm the diagnosis of diabetes led to a relative risk reduction of 32%. In addition, acarbose normalized glucose tolerance in many persons. Weight decreased modestly with acarbose and increased with placebo, with a net difference of 0.6 kg. Acarbose
also decreased the likelihood of development of hypertension by 34%.

Thomas Buchanan (Los Angeles, CA) discussed TZD therapy in the prevention of diabetes, giving data from the Troglitazone in Prevention of Diabetes (TRIPOD) study. The relationship between insulin sensitivity and insulin secretion predicts that the disposition index, a measure of β-cell compensation for insulin resistance, is the best measure of β-cell function. As persons develop worsening insulin sensitivity, those who develop diabetes fail to show compensatory increase in insulin secretion. Both short-term and long-term changes in insulin sensitivity and in glycemia may affect the risk of diabetes, suggesting that it is possible to produce “β-cell rest” by improving insulin sensitivity. In the TRIPOD study (2), 236 women who had had gestational diabetes were treated with troglitazone (TGZ) or placebo, with the 30-month follow-up being 5.4 vs. 12.1% of the annual rate of development of diabetes. Subjects in the placebo and TGZ groups gained 1.6 and 1.9 kg yearly, respectively. The change in insulin sensitivity was not itself predictive of diabetes risk, but the change in insulin output after an intravenous (IV) glucose load predicted progression to diabetes, favoring the hypothesis that “it wasn’t how far they moved that drove their β-cell rest, [rather] it’s where they started” at higher initial insulin secretion that was associated with protection from diabetes. “The one thing that was associated most strongly with protection from diabetes,” Buchanan stated, “was a reduction in the chronic secretory demands that were placed on the β-cell by chronic insulin resistance.” In post-trial follow-up for 8 months, those who had received TGZ had continued protection, suggesting that a fundamental change had occurred. At 8 months the placebo group had lost ~40% of β-cell function and had decreased insulin sensitivity, whereas the group previously treated with TGZ showed no change in insulin sensitivity or secretion.

Recalling the U.K. Prospective Diabetes Study (UKPDS) finding that, despite treatment, β-cell function declines progressively in patients with type 2 diabetes, Buchanan interpreted the TRIPOD data to suggest that TGZ treatment of individuals with IGT leads to maintenance of insulin secretory capacity, while treatment at the time of development of diabetes also stabilizes β-cell function, but at a 30% lower level. He pointed out that our current approach to diabetes treatment is insufficient to produce the degree of β-cell rest that was seen in TRIPOD. In a follow-up study, ongoing prevention of diabetes appears to occur with rosiglitazone (RGZ).

Approaches to diabetes treatment, then, include treating the complications of diabetes, treating hyperglycemia, and treating progressive β-cell dysfunction, which can be detected clinically by rising glucose concentrations within the normal range. “Screening is the hard part,” Buchanan suggested, and one should consider pharmacologic treatment of persons with minimally increased glucose levels that continue to rise over time despite attempts at diet and exercise.

In a further report at the ADA meeting, Buchanan et al. (140-OR) compared 56 women randomized to treatment with TGZ for 3.5 years for prevention of diabetes with 65 women randomized to placebo (abstract numbers refer to the abstracts of the 62nd ADA Scientific Sessions, Diabetes 51 [Suppl. 2], 2002). In the former group, insulin sensitivity, acute insulin responses to IV glucose, or glucose levels after OGTT did not change significantly 8 months after the end of the trial, while the latter group showed 26 and 39% falls in insulin sensitivity and insulin response and a 10% increase in glucose levels during the OGTT. Twenty-one women in the late intervention group received TGZ when diabetes developed, showing a 30% fall in insulin secretory response during 1.9 years on placebo, without subsequent change during 2.2 years of TGZ treatment or during the subsequent 8 months. Buchanan concluded that TGZ “arrested the decline in β-cell function,” and that TGZ prior to diabetes onset “resulted in greater preservation of β-cell function than later treatment based on development of diabetes.” Xiang et al. (703-P) presented the TRIPOD findings of annual carotid intima-media thickness (IMT) measurements in 99 women receiving placebo and in 93 receiving TGZ, showing increase of 9.4 6.5 mm/year. TGZ nonresponders, whose insulin sensitivity failed to increase after 3 months, comprising one third of that group, showed mean 10.6 mm/year increase in carotid IMT, while the TGZ responders showed mean increase in carotid IMT of 5.2 mm/year, suggesting increase in insulin sensitivity to be related to the antiatherosclerotic effect.

In a cautionary study, however, Shadid and Jensen (580-P) treated 24 persons with upper-body obesity randomized to either a diet and exercise program versus pioglitazone (PGZ) 30 mg daily for 21 weeks, showing weight decrease from 101 to 97 vs. 99 to 85 kg, with body fat decreasing from 38 to 31% vs. increasing from 40 to 41% and with visceral fat by CR scanning decreasing from 207 to 112 vs. increasing from 155 to 167 cm². Insulin sensitivity increased 153 vs. 36%, leading the authors to suggest that “TZD therapy should not substitute for lifestyle modification in the treatment of high-risk obesity.” Investigating sulfonylurea (SU) as therapy in primary prevention of type 2 diabetes, Osei et al. (1198-P) treated nine African-American subjects with IGT with glipizide GITS for 24 months. Compared with nine receiving placebo, glucose levels decreased and serum insulin increased, and insulin sensitivity increased with a doubling of the disposition index. Among 18 persons with normal glucose tolerance treated with glipizide GITS, however, insulin sensitivity decreased in comparison to 34 placebo-treated control subjects; thus, further study is needed.

Robert Sherwin (New Haven, CT) asked “how should we treat type 2 diabetes and how should we try to prevent type 2 diabetes in the future?” Certainly, diabetes is an important problem, with easily defined end points and safe, effective methods of treatment that lead to definite benefit. Whether the cost of finding cases and intervening is acceptable is uncertain. Sherwin recalled Maimonides’ insight some 800 years ago that any illness that can be treated by diet alone should not be treated otherwise. Reversion to normal glucose tolerance is frequent, and this occurs twice as frequently with lifestyle intervention, which has had impact in many studies carried out worldwide. With seven to nine group sessions during the first year and four sessions per year subsequently in motivated participants in the Chinese and Finnish studies, and with weekly sessions for 6 months and frequent follow-up thereafter in the DPP, approximately half of the participants reached the goal. Sherwin noted that “there was some slippage over time” in all reported studies. Lifestyle intervention, he summarized, “is difficult to accomplish and maintain, but it can be accomplished,
Perspectives on the News

at least for a while.” Compared with pharmacologic treatment, this approach “wins hands down [. . . ] but may not be feasible in many patients, may not be sustainable in the real world, and may not even be cost-effective.” In the U.S., this may be particularly difficult because of reimbursement issues, despite the greater efficacy of lifestyle than metformin in the DPP. He suggested that lifestyle interventions beginning with children would be appropriate.

Sherwin suggested that acarbose appears to have similar efficacy to metformin, and that both are safe agents that would probably require lifelong treatment, while he urged caution in considering use of TZDs until more study results are available. “How long a delay will we need to have a significant impact on complications? We don’t know, although it is likely that short-term delay probably does not have enormous impact.” There is “circumstantial evidence,” he stated, that metformin and TZDs may decrease cardiovascular disease (CVD). He suggested use of metformin in younger and more overweight individuals, consideration of α-glucosidase inhibitors as an alternative approach, and more research in TZD treatment, and he pointed out that the decision to avoid pharmacologic approaches prior to development of diabetes is certainly an option at the current state of our knowledge. Coming drugs, such as those related to glucagon-like peptide (GLP)-1, may have “a lot of potential down the road,” and short-acting secretagogues may be useful. Two relevant studies of CVD treatment he cited are those with pravastatin, which decreased diabetes by nearly 30% in the WOSCOPS (3), and with ramipril, which decreased diabetes by nearly 34% in the HOPE trial (4). We should begin, Sherwin concluded, with lifestyle intervention plus aspirin “and where appropriate [. . . ] statins plus ACE inhibitors.” After 3 months, “the clinician has the option to decide [. . . ] whether we should add glucose-lowering drugs.” Currently, we initiate treatment at the glycemic level associated with microvascular complications, but macrovascular disease begins to develop long before this, and “it’s clear that we need to intervene with the agents that lower cardiovascular risk [. . . ]. My guess is that we will [add treatment to] lower glucose.” Asked whether he currently endorses screening for IGT, he suggested “as a clinician” that this be done for high-risk patients, but that one cannot yet advocate this generally. Asked what he would consider to indicate a “failing” lifestyle intervention, he suggested that increases in FPG and body weight “is a very reasonable approach [. . . ] to see whether the patient is beginning to slip or not.” He also suggested that advice by politicians and other public figures to the general public to lose 10 lbs and to exercise 30 min per day might over time have an effect similar to that which smoking cessation has had for the American population.

Pharmacologic obesity treatment
Shi et al. (1707-P) studied rats with diet-induced obesity, showing 7, 5, 7, and 12% weight loss with the monamine reuptake inhibitor sibutramine; the CNS and peripheral sympathomimetic ephedrine; the GABAergic agent topiramate, and the CNS sympathomimetic phentermine, and 3–5% weight loss with leptin. Combinations of leptin with each of the above 4 oral drugs resulted in substantially greater weight loss (10–19%) than leptin alone or each of the oral drugs alone. Leptin alone, after withdrawal of ephedrine, sustained the weight losses initially achieved either by ephedrine alone or by the combination of leptin and ephedrine. Bray et al. (1727-P) evaluated 385 obese persons treated with a reduced calorie diet with either placebo or topiramate 64, 96, 192, or 384 mg daily for 24 weeks, showing respective weight loss of 2.6, 5, 4.8, 6.3, and 6.3% of baseline, although adverse effects included paresthesia (36–50%), memory difficulty (11–21%), fatigue (16–18%), and somnolence (9–21%).

Rissanen and Holland (1694-P) reported pooled data from seven multicenter, doubleblind 24- or 52-week trials in overweight subjects with type 2 diabetes and HbA1c >8%; of these patients, 435 were randomized to placebo and 483 to orlistat. Results showed that the homeostatic model assessment (HOMA) measure of insulin resistance decreased from 8.9 to 8.5 vs. 8.4 to 6.8, respectively, with similar effects in persons receiving metformin and SUs. Similar analysis from these trials by Jacob et al. (1693-P) analyzed persons treated with metformin ≥2 g daily, 156 receiving placebo versus 166 receiving orlistat, with a fall in HbA1c of 0.4 vs. 1.7%, and individuals treated with maximal or near maximal doses of sulfonylureas, 142 receiving placebo vs. 147 orlistat, with decrease in HbA1c of 0.1 vs. 0.7%. Finally, De Fronzo and Pi-Sunyer (1691-P) analyzed these trials, comparing the effect of orlistat in patients with type 2 diabetes at differing baseline HbA1c levels, showing that at baseline HbA1c <7%, 8%, 9%, 10%, and 11%, placebo-treated pts had decrease in HbA1c of 0.4, 0.5, 0.8, 1.3, and 1.5%, while those treated with orlistat had respective decreases of 0.8, 1.0, 1.3, 1.5, and 2.2%, suggesting the drug to be “a useful adjunctive treatment . . . at all levels of glycemic control.”

Cell biology of glucose transport
Samuel W. Cushman (Bethesda, MD) discussed the cell biology of glucose transport. The glucose transporters are GLUT1, present in virtually all tissues; GLUT2, seen in the β-cell, liver, and kidney, tissues requiring glucose equilibration across both intra- and extracellular space GLUT3, present in the brain; and GLUT4, the insulin-stimulated glucose transporter. All exist in two conformations, do not require energy for glucose transport, and have 12 membrane-spanning domains and large extra and intracellular domains responsible for glucose entry and exit. Insulin can increase either the turnover rate or the number of functional glucose transporters. In the late 1970s, Cushman’s lab showed that membrane fractions from isolated rat adipose cells show virtually no transporters, whereas a low-density microsome fraction contains virtually all, while <10 min after addition of insulin, the transporters redistribute to the plasma membrane fraction, with subsequent addition of insulin antibody returning the transporters to the microsome location (5). In the basal state, then, glucose transporters, particularly GLUT4, are sequestered in an intracellular pool, with insulin sending signals that cause glucose transporter vesicles to move from the intracellular pool to the plasma membrane, where they dock and fuse with the plasma membrane. Confocal microscopy shows that in both the basal and the insulin-stimulated state, glucose transporters have a punctate appearance, indicating aggregates rather than separate units, with distribution between lipid droplets in the cytoplasm in the absence of insulin and on the cell surface in its presence.

In skeletal muscle preparations, both insulin and contraction increase glucose transport activity, with the two stimuli
showing additive effect in glucose transport movement to the plasma membrane. The response to contractions is independent of and parallel to that to insulin, which Cushman deemed “a direct explanation for the important role of exercise treatment for diabetes.” Adipocyte insulin resistance in a variety of diabetes models involves downregulation in the total number of glucose transporters as well as in basal glucose transport activity. In an animal model lacking GLUT4 expression in adipocytes, glucose transporter activity decreases in both adipocytes and skeletal muscle, suggesting a hormonal mechanism, which Cushman speculated might involve deficiency of an insulin-sensitizing adipocyte product. GLUT4 is one of the candidate genes that have been shown to have decreased expression in normoglycemic insulin-resistant individuals.

**Molecular mechanisms of insulin secretion**

Susumu Seino (Chiba, Japan) discussed regulation of insulin secretion by intracellular signals based on β-cell input from glucose and other nutrients, neurohormones, and other influences. Glucose-induced insulin secretion involves metabolism of glucose to increase ATP, closing the ATP-sensitive potassium (K<sub>ATP</sub>) channel, leading to cell depolarization with subsequent calcium entry via voltage-dependent calcium channels (VDCCs). The incretins GLP-1 and glucose-dependent insulinotropic polypeptide (also known as gastric inhibitory polypeptide [GIP]) potentiate glucose-induced insulin secretion via cAMP signaling. The K<sub>ATP</sub> channel is a metabolic sensor in many tissues acting to link cell metabolism to electrical activity. The β-cell K<sub>ATP</sub> channel includes four potassium inward rectifier (Kir) 6.2 and four sulfonylurea receptor (SUR)-1 subunits. Kir6.2 and the ATP-binding cassette (ABC) protein SUR have been characterized. Coexpression of Kir6.2 and SUR1 generate potassium channels that are closed by ATP. Types of K<sub>ATP</sub> channels are Kir6.2/SUR1 in β-cell and ventromedial hypothalamic neurons, Kir6.2/SUR2A in cardiomyocytes, Kir6.2/SUR2B in smooth muscle cells, and Kir6.1/SUR2B in vascular smooth muscle. Both glucose and tolbutamide initiate a membrane action potential via K currents in the β-cell. Glucose causes an abrupt spike, while tolbutamide leads to sustained increase intracellular calcium levels. Thus, glucose- and SU-induced insulin secretion both depend critically on the activity of the β-cell K<sub>ATP</sub> channel.

The cAMP sensor plays a complementary role. GLP-1 and GIP attach to G-protein–coupled receptors, activating adenylate cyclase to increase cAMP, which activates protein kinase A (PKA) and also acts directly on the insulin exocytotic machinery via a binding protein called the cAMP sensor, also referred to as cAMP-guanine nucleotide exchange factor II (GEFII). SUR1 interacts with cAMP-GEFII via a target molecule, Rab3-interacting molecule 2 (Rim2) (6). cAMP-GEFII-Rim2 bind with Rab3A to form a complex that appears to be involved in insulin secretory granule exocytosis. Using an antisense oligodeoxynucleotide (ODN) against cAMP-GEFII and studying incretin-potentiated insulin secretion, Seino showed no effect on the PKA regulatory subunit, Rim2, or Rab3A, but did show decreased insulin secretion. Both with a PKA inhibitor (H-89) and with the antisense ODN, GIP-potentiated insulin secretion was further reduced, suggesting PKA-dependent and -independent mechanisms. CAMP-GEFII is involved in both first- and second-phase of cAMP-potentiated insulin secretion. In another study, a deletion mutant of Rim2 retaining the cAMP-binding region showed a dominant negative inhibition of the interaction with Rim2. Overexpression of this mutation inhibited insulin secretion, and subcellular localization studies showed Rim2 to colocalize with insulin. Thus, in addition to the PKA-dependent mechanism involving phosphorylation, there is a PKA-independent mechanism of cAMP effect mediated by Rim2 (and GTP-Rab3).

Seino noted that a rise in intracellular calcium, either from calcium influx or from mobilization of intracellular stores, triggers insulin exocytosis. The VDCCs (of which there are a number of types) have α subunits that interact with Rim1 and Rim binding protein, as well as β subunits that interact with a Ras-related small G-protein, Kir/Gem. (As an example of the alphabet soup of cell biology, the initials stand for “[tyrosine] kinase-inducible Ras-like/ [immediate early] gene expressed [in] mitogen-stimulated [T-cells]” (7).) Kir/Gem is activated by Ca<sup>2+</sup>/calmodulin, and it blocks the activity of VDCCs by inhibiting the cell-surface expression of the α subunit. It appears that the α1 subunit allows trafficking and that Gem blocks the interaction between the β- and α1 subunits. The physiologic relevance of Gem in insulin secretion is shown by overexpression experiments, where glucose-induced intracellular calcium rise and insulin secretion are inhibited. Gem may act physiologically to protect against intracellular calcium overload, but could play a role in inducing insensitivity of β-cell to various stimuli.

In vivo, recovery from insulin-induced hypoglycemia is severely impaired in “knockout” mice not expressing Kir6.2, with decreased glucagon secretion. In isolated islets, however, the α-cells of these mice show normal glucagon secretion. In the brain, neuroglucopenia or 2-deoxyglucose activate autonomic neurons to stimulate glucagon secretion, which is not seen in the knockout. Ventromedial hypothalamus (VMH) neurons contain high concentrations of Kir6.2 and show increased firing rate with hypoglycemia in the wild type, but the knockout shows a high basal firing rate without increase by hypoglycemia. These cells, then, show glucose response via the same Kir6.2/SUR1 K<sub>ATP</sub> channel that functions in β-cells (8). In further analysis of this model, Miki et al. (1492-P) reported increased glucose-lowering effect of insulin and increased skeletal muscle glucose uptake, suggesting that the K<sub>ATP</sub> channel may be involved in glucose uptake. Thus, the current model of the β-cell is quite complex, with the K<sub>ATP</sub> channel, cAMP-GEFII, Rim2, Rab3, and Gem all playing roles and presumably being involved in the pathogenesis of β-cell dysfunction in diabetes, as well as offering potential targets for new therapies. “The more we learn about the interior of the β-cell,” Seino concluded, “the more complex is the signaling.” Future directions of research will include studies at the cell level to assess spatial and temporal regulation of molecular interactions that integrate the various signaling pathways, at the organ level to understand functional interactions between the β-cell and endocrine and nervous systems, and development of integrative information models of overall mechanisms of insulin secretion.

A number of reports dealt with aspects of β-cell function. Campbell and Macfarlane (1564-P) reported that insulin, GLP-1, thyroid hormone, heparin-binding epidermal growth factor, and tumor necrosis factor-β all increase β-cell
expression of the PDX1 (pancreatic-duodenal homeobox 1) gene, which is involved both in development of the pancreas and in regulation of adult islet \( \beta \)-cell function. Wang et al. (1529-P) studied gene expression and protein phosphorylation of a number of protein kinases of \( \beta \)-cells exposed to the free fatty acid (FFA) oleate, showing decreased activity of PKA/cAMP, c-Jun NH\( \text{\textsubscript{2}} \)-terminal kinase (JNK), and integrin/focal adhesion kinase (FAK) signaling pathways and increased protein kinase C (PKC) and mitogen-activated protein (MAP) kinase pathway activity. Using a global gene expression microarray of 12,488 sequences, ~250 genes related to glucose metabolism, signal transduction, and transcription factors involved in cell proliferation and differentiation were decreased by at least half, and 26 genes involved in FFA metabolism showed doubling or more of activity. The antioxidant N-acetyl cysteine prevented the global decrease in gene expression, suggesting a role of free radicals.

Chen et al. (1733-P) described paradoxical SU-induced \( \alpha \)-cell effects in high fat-fed mice, which develop hyperinsulinemia. Overt hyperglycemia and insulin deficiency developed after 1 week of high-dose tolbutamide or glyburide administration, with decreased pancreatic insulin content, reversible either with administration of the K\( _{\text{ATP}} \) channel opener diazoxide or with SU withdrawal. Ritzel et al. (51-OR) studied islets cultured at 4 and 11 mmol/l glucose concentrations, showing decreased insulin content and insulin secretion at the higher level. Culture with the SUR1/Kir6.2 K\( _{\text{ATP}} \) channel opener, NN414 suppressed insulin secretion and increased islet insulin content threefold, with restoration of the insulin secretory response to glucose when returned to a 4-mmol/l glucose concentration. In a study with this agent in humans, Zdravkovic et al. (476-P) administered NN414 at bedtime for 1 week to 24 diet-treated patients with type 2 diabetes. Insulin secretion was inhibited beginning 1 h following treatment and lasting 2 h, without significant hyperglycemia, and with a trend to increased insulin secretion following a glucose load the morning following the final dose, suggesting that \( \alpha \)-cell rest could increase \( \alpha \)-cell function in subjects with type 2 diabetes.

In an interesting clinical study, Butler et al. (1502-P) presented an autopsy study of pancreas tissue obtained from 124 persons. Among 91 with BMI >27 kg/m\(^2\), \( \beta \)-cell mass was 52% greater than among 33 with BMI <25, but the 41 obese and 16 nonobese persons with type 2 diabetes had \( \alpha \)-cell mass around 60% of that among persons without diabetes, while 15 obese subjects with FPG between 110 and 125 mg/dl had an intermediate decrease in \( \alpha \)-cell mass.

Secretagogue clinical studies

Dunseath et al. (391-P) described the response to repaglinide 15 min before a standard meal in 16 diet-treated individuals with type 2 diabetes. There was no change in glucose increment over the first 30 min. Among eight with FPG <162 mg/dl, whose mean HbA\(_{1c}\) was 7.4%, the glucose increment over 4 h decreased 12, 20, 23, and 22% with 0.5-, 1-, 2-, and 4-mg doses, while those with FPG >162 mg/dl and a mean HbA\(_{1c}\) of 9.6% showed a 18% decrease in glucose with the 2-mg dose, without significant postmeal glucose lowering at the other doses. A dose-related increase in insulin response was seen in both groups, patients with FPG >162 had 25–29% lower insulin responses. Salman et al. (537-P) treated 64 type 2 diabetic persons with repaglinide, starting at 0.5 mg before meals, or glimepiride, starting at 1 mg daily, showing decreases in HbA\(_{1c}\) of 2.4 and 2.7%, respectively, over 12 weeks, without weight gain. Mealtime glucose excursions improved only with repaglinide at dinner, and hypoglycemia occurred in none versus two individuals in the respective groups, suggesting some benefit of the latter agent. Saad et al. (536-P) treated 114 subjects on diet alone with repaglinide 0.5–4 mg vs. nateglinide 60–120 mg before meals, showing a fall in FPG from 217 vs. 209 mg/dl by 52 vs. 24 mg/dl at 8 weeks. In 165 persons receiving metformin 2 g daily, FPG fell from 189 vs. 190 mg/dl by 39 vs. 22 mg/dl, suggesting the former agent to have a greater effect on fasting glucose.

Korytkowski et al. (423-P) treated 11 obese subjects with type 2 diabetes with glimepiride for 4 months, showing a 43 mg/dl decrease in FPG to 144 mg/dl and an 18% decrease in basal glucose production, with a 27% increase in fasting insulin and 64 and 45% increases in first- and second-phase insulin secretion, respectively, but without change in insulin sensitivity. However, Kabadi and Kabadi (416-P) treated 8 type 2 diabetic individuals with HbA\(_{1c}\) >7% with insulin alone and 12, 14, and 12 persons with insulin plus 2.55 g metformin, 8 mg glimepiride, or both, respectively, lowering FPG to 81–121 mg/dl for 4 months, with similar body weight and HbA\(_{1c}\) in all groups. The insulin dose was 82, 51, 40, and 23 units/day, respectively, in the four groups, leading the authors to speculate on an insulin-sensitizing effect of glimepiride and to suggest synergistic benefit of the combination with metformin.

GLP-1

Riedel et al. (1404-P) studied the cellular mechanism of action of PKA on the \( \beta \)-cell K\( _{\text{ATP}} \) channel, showing in vitro that PKA decreased the K\( _{\text{ATP}} \) current with equimolar ATP and ADP levels, while increasing it with higher ADP concentrations. These observations suggest that GLP-1, which increases cAMP and activates PKA, closes the K\( _{\text{ATP}} \) channel when the ATP-ADP ratio is high (as seen with high glucose levels), while opening K\( _{\text{ATP}} \) channels at low ATP-ADP ratios (as would be present with low glucose levels), thus indicating a potential cellular mechanism for the observed glucose-sensitivity of GLP-1. Ramer et al. (1403-P) showed that in vivo expression of the GLP-1 receptor is restricted to \( \beta \)-cells in normal rat, mouse, and human intact pancreatic islets, suggesting that glucagon suppression by GLP-1 occurs indirectly, either by a paracrine factor released from \( \beta \)-cells or via vagal nerve efferents.

GLP-1 shows rapid turnover in circulation via the action of dipeptidyl peptidase IV (DPP IV), modulating its effect. Conarello et al. (271-OR) reported that mice not expressing DPP IV, which have elevated GLP-1 and insulin levels and reduced glucose levels following oral dose of glucose, fail to show the accelerated weight gain occurring with high-fat diet. In addition, they show improved glucose tolerance on both low- and high-fat diets, which further suggests a benefit of DPP IV inhibition in treating diabetes and obesity. Lenhard and Croom (1392-P) reported that a PPAR\( \gamma \) ligand, GW7845, decreased DPP IV activity 43% in a rat model while increasing DPP IV mRNA expression in liver and kidney by 41 and 22%, respectively, suggesting a potential additional mechanism of action of these agents. Plamboeck et al. (1400-P) showed that addition of the neutral endopeptidase inhibitor candesartan to the specific DPP
Ghrelin

Ghrelin is the endogenous ligand of the growth hormone secretagogue receptor. It also is secreted by the oxyntic cells of the stomach and from the proximal small bowel in the early phases of eating, acting to increase food intake and to lower energy expenditure in rodent models and to decrease glucose-stimulated insulin secretion. McCowen et al. (1397-P) observed that increasing circulating insulin levels in a rodent model, either with glucose infusion or with a hyperinsulinemic-euglycemic clamp, suppressed ghrelin to 52 and 63%, respectively, of baseline levels, suggesting this to be a major factor controlling ghrelin secretion. Pacini et al. (1399-P) administered parenteral glucose 1 g/kg with or without ghrelin 50 nmol/kg in normal mice, showing that ghrelin decreased both early and total insulin secretion, without change in insulin sensitivity. Mice with lower insulin sensitivity did not show this insulin-suppressing effect.

Jingouda et al. (1390-P) compared 21 persons with normal glucose tolerance, 20 with impaired glucose tolerance, and 17 with type 2 diabetes, showing that fasting ghrelin levels were similar at 524, 467, and 488 pg/ml, with multivariate analysis showing significant negative relationship to age and serum insulin but no significant effect of obesity, glycemia, or plasma leptin. Teff et al. (1672-P) compared responses to high fructose versus high glucose meals in normal women. Glucose and insulin increases were approximately one-third lower, with a 21–33% lower leptin response. Ghrelin levels decreased 25–30% with glucose but did not change with fructose, suggesting that these hormonal changes could lead to increased caloric intake and contribute to weight gain and obesity during long-term consumption of diets high in energy from fructose.

Peroxisome proliferator–activated receptors

Pro12Ala. The common Pro12Ala polymorphism with replacement of proline-12 by alanine in the transcription factor PPARα2 decreases the activity of this regulator of adipogenesis, thereby decreasing levels of obesity, and is associ-
ated with reduced risk of type 2 diabetes and increased insulin sensitivity, which is a somewhat paradoxical finding in view of our use of PPARα agonists in the treatment of diabetes. Dahl et al. (1053-P) reported that in analysis of 95 healthy, normal glucose-tolerant persons who had had intramyocellular lipid (IMCL) measurement by magnetic resonance spectroscopy, insulin sensitivity measured by euglycemic clamp, and genotyping for a number of polymorphisms related to diabetes and to insulin sensitivity, IMCL was inversely correlated with insulin sensitivity. However, those with Pro12Ala had both higher insulin sensitivity and higher IMCL, suggesting alteration of the normal relationship. Tschritter et al. (1093-P) reported that in analysis of 95 healthy, normal glucose-tolerant persons who had had intramyocellular lipid (IMCL) measurement by magnetic resonance spectroscopy, insulin sensitivity measured by euglycemic clamp, and genotyping for a number of polymorphisms related to diabetes and to insulin sensitivity, IMCL was inversely correlated with insulin sensitivity. However, those with Pro12Ala had both higher insulin sensitivity and higher IMCL, suggesting alteration of the normal relationship.

**Effects of PPARα, δ, and γ agonists.** Bergeron et al. (139-OR) presented a study in Zucker diabetic fatty rats before onset of diabetes, showing improvement with both a non-TZD PPARγ agonist and the PPARα agonist fenofibrate; the latter agent both increased insulin sensitivity and prevented weight gain in the model. Kim et al. (564-P) reported a similar effect of fenofibrate in decreasing visceral and intramuscular fat and in improving insulin response in a rat model. Lewis et al. (566-P) administered submaximal doses of GW409494, a dual PPARα/γ agonist, to obese Rhesus monkeys, decreasing triglyceride 65% and non-HDL cholesterol 29%, with a 15% increase in HDL cholesterol. Addition of the PPARα agonist GW501516 led to 75, 34, and 48% respective changes. The HDL cholesterol change, in particular, was greater than that seen with the dual PPARα/γ agonist, suggesting that triple PPAR treatment may hold promise for the dyslipidemia of type 2 diabetes and the metabolic syndrome. The same authors (567-P) showed that in a rodent model of type 2 diabetes, a triple PPAR approach, using different agents, reduced glucose and FFA levels and increased brown adipose tissue mass. Lu et al. (568-P) described rodent studies with PN2034, a non-TZD PPARδ modulator, which increased PPARα activity and selectively increased PPARγ in some cell lines, but decreased glucose similarly to RGZ with, however, a lesser degree of weight gain and with improvement in steatohepatitis, which is not seen with RGZ in this model.

Saad et al. (143-OR) treated 177 individuals with type 2 diabetes and triglyceride >150 mg/dl with placebo or with the dual PPARα/γ agonist ragaglitazar (RGR) or PGZ 45 mg daily for 12 weeks. Triglyceride decreased by 18, 45, 67, and 56% with RGR 0.1, 1, 4, and 10 mg and by 45% with PGZ. HDL cholesterol increased 3, 17, 28, and 8% vs. 12% with PGZ; LDL cholesterol increased 10% with the lowest dose and 11% with PGZ while decreasing 6, 14, and 19% with the 1, 4, and 10 mg RGR doses. FPG decreased 32, 71, 97 and 100 mg with the four RGR doses and 66 mg/dl with PGZ, and weight increased 1, 4, 7, and 8 vs. 3 kg with PGZ. Strand et al. (583-P) treated 200 type 2 diabetic persons with placebo or with RGR 0.1, 0.25, 1, 2, or 7 mg daily for 12 weeks, showing placebo-adjusted decreases in HbA1c of 0.3, 0.6, 0.9, 1.0, and 1.5%; in FPG of 9, 12, 22, 33, and 36%; in triglyceride of 29, 34, 37, 53, and 49%; and in FFA of 9, 18, 39, 42, and 66%; and increase in HDL cholesterol of 17, 12, 24, 34, and 27%, respectively. Both studies reported edema and reversible reductions in red and white cell counts as side effects.

**Thiazolidinediones.** In an important cautionary study, Delea et al. (385-P) used a health insurance claims database with information on some 17 million patients to examine the risk of developing congestive heart failure (CHF) in 5,445 subjects following initiation of TZD, as compared with that in 28,137 diabetic control subjects. The investigators controlled for age; history of CVD and diabetes complications; use of ACE inhibitors, β-blockers, and insulin; numbers of comorbidities and of HbA1c tests; and costs prior to start of treatment. Of those begun on a TZD, 8.2% vs. 5.3% of control subjects were predicted to develop CHF during the subsequent 36 months.

Lee et al. (428-P) reported that 15 persons with type 2 diabetes receiving metformin 2 g and TGZ 400 mg daily for 3 months showed similar 6% increases in HDL cholesterol, with a 12% increase during a subsequent 3 months on combination treatment. LDL decreased 8% and increased 8%, respectively, and showed no change with the respective treatments, and triglyceride levels decreased 15 and 16%, respectively, with a 27% decrease on combination treatment. Fasting FFAs did not change with metformin, decreased 30% with TGZ, and decreased 17% with the combination, while post-prandial FFAs decreased 33, 49, and...
53%, respectively. The authors comment that these effects suggest that further study directed at CVD and β-cell function of TZD, metformin, and the combination would be of importance in view of these important effects on diabetic dyslipidemia. Kelley et al. (142-OR) randomized 12 vs. 11 persons with type 2 diabetes to metformin 2 g daily vs. RGZ 8 mg daily, showing a similar decrease in HbA1c at 4 months from 7.8 to 6.9% vs. 8.3 to 7.0%, with 77 vs. 52% increases in euglycemic clamp insulin sensitivity. The hepatic fat index improved, however, and visceral fat decreased with RGZ but not with metformin.

Tanaka et al. (543-P) administered a TZD to 22 nonobese type 2 diabetic individuals with a mean BMI of 21.2 kg/m² and an HbA1c of 8.5%. Eighteen had more than a 25% decrease in other treatment (SU and/or insulin) or a more than 0.7% decrease in HbA1c at 6 months, suggesting benefit for nonobese as well as for obese patients. Goldstein et al. (398-P) studied 365 subjects receiving glyburide/metformin tablets 7.5/1,500 or 10/2,000 mg daily with HbA1c 7–10%, showing that at 24 weeks, addition of RGZ 4–8 mg/day decreased HbA1c 1% and FPG 49 mg/dl in comparison to placebo. Schwartz et al. (961-P) reported that among 33 persons with type 2 diabetes treated with TZD for 17 months, bone density showed decrease compared with 431 diabetic persons not receiving this agent, suggesting a need for study to assess this potential adverse effect.

**References**