

Incretin Concepts

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This is the third of a series of articles based on presentations at the American Diabetes Association Scientific Sessions held 5–9 June 2009 in New Orleans, Louisiana, pertaining to incretin physiology and incretin-based treatment approaches.

Central nervous system effects of glucagon-like peptide 1

At a symposium on nonislet effects of glucagon-like peptide 1 (GLP-1) at the American Diabetes Association (ADA) Scientific Sessions, Remy Burcelin (Toulouse, France) reviewed the controversy as to the extent of GLP-1 action mediated in the central nervous system versus peripheral effects, advancing the concept that a central effect of GLP-1 may be to induce insulin secretion, but showing studies suggesting that central administration of GLP-1 decreases muscle glycogen—an effect blocked with a GLP-1 receptor antagonist (1). If the central effect of GLP-1 is to increase insulin secretion and to reduce peripheral glucose utilization, it would be expected to increase hepatic glycogen stores, which could be useful in preparation for situations of decreased nutrient availability. The nature of the signal sent to muscle may be understood by recognizing that muscle glucose utilization is controlled by muscle blood flow (2). In his group's study of muscle blood flow, central GLP-1 administration blocked the increase in muscle blood flow seen with insulin and glucose. Mice not expressing the GLP-1 receptor do not show this inhibition of vasodilation and therefore have greater insulin sensitivity with administration of GLP-1. Addressing central GLP-1 signaling mechanisms, Burcelin noted that hypothalamic protein kinase C (PKC) is increased with central GLP-1, whereas the central administration of the PKC inhibitor calphostin C prevented the inhibitory effect of GLP-1 on muscle glucose uptake. In contrast, activation of brain

PKC by phorbol-12-myristate, 13-acetate infusion induced insulin resistance and inhibited vasodilation. Although there are more than 12 PKCs, anti-PKC ϵ appears to block this GLP-1 effect. High-fat diet-induced diabetes is associated with insulin resistance (not seen in mice not expressing the GLP-1 receptor) and increased GLP-1-dependent brain PKC activity, with PKC inhibition reversing the insulin resistance and restoring the vasodilatory action of insulin plus glucose. Burcelin hypothesized that the central effect of GLP-1 activates the sympathetic nervous system causing vasoconstriction, while the peripheral effect of GLP-1 has the opposing action of causing vasodilation.

Cardiac effects of GLP-1

Richard Shannon (Philadelphia, PA) discussed cardiac effects of GLP-1. The term “preconditioning” refers to interventions mitigating myocardial infarction size when carried out in advance of the insult. Such measures may be early or late phase. “Postconditioning” refers to the restitution of contractile dysfunction following an insult. Contractile abnormalities after ischemia involve myocardial hibernation, whereas myocardial stunning involves acute flow-function mismatch following a brief period of complete ischemia.

Early preconditioning involves upregulation of the protein-serine-threonine kinase and key intracellular regulator Akt, altering mitochondrial transport perhaps involving a KATP channel, with pharmacological mediators including adenosine and bradykinin. Mitochondrial ischemia leads to apoptosis and necrosis. Ischemic preconditioning activates Akt, increasing intracellular calcium concentrations and decreasing the mitochondrial electrochemical gradient. Late-phase preconditioning is different; it involves transcription factor activation leading to a new class of mediators. Coronary stenosis decreases contractility with P30 mitogen-

activated protein kinase involved with direct suppression of mitochondrial electrochemical gradients.

The cardioprotective effects demonstrated for GLP-1 have typically been studied in the acute phase, with the agent particularly potent when given prior to an acute insult. The process is cyclic AMP dependent that involves phosphatidylinositol 3-kinase (PI3K) and Akt, inhibiting proapoptotic pathways. In chronic heart failure models with rapid pacing, a form of chronic stunning develops, associated with insulin resistance and decreased myocardial glucose uptake. With chronic GLP-1 infusion, myocardial glucose uptake increases, without change in insulin levels but with profound suppression of glucagon, and all cardiac function parameters in such a model improve. There are GLP-1 receptors in the myocardium (3). GLP-1 receptor downregulation occurs with infusion, however, and Shannon noted that it is difficult to show an effect of GLP-1 on cardiac myocyte calcium permeability, so that the exact mediators of GLP-1 cardiac effect are uncertain. Furthermore, the cardiac GLP-1 receptor may not respond to the long-acting analogs developed for glycemic treatment, and there is evidence that some cardiac GLP-1 effects are mediated by GLP-1 (9-36)—the product of action of dipeptidyl peptidase (DPP)-4 on GLP-1.

Metabolic effects of GLP-1 mediated by direct action

Alan Cherrington (Nashville, TN) discussed *in vitro* actions of GLP-1 in muscle and liver and reviewed his studies showing evidence of direct effects on these tissues in his canine studies, further studies of direct effects in man, and the concept of portal vein glucose sensing.

In vitro studies show that GLP-1 increases muscle glucose uptake and glycogen formation (4), an effect inhibited by the PI3K inhibitor wortmannin, suggesting activation of intracellular glucose metabolism pathways (5). Cherrington commented that it is controversial whether such direct metabolic effects of GLP-1 occur, but given the number of positive findings, he expressed his sense that there is such a phenomenon. Similar studies suggest hepatic effects of GLP-1 (6). The studies require, however, very

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high GLP-1 levels and therefore may not be physiologically relevant, although important in demonstrating that there is a receptor and a signaling mechanism.

Cherrington reviewed a number of canine studies. In a study of depancreatized dogs given somatostatin to suppress endogenous islet function and given infusions of insulin and glucagon, with blood glucose clamped at 180 mg/dl, GLP-1 infusion did not change insulin or glucagon levels; glucose levels were identical, and glucose production rates were similar with and without GLP-1, but glucose utilization was greater with the infusion (7). Similar results have been reported with infusion of exenatide, also with evidence of direct hepatic effect (8). Human studies have shown that GLP-1 decreased glucose production (9) and increases glucose utilization (10). There is, then, evidence that both muscle and hepatic glucose uptake can be affected by GLP-1 independent of its islet effects, but Cherrington pointed out that it is not known whether these effects are centrally mediated or direct. In his studies, net hepatic glucose balance can be measured with direct blood flow and portal, arterial, and hepatic vein cannulation. Comparing effects of peripheral, portal, and hepatic artery GLP-1 infusion in dogs receiving somatostatin plus glucose plus insulin plus glucagon, arterial GLP-1 concentrations were ~50 pmol/l in all studies, while with portal and hepatic infusions hepatic levels were ~100 pmol/l, putting the range around that seen with oral glucose ingestion. With portal infusions, portal vein GLP-1 levels were higher (hence activating portal vein sensors, if such were to be present) (11). Glucose levels increased to 225 mg/dl in all studies. Hepatic glucose uptake did not increase with peripheral GLP-1 administration but increased with either portal or hepatic artery administration, suggesting either a direct hepatic effect or hepatic GLP-1 receptors activating central signaling causing increased glucose uptake. Although Cherrington thought that it is unlikely that this would play a physiological role, he pointed out that it may be relevant to the effect of GLP-1 analog-based treatment. When portal GLP-1 administration was compared with hepatic arterial GLP-1 administration, there was no change in either insulin or glucagon levels, but the glucose infusion requirement was greatest with portal GLP-1 and intermediate with hepatic artery GLP-1 compared with levels seen in control animals (12).

Thus, Cherrington suggested, GLP-1 does increase glucose uptake, and portal glucose administration appears to be required for the effect of GLP-1 on muscle glucose utilization.

Possible role of GLP-1 (9-36)

Michael Brownlee (New York, NY) discussed evidence suggesting a role of GLP-1 (9-36) in diabetic complications. Hyperglycemia-induced mitochondrial overproduction of reactive oxygen species (ROS) activates four major pathways of diabetic cellular damage. Intracellular hyperglycemia increases mitochondrial ROS causing DNA strand breaks in the nucleus activating poly(ADP-ribose) polymerase, which leads to the increases in glyceraldehyde-3-phosphate dehydrogenase (GAPDH), leading to accumulation of glycolytic metabolites, resulting in increased polyol pathway flux and increased methylglyoxal, which in turn increases advanced glycation end product levels as well as increases expression of its receptor RAGE, a toll-like receptor. GAPDH also activates PKC that leads to proinflammatory pathway activation, and GAPDH increases polyol pathway activity (13). Hyperglycemia also inhibits the critical antiatherogenic enzymes endothelial nitric oxide synthase (eNOS) and prostacyclin synthase, potentially exacerbating atherosclerosis (14,15). In insulin-resistant models, fatty acids also increase ROS, activating and inactivating the same pathways (16).

Although it has been thought that the product of DPP-4 action on GLP-1, GLP-1 (9-36), is inactive (17), Brownlee reasoned that a potential role of GLP-1 (9-36) would be to inactivate the various processes leading to ROS after nutrient ingestion. He showed evidence that GLP-1 (9-36) amide prevents ROS induced by high glucose or fatty acids in insulin-resistant states. In human aortic endothelial cells, prostacyclin synthase and eNOS are inhibited both by high glucose and by oleic acid, with prevention by GLP-1 (9-36). Normal humans lose prostacyclin synthase activity after ~3 h of glucose infusion to levels of 10 mmol/l, lasting for the subsequent 24 h. Diabetic mice not expressing the GLP-1 receptor, furthermore, show inhibition both of eNOS and of prostacyclin synthase activity, which can be reversed by administration of GLP-1 (9-36).

Incretin-based treatment approaches

Clinical and basic science information was presented for a number of agents acting on the incretin system at the ADA Scientific Sessions. Jessen et al. (abstract 1527) administered GLP-1 with a DPP-4 inhibitor and showed a lesser duration of suppression of food intake than that seen with exenatide, suggesting that exenatide may have effects differing from those of GLP-1 beyond its lack of susceptibility to degradation by DPP-4. The GLP-1 receptor antagonist exendin (9-39) was reported by Stanley et al. (abstract 2) to reduce hyperinsulinemia and prevent hypoglycemia associated with mutations in the KATP channel, suggesting that GLP-1 receptor activation may play a role in the pathogenesis of hyperinsulinism and that antagonism of the receptor may have therapeutic benefits. Exenatide was the subject of ongoing studies with reports of an inhaled form and two different weekly forms of the agent. Liraglutide, a daily GLP-1 mimetic, was the subject of a number of reports. Albiglutide, a large recombinant protein with both albumin and GLP-1 moieties (18), with sustained biological action over a period of ≥ 1 week (19); taspoglutide; LY2189265, a DPP-4-protected GLP-1 analog covalently linked to an Fc fragment of human IgG4; and NN9535 (about which no data were presented at the meeting) are other GLP-1 receptor agonists being studied with evidence of efficacy at weekly (or longer) dosing intervals.

Exenatide immediate release

Shen et al. (abstract 366) analyzed cardiovascular safety among 2,279 subjects receiving exenatide versus 1,629 control subjects and found 20 and 39% reduction in cardiovascular end points with various methodologies; although the mean reduction in events was not significant for either agent, the 95% confidence limits did not include an increase in events by >30%, suggesting that these agents are likely to be safe in terms of cardiovascular events. Bruce et al. (abstract 578) studied the same population, finding that transient, mild-to-moderate nausea occurred in 39% of subjects receiving exenatide compared with 9% of control subjects, vomiting in 13% compared with 3%, and pancreatitis in 0.3% compared with 0.3%, suggesting adequate gastrointestinal tolerability of the agent. Horton et al. (abstract 611) analyzed an electronic medical record database that contains information on 6,280, 5,861, and 32,398

patients receiving exenatide, sitagliptin, and insulin, with weight losses of 3 and 1.1 kg and gain of 0.6 kg, respectively. Weight loss in the former two groups was associated with reduction in blood pressure and triglyceride levels; those patients receiving exenatide with weight loss >4.5 kg had reduction in LDL cholesterol as well.

Arnolds et al. (abstract 526) treated 48 type 2 diabetic subjects with metformin and insulin glargine titrated over 4–8 weeks to a fasting glucose \leq 100 mg/dl (75% reached this goal). Subsequently, exenatide, sitagliptin, or neither was added for 4 weeks, with both incretin treatments associated with 16% reduction in 6-h postprandial glucose excursion; in fasting glucose, to 82 and 84 vs. 89 mg/dl; and in A1C, to 6.5 and 6.4 vs. 6.7%. Weight decreased 0.9 kg, increased 0.1 kg, and increased 0.4 kg with the respective treatments, suggesting that addition of either a GLP-1 mimetic or a DPP-4 inhibitor may similarly benefit insulin-treated type 2 diabetic patients. Jogi et al. (abstract 615) treated 8 subjects receiving metformin with pioglitazone 45 mg daily and 10 such subjects with both pioglitazone and exenatide for 6 months. Pioglitazone alone decreased A1C from 7.9 to 7.2% and increased adiponectin 68%, while combined treatment decreased A1C from 7.5 to 6.5% and increased adiponectin 181%, although not significantly reducing weight. Christofides et al. (abstract 572) treated 132 subjects with exenatide and various combinations of metformin and pioglitazone, while discontinuing sulfonylureas, with baseline A1C 7.1%, and found that at 21 months among 47 subjects remaining for observation, A1C was 6.3%, with 1.7 kg weight loss. They also treated 109 type 2 diabetic subjects receiving insulin, with baseline A1C 8.1%, with exenatide; 43 were followed through 21 months and had mean A1C 7.3% and 4.3 kg weight loss. Samarasinghe et al. (abstract 530) reported on 22 insulin-receiving type 2 diabetic patients treated with exenatide for at least 3 months and found 0.2% reduction in A1C and in weight by 2.2 kg at 3 months; most patients either reduced or discontinued insulin treatment. Hamdy et al. (abstract 539), however, reported on 133 subjects treated with exenatide and observed for at least 2 years and found that 84 continued the agent throughout the period of observation, with 7.9-pound weight loss, but with A1C increasing from 7.9 to 8.0% over an average of 30 months.

Forty-nine patients stopped exenatide after a mean of 17 months, with 3.7-pound weight loss, and again without significant change in A1C, suggesting dissociation in durability between weight reduction and metabolic improvement.

Baughman et al. (abstract 160) and Costello et al. (abstract 446) compared exenatide with inhaled GLP-1 adsorbed onto Technosphere microparticles in acute studies, finding reduction in gastric emptying to be the principal mechanism of the effect of the injected preparation, whereas inhaled GLP-1 had a considerably greater insulin-stimulatory effect, with less effect on gastric emptying and causing nausea in just 1 of 20 subjects receiving the agent. The glucose-lowering effect of the agent was greater in those subjects with higher baseline glucose levels.

Exenatide once weekly

Kim et al. (abstract 159) followed 181 subjects who received either exenatide twice daily or the once-weekly exenatide preparation for 30 weeks, followed (for 135 participants) by 70 weeks of the weekly preparation, and reported that A1C decreased from 8.3 to 6.5%, fasting glucose from 167 to 130 mg/dl, and weight from 100 to 96.4 kg. Nausea occurred in 8% of subjects during the period from 30 to 100 weeks. Bergenstal et al. (abstract 6-LB) treated 160 type 2 diabetic subjects with exenatide weekly, 166 with sitagliptin 100 mg daily, and 165 with pioglitazone 45 mg daily. From baseline A1C of 8.5%, levels decreased 1.6, 0.9, and 1.2% with the three agents; fasting glucose decreased by 32, 16, and 27 mg/dl; and weight decreased by 2.7 and 0.9 kg versus increasing by 3.2 kg, respectively. Wang et al. (abstract 553) studied 224 type 2 diabetic subjects receiving a different extended-release form of exenatide, conjugated to recombinant human albumin, and found reductions in A1C by 1.4, 0.8, 0.8, and 0.4% with 3.0, 2.0, and 1.5 mg and placebo doses, respectively, with modest weight loss and tolerable gastrointestinal side effects.

Liraglutide

Rosenstock et al. (abstract 558) compared the pharmacokinetics of exenatide with that of liraglutide and found the former to show peak activity during the first 4 h after dosing, with reduction to baseline after 8 h, whereas liraglutide led to relatively consistent elevations in levels over 24 h. Finer et al. (abstract 1729) treated

176 obese pre-diabetic subjects with liraglutide 1.2, 1.8, 2.4, and 3.0 mg daily and reported normal glucose tolerance in 69, 96, 88, and 96% after 20 weeks, whereas only 41% of subjects treated with orlistat 120 mg thrice daily and 46% of control subjects showed normalization of glucose tolerance. Seino et al. (abstract 536) randomized 400 type 2 diabetic Japanese patients to liraglutide 0.9 mg compared with glyburide 2.5 mg daily and found A1C reduction of 1.7 vs. 1.2% at 24 weeks, with hypoglycemia occurring 0.8 vs. 5.5 times per person per year and diarrhea in 6.3 vs. 3.8% of the two groups. Garber et al. (abstract 162) compared liraglutide with glimepiride for a 2nd year in 321 of 440 subjects completing a 1-year study, finding A1C reduction from 8.1 to 6.9% with 1.8 mg and from 8.0 to 7.1% with 1.2 mg liraglutide daily doses, while decreasing from 8.0 to 7.5% with glimepiride; weight decreased 2.7 and 2.1 kg, while increasing 1.1 kg; and hypoglycemia occurred 0.3, 0.2, and 1.8 times per person per year with the respective treatments. Nauck et al. (abstract 459) compared 2,284 patients who received liraglutide as substitute for an oral hypoglycemic agent with 1,683 patients who received add-on of liraglutide to existing treatment in six randomized phase 3 trials. A1C decreased from 8.3 to 7.0% compared with 8.4 to 7.4% with the 1.8-mg dose and showed similarly greater reduction with the 1.2-mg dose, whereas reductions in weight and in blood pressure were similar with substitution and with add-on. Fonseca et al. (abstract 545) performed a meta-analysis of 1,363 and 896 subjects receiving liraglutide 1.8 and 1.2 mg daily compared with 524 receiving placebo for 26 weeks and found a reduction in systolic blood pressure by 2.5, 2.6, and 0.2 mmHg.

Other GLP-1 receptor agonists

Rosenstock et al. (abstract 163), Reusch et al. (abstract 461), and Stewart et al. (abstract 598) treated 356 type 2 diabetic patients with varying doses of albiglutide and with exenatide twice daily for 16 weeks and reported A1C reductions from baseline of 8% by 0.9% with albiglutide 30 mg weekly, by 0.8% with 50 mg every other week, and by 0.9% with 100 mg monthly, whereas reductions of 0.5% and 0.2%, respectively, were seen with exenatide and placebo (20). Fasting glucose decreased 26, 24, and 22 mg/dl with the three albiglutide doses, 14 mg/dl with exenatide, and 2 mg/dl with placebo. The

decrement in fasting glucose varied over time with the biweekly and monthly regimens, suggesting that weekly dosing would be optimal. Nausea and/or vomiting occurred in 46% of subjects receiving exenatide and in 29, 54, and 56% of those receiving 30-, 50-, and 100-mg doses weekly, biweekly, and monthly, respectively. Seino et al. (abstract 581) administered the agent to 40 Japanese type 2 diabetic subjects and reported a half-life just over 5 days, also with highest side effect frequency and lowest efficacy with the 100-mg monthly dose (21).

Umpierrez et al. (abstract 12-LB) treated 262 obese type 2 diabetic subjects with LY2189265 for 16 weeks, reporting a reduction in A1C from basal level averaging 8.2% by 0.3% with placebo, 1.3% both with 0.5 and with 1.0 mg weekly, and 1.5% with 2.0 mg weekly. Fasting glucose decreased by 9, 38, and 48 mg/dl, respectively, and weight loss of 1.6, 1.4, and 2.5 kg was recorded at 0.5-, 1.0-, and 2.0-mg weekly doses. Nausea occurred in 13%, diarrhea in 9%, and abdominal distension in 8% of treated patients. Barrington et al. (abstract 161) reported a 5-week study with this agent of 43 type 2 diabetic patients and found A1C reductions of 0.7 to 1.3% with 0.05- to 8-mg weekly doses.

Sewing et al. (abstract 323) and Sebkova et al. (abstract 593) studied taspoglutide in the Zucker diabetic fatty rat model, reporting weight loss, improved glycemia, and >30% reduction in glucose-dependent insulinotropic peptide (GIP) and 70% reduction in peptide-YY (PYY) levels after glucose challenge without change in fasting levels, the latter perhaps reflecting suppression of α -cell activity by GLP-1 receptor activation. Treatment also improved homeostasis model assessment-insulin sensitivity and 1,5-anhydroglucitol, a measure of postprandial glycemia. A human study has been reported with this agent (22).

Oral agents acting via the incretin system

A novel set of G-coupled protein receptors (GPRs) involved in incretin systems appears to be activated physiologically by specific long-chain fatty acids and their derivatives, playing roles in the effects of fats on islet (and incretin) function and potentially offering a pathway in development of new therapeutic agents (23). Lauffer et al. (abstract 151) studied the α -cell receptors GPR40, GPR120, and GPR119 and reported stimulation of

these receptors to acutely increase GLP-1 secretion, as well as to enhance glucose-induced insulin secretion. Chronically, GPR119 agonists reduced but a GPR 40/120 agonist increased α -cell apoptosis. One GPR 119 agonist, but not another, and an agonist of both GPR 40 and GPR120 reduced α -cell proliferation, suggesting that GPR119 agonists might have promise in offering combined stimulation of both GLP-1 and insulin secretion. Roberts et al. (abstract 164) administered an orally available GPR119 agonist, MBX-2982, in rodent diabetes models and found a decrease in blood glucose after oral glucose with increase in active GLP-1 levels, reduction in gastric emptying, and delay in the time to onset of diabetes in a high-fat diet-fed model, with effects increased by the DPP-4 inhibitor sitagliptin. In subjects with elevated fasting glucose, MBX-2982 lowered blood glucose and increased the insulin secretory response to glucose. Tanaka et al. (abstract 464) studied another GPR119 agonist, AS1907417, similarly showing glucose lowering in diabetes rodent models with preservation of β -cell function. Swain et al. (abstract 453) administered an agent acting both to inhibit DPP-4 and to activate GPR119, showing greater glucose-lowering effect in a rodent model than that seen with sitagliptin. In another study of overlap between a β -cell stimulatory agent and the α -cell, Kitahara et al. (abstract 1427) reported that nateglinide increased portal blood GLP-1 levels in a rodent model and that in vivo incubation of human intestinal α -cells with nateglinide stimulated GLP-1 release in a dose-dependent fashion, associated with increase in intracellular calcium, but unaffected by potassium-ATP channel opening agents or by sulfonylureas, suggesting that the agent has a more direct effect in increasing α -cell intracellular calcium levels.

Transcription factor 7-like 2 (TCF7L2) gene variants are strongly associated with type 2 diabetes. Maedler et al. (abstract 1160) reported that decreased TCF7L2 protein is seen with these variants in association with reduced expression of islet GLP-1 and GIP receptors and with reduced glucose-stimulation of insulin secretion by GLP-1 and GIP. It is interesting to speculate that the presence of the at-risk polymorphisms might be a marker for differences in response to incretin-based treatments. Kawamori et al. (abstract 90-LB) administered GLP-1 to mice lacking β -cell insulin receptors and to controls and found that the knockout

mice increased acute GLP-1-mediated glucose lowering and improved glucose tolerance and insulin secretory response to oral glucose, with evidence of β -cell proliferation. The β -cell insulin receptor may then mediate direct short-loop feedback inhibition by insulin, with β -cell insulin resistance then paradoxically enhancing insulin secretion.

The DPP-4 inhibitors, increasing circulating levels of GLP-1 and GIP, are clinically available and were the subjects of a number of reports at the meeting, including meta-analyses of multiple studies of specific agents and long-term extension studies of earlier phase 3 clinical trials. Wolf et al. (abstract 8-LB) studied overall acute coronary end points, major acute coronary end points, and total and cardiovascular mortality and found that in comparison with 3,356 type 2 diabetic subjects receiving saxagliptin, rates of the various events increased 63%, doubled, tripled, and quadrupled, respectively, in 1,251 control subjects not receiving the agent, suggesting cardiovascular safety. DeFronzo et al. (abstract 547) presented a 2-year follow-up of 743 metformin-treated type 2 diabetic subjects (with initial A1C of 8.0%) randomized to addition of saxagliptin versus placebo; placebo-adjusted reductions in A1C of 0.6, 0.7, and 0.5% were seen in 181, 184, and 177 subjects randomized to saxagliptin 2.5, 5, and 10 mg daily, respectively. Although 58, 52, and 57% of these groups discontinued (or were given rescue treatment with pioglitazone) for lack of glycemic control, 72% of those in the placebo group discontinued or required rescue treatment. Pratley et al. (abstract 462) compared the effect of alogliptin in 1,611 type 2 diabetic subjects aged <65 years and in 455 subjects aged \geq 65 years, showing placebo-adjusted A1C reduction by 0.5–0.6% from baseline levels of 8–8.4% that were similar in younger and older subjects, although with adverse events leading to discontinuation reported in 2% of younger but in 4% of older patients. Linagliptin, placebo, or glimepiride was administered to 333 metformin-treated type 2 diabetic subjects with baseline A1C 8.3%; 0.7–0.8% placebo-corrected A1C reduction was found with linagliptin (5 mg and 10 mg), but 0.9% reduction in A1C was reported with glimepiride at 12 weeks. Hypoglycemia occurred in no patients receiving placebo or linagliptin and in three patients receiving glimepiride. Linke et al. (abstract 596) reported improvement in an experimen-

tal model of wound healing in a diabetic rodent model with linagliptin treatment, which might reflect the improvement in glycemia with the agent or a nonglycemic benefit, and Jin et al. (abstract 833) reported reduction in peripheral nerve degeneration in a diabetes-related rodent model treated with vildagliptin—another benefit that might be attributed to either glycemic change or non-glucose-mediated effect.

Vilsboll et al. (abstract 588) randomized 641 type 2 diabetic patients receiving insulin alone or with metformin to addition of sitagliptin compared with placebo. A1C decreased from 8.7% by 0.6% with sitagliptin versus not changing with placebo, although 16% compared with 8% had hypoglycemic events. Williams-Herman et al. (abstract 540) reported a 2-year follow-up of sitagliptin monotherapy in 147 subjects, with reduction in mean A1C from a baseline of 8.5% to 6.9% in the 32 patients remaining in the study, and of sitagliptin addition to metformin in 852 patients, with A1C decreasing from a baseline of 8.0% to 6.9% in the 347 patients remaining. The substantial decrease in numbers of participants makes it difficult to evaluate the durability of benefit of the agent. Yoon et al. (abstract 522) treated 520 treatment-naïve type 2 diabetic patients who had baseline A1C of 9.5% with sitagliptin 100 mg plus pioglitazone 30 mg daily or with pioglitazone alone for 24 weeks and found A1C reduction of 2.4 vs. 1.5%, with greater improvement in insulin and C-peptide responses to a meal challenge in the former group. Approximately 1% of patients in both groups had hypoglycemia, 6 vs. 7% had gastrointestinal adverse events, and 3 vs. 4% had edema. Aaboe et al. (abstracts 605 and 606) randomized 22 metformin-treated type 2 diabetic subjects to sitagliptin compared with placebo for 12 weeks; the former group exhibited improved insulin secretory responses to glucose and arginine, demonstrable after the 1st week of treatment. PYY (total) levels decreased 26%, with PYY (3-36) levels reduced 63%, whereas PYY (1-36) levels increased 24%, reflecting the action of DPP-4 on PYY and, perhaps, short-loop negative feedback of PYY (1-36). The researchers speculate that the lack of weight loss seen clinically with DPP-4 inhibitors may be due to reduction in circulating PYY (3-36) levels with the agents, based on understanding of the physiological effects of the two PYY species (24).

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References

1. Knauf C, Cani PD, Perrin C, Iglesias MA, Maury JF, Bernard E, Benhamed F, Grémeaux T, Drucker DJ, Kahn CR, Girard J, Tanti JF, Delzenne NM, Postic C, Burcelin R. Brain glucagon-like peptide-1 increases insulin secretion and muscle insulin resistance to favor hepatic glycogen storage. *J Clin Invest* 2005;115:3554–3563
2. Duplain H, Burcelin R, Sartori C, Cook S, Egli M, Lepori M, Vollenweider P, Pedrazzini T, Nicod P, Thorens B, Scherrer U. Insulin resistance, hyperlipidemia, and hypertension in mice lacking endothelial nitric oxide synthase. *Circulation* 2001;104:342–345
3. Ban K, Noyan-Ashraf MH, Hofer J, Bolz SS, Drucker DJ, Husain M. Cardioprotective and vasodilatory actions of glucagon-like peptide 1 receptor are mediated through both glucagon-like peptide 1 receptor-dependent and -independent pathways. *Circulation* 2008;117:2340–2350
4. Villanueva-Peñacarrillo ML, Alcántara AI, Clemente F, Delgado E, Valverde I. Potent glycogenic effect of GLP-1(7-36)amide in rat skeletal muscle. *Diabetologia* 1994;37:1163–1166
5. González N, Acitores A, Sancho V, Valverde I, Villanueva-Peñacarrillo ML. Effect of GLP-1 on glucose transport and its cell signalling in human myocytes. *Regul Pept* 2005;126:203–211
6. Villanueva-Peñacarrillo ML, Delgado E, Trapote MA, Alcántara A, Clemente F, Luque MA, Perea A, Valverde I. Glucagon-like peptide-1 binding to rat hepatic membranes. *J Endocrinol* 1995;146:183–189
7. Sandhu H, Wiesenthal SR, MacDonald PE, McCall RH, Tchipashvili V, Rashid S, Satkunarajah M, Irwin DM, Shi ZQ, Brubaker PL, Wheeler MB, Vranic M, Efendic S, Giacca A. Glucagon-like peptide 1 increases insulin sensitivity in depancreatized dogs. *Diabetes* 1999;48:1045–1053
8. Zheng D, Ionut V, Mooradian V, Stefanovski D, Bergman RN. Exenatide sensitizes insulin-mediated whole-body

- glucose disposal and promotes uptake of exogenous glucose by the liver. *Diabetes* 2009;58:352–359
9. Prigeon RL, Quddusi S, Paty B, D'Alessio DA. Suppression of glucose production by GLP-1 independent of islet hormones: a novel extrapancreatic effect. *Am J Physiol Endocrinol Metab* 2003;285:E701–E707
10. Vella A, Shah P, Basu R, Basu A, Camilleri M, Schwenk FW, Holst JJ, Rizza RA. Effect of glucagon-like peptide-1(7-36)-amide on initial splanchnic glucose uptake and insulin action in humans with type 1 diabetes. *Diabetes* 2001;50:565–572
11. Dardevet D, Moore MC, DiCostanzo CA, Farmer B, Neal DW, Snead W, Lautz M, Cherrington AD. Insulin secretion-independent effects of GLP-1 on canine liver glucose metabolism do not involve portal vein GLP-1 receptors. *Am J Physiol Gastrointest Liver Physiol* 2005;289:G806–G814
12. Johnson KM, Edgerton DS, Rodewald T, Scott M, Farmer B, Neal D, Cherrington AD. Intraportal GLP-1 infusion increases nonhepatic glucose utilization without changing pancreatic hormone levels. *Am J Physiol Endocrinol Metab* 2007;293:E1085–E1091
13. Brownlee M. Biochemistry and molecular cell biology of diabetic complications. *Nature* 2001;414:813–820
14. Kobayashi T, Tahara Y, Matsumoto M, Iguchi M, Sano H, Murayama T, Arai H, Oida H, Yurugi-Kobayashi T, Yamashita JK, Katagiri H, Majima M, Yokode M, Kita T, Narumiya S. Roles of thromboxane A(2) and prostacyclin in the development of atherosclerosis in apoE-deficient mice. *J Clin Invest* 2004;114:784–794
15. Kuhlencordt PJ, Gyurko R, Han F, Scherrer-Crosbie M, Aretz TH, Hajjar R, Picard MH, Huang PL. Accelerated atherosclerosis, aortic aneurysm formation, and ischemic heart disease in apolipoprotein E/endothelial nitric oxide synthase double-knockout mice. *Circulation* 2001;104:448–454
16. Du X, Edelstein D, Obici S, Higham N, Zou MH, Brownlee M. Insulin resistance reduces arterial prostacyclin synthase and eNOS activities by increasing endothelial fatty acid oxidation. *J Clin Invest* 2006;116:1071–1080
17. Moller DE. New drug targets for type 2 diabetes and the metabolic syndrome. *Nature* 2001;414:821–827
18. Baggio LL, Huang Q, Brown TJ, Drucker DJ. A recombinant human glucagon-like peptide (GLP)-1-albumin protein (albugon) mimics peptidergic activation of GLP-1 receptor-dependent pathways coupled with satiety, gastrointestinal motility, and glucose homeostasis. *Diabetes* 2004;53:2492–2500

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19. Bush MA, Matthews JE, De Boever EH, Dobbins RL, Hodge RJ, Walker SE, Holland MC, Gutierrez M, Stewart MW. Safety, tolerability, pharmacodynamics and pharmacokinetics of albiglutide, a long-acting glucagon-like peptide-1 mimetic, in healthy subjects. *Diabetes Obes Metab* 2009;11:498–505
20. Rosenstock J, Reusch J, Bush M, Yang F, Stewart M; the Albiglutide Study Group. Potential of albiglutide, a long-acting GLP-1 receptor agonist, in type 2 diabetes: a randomized controlled trial exploring weekly, biweekly, and monthly dosing. *Diabetes Care* 2009;32:1880–1886
21. Seino Y, Nakajima H, Miyahara H, Kurita T, Bush MA, Yang F, Stewart MW. Safety, tolerability, pharmacokinetics and pharmacodynamics of albiglutide, a long-acting GLP-1-receptor agonist, in Japanese subjects with type 2 diabetes mellitus. *Curr Med Res Opin* 2009;25:3049–3057
22. Nauck MA, Ratner RE, Kapitza C, Berria R, Boldrin M, Balena R. Treatment with the human once-weekly glucagon-like peptide-1 analog taspoglutide in combination with metformin improves glycaemic control and lowers body weight in patients with type 2 diabetes inadequately controlled with metformin alone: a double-blind placebo-controlled study. *Diabetes Care* 2009;32:1237–1243
23. Kebede MA, Alquier T, Latour MG, Poitout V. Lipid receptors and islet function: therapeutic implications? *Diabetes Obes Metab* 2009;11(Suppl. 4):10–20
24. Ballantyne GH. Peptide YY(1-36) and peptide YY(3-36): Part I. Distribution, release and actions. *Obes Surg* 2006;16:651–658