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In Brief

Impaired insulin secretion, increased hepatic glucose production, and decreased peripheral glucose utilization are the core defects responsible for the development and progression of type 2 diabetes. However, the pathophysiology of this disease also includes adipocyte insulin resistance (increased lipolysis), reduced incretin secretion/sensitivity, increased glucagon secretion, enhanced renal glucose reabsorption, and brain insulin resistance/neurotransmitter dysfunction. Although current diabetes management focuses on lowering blood glucose, the goal of therapy should be to delay disease progression and eventual treatment failure. Recent innovative treatment approaches target the multiple pathophysiological defects present in type 2 diabetes. Optimal management should include early initiation of combination therapy using multiple drugs with different mechanisms of action. This review examines novel therapeutic options that hold particular promise.

Novel Agents for the Treatment of Type 2 Diabetes

Ralph A. DeFronzo, MD, Curtis L. Triplitt, PharmD, CDE, Muhammad Abdul-Ghani, MD, and Eugenio Cersosimo, MD

From 1987 to the present, our understanding of the pathophysiology of type 2 diabetes has expanded from the triumvirate of β-cell–, muscle-, and liver-related defects[1] to the "ominous octet" described in the 2008 Banting Lecture[2] (Figure 1). We have learned that β-cell failure occurs much earlier in the natural history of type 2 diabetes than previously appreciated, and there is growing evidence that therapeutic interventions that slow or delay the progression of β-cell failure can lead to more durable glycemic control. Currently available antidiabetic agents target multiple pathophysiological mechanisms present in type 2 diabetes (Figure 2), but glycemic control in patients with
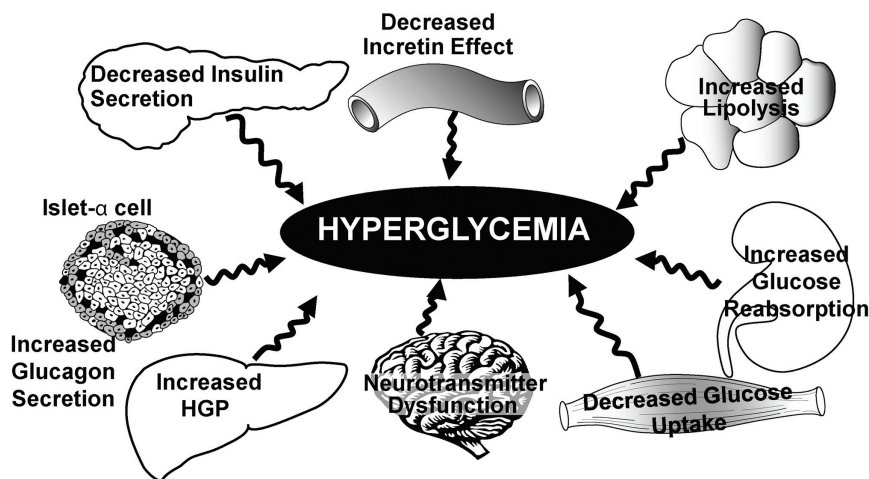
Figure 1. The ominous octet. Multiple defects contribute to the development of glucose intolerance in type 2 diabetes. HGP, hepatic glucose production.
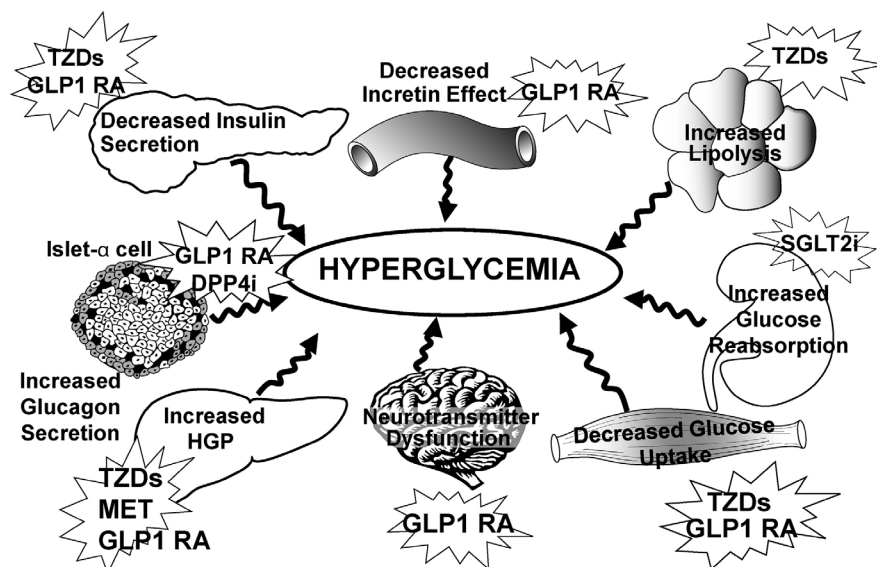

Figure 2. Pathophysiological abnormalities targeted by currently available antidiabetic medications. DPP4i, dipeptidyl peptidase-4 inhibitor; GLP1 RA, glucagon-like peptide-1 receptor agonist; HGP, hepatic glucose production; MET, metformin; SGLT2i, sodium glucose co-transporter 2 inhibitor; TZD, thiazolidinedione.

type 2 diabetes remains poor, with ~ 50% of such individuals in the United States having an A1C > 7.0%. In this article, we review novel therapeutic approaches based on the pathophysiology of type 2 diabetes. To appreciate what future therapies may represent potential targets for the disease, we briefly review the pathogenesis of type 2 diabetes.

β-Cell Function

The fundamental core defects responsible for type 2 diabetes are impaired insulin secretion resulting from declining β-cell function, decreased glucose uptake by peripheral (muscle) tissues, and increased hepatic glucose production (HGP) secondary to augmented gluconeogenesis.[1,2] Insulin secretion is increased early in the course of the disease, as the pancreas attempts to compensate for the elevated fasting plasma glucose (FPG) concentration and underlying insulin resistance. However, as the FPG concentration continues to rise, β-cells are no longer able to sustain their increased rate of insulin secretion, and as insulin secretion begins to decline, impaired glucose tolerance (IGT) and eventually overt diabetes ensue.[3–6] Increased HGP and decreased muscle glucose uptake further contribute to

the state of hyperglycemia,[7,8] which places further stress on the β-cells and establishes a negative feedback loop through which metabolic decompensation—glucotoxicity[9] and lipotoxicity[10]—contributes to β-cell failure and worsening insulin resistance.

Importantly, the plasma insulin response to glucose does not provide information about the health of the β-cell. The β-cell responds to an increment in plasma glucose concentration with an increment in plasma insulin, and this feedback loop is influenced by the severity of insulin resistance. Thus, β-cell function is best characterized by the insulin secretion/insulin resistance (disposition) index (ΔINS/ΔGLU ÷ IR, in which I = insulin and G = glucose).[4,11,12] Studies from our group[3–5] have established that β-cell failure occurs early in the natural course of type 2 diabetes and is more severe than originally appreciated (Figure 3). As the 2-hour plasma glucose concentration in normal glucose tolerant (NGT) subjects increases from < 100 to 100–119 to 120–139 mg/dl, there is an ~ 60% decline in β-cell function. In the upper tertile of IGT (2-hour plasma glucose during an oral glucose tolerance test [OGTT] = 180–199 mg/dl), β-cell function has declined by 75–80%.[4,5,11,12] More worrisome than the loss of β-cell function is the progressive loss of β-cell mass that starts during the prediabetic stage and continues progressively with worsening diabetes. Thus, treatment strategies for patients with type 2 diabetes should include agents that delay or prevent β-cell apoptosis.[13]

By the time individuals reach the upper tertile of IGT, most are maximally or near-maximally insulin resistant and have lost the majority (75–80%) of their β-cell function. Therefore, treatment strategies for patients with type 2 diabetes should include agents that preserve β-cell function and ideally have the potential to prevent or delay β-cell apoptosis.

Insulin Resistance and Type 2 Diabetes

Insulin resistance is a key pathophysiological abnormality in type 2 diabetes and occurs early in the natural history of the disease.[1,2,4,8,11,14] Both the liver and muscle are severely resistant to insulin action. A strong correlation exists between the increase in HGP and the increase in FPG concentration in type 2 diabetes.[1,2] The increased
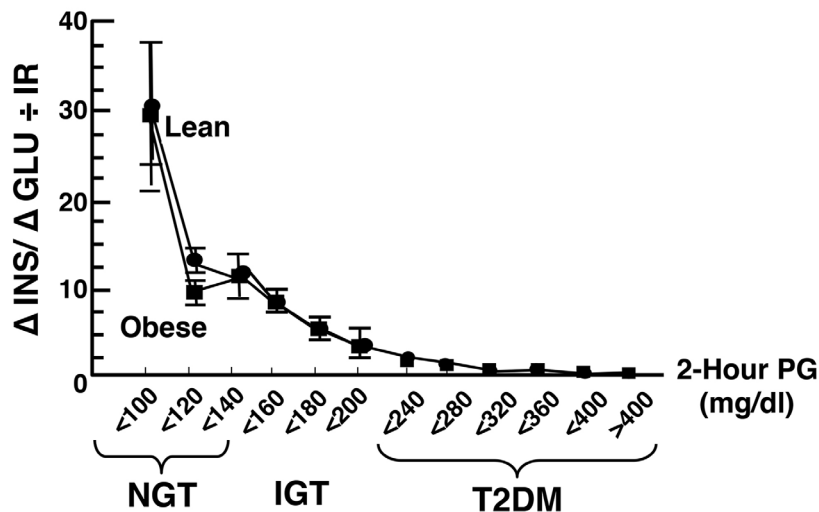
Figure 3. Insulin secretion/insulin resistance (disposition) index (ΔINS/ΔGLU ÷ IR) in subjects with normal glucose tolerance (NGT), impaired glucose tolerance (IGT), and type 2 diabetes (T2DM) as a function of the 2-hour plasma glucose (PG) concentration during the OGTT (see text for a more detailed discussion). ΔINS/ΔGLU = increment in plasma insulin concentration/increment in plasma glucose concentration during oral glucose tolerance testing. The curves for lean and obese individuals are shown separately. IR = insulin resistance measured with the insulin clamp technique.

rate of HGP occurs in the presence of fasting plasma insulin concentrations that are elevated two- to threefold, indicating severe resistance to the suppressive effect of insulin on HGP. When insulin is infused to mimic levels seen after ingestion of a standard meal, HGP suppression is markedly impaired.[15] All of the increase in HGP is secondary to an accelerated rate of hepatic gluconeogenesis.[16]

Studies using the gold-standard euglycemic insulin clamp technique[17] have shown that skeletal muscle is severely resistant to insulin and accounts for 85–90% of the impairment in total body glucose disposal in people with type 2 diabetes.[2,8,14,18] Multiple intracellular defects in insulin action, including decreased glucose transport and phosphorylation, reduced glycogen synthesis, and impaired glycolysis and glucose oxidation, contribute to the insulin resistance.[2,19] Most importantly, studies from our laboratory have demonstrated that more proximal defects in the insulin receptor signal transduction cascade play a major role in the muscle insulin resistance observed in type 2 diabetes.[2,11,14,20,21] However, it is important to note that, although insulin resistance is well established in the liver and muscle in the early phase of the disease, overt hyperglycemia and

diabetes do not develop without the onset of progressive β-cell failure.[1,2,12]

From the Triumvirate to the Ominous Octet
In addition to the triumvirate of β-cell failure and insulin resistance in muscle and liver, specific organ systems, including the adipocyte (accelerated lipolysis), gastrointestinal (GI) tract (incretin deficiency/incretin resistance), pancreatic α-cell (hyperglucagonemia), kidney (increased glucose reabsorption/threshold), and brain/central nervous system (CNS) (insulin resistance), play key roles in the pathogenesis of type 2 diabetes. These multiple defects have been referred to as the "ominous octet" (Figure 1).[2]

Disharmonious quartet
Deranged adipocyte metabolism and altered fat topography play an important role in the pathogenesis of glucose intolerance in type 2 diabetes.[2,10] Fat cells are resistant to the antilipolytic effect of insulin, leading to elevated plasma free fatty acid (FFA) concentrations[15] and increased intracellular levels of toxic lipid metabolites (fatty acyl coenzyme A [FACoA], diacylglycerol [DAG], and ceramide) that cause insulin resistance in muscle and liver[22] and promote β-cell failure.[23] Fat cells are in a state of chronic inflammation and secrete excessive amounts of insulin resistance–inducing, inflam-

matory, and atherosclerosis-provoking cytokines (tumor necrosis factor α, interleukin-6, resistin, and angiotensinogen) and fail to secrete normal amounts of insulin-sensitizing adipocytokines (adiponectin).[10]

Quintessential quintet
People with type 2 diabetes also have a diminished incretin effect.[2,24,25] The incretin hormones glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) account for 90% of the incretin effect and play a pivotal role in maintaining normal glucose homeostasis. Both GLP-1 and GIP augment insulin secretion, and GLP-1 also inhibits glucagon secretion, delays gastric emptying, and suppresses appetite.[26] Although some studies have demonstrated a modest defect in GLP-1 secretion in type 2 diabetes, other studies have documented normal or even increased GLP-1 secretion.[27] To the contrary, severe resistance to the stimulatory effect of GLP-1 on β-cell secretion of insulin has been a consistent finding.[28]

Setaceous sextet
Increased glucagon secretion by the α-cell and enhanced hepatic sensitivity to glucagon also play a key role in type 2 diabetes pathophysiology.[29,30] Glucagon is pivotal in maintaining the elevated basal rate of HGP in people with type 2 diabetes.[29,30] Plasma glucagon concentrations are increased in patients with IGT and type 2 diabetes compared to individuals with NGT[29,30] despite their hyperglycemia and hyperinsulinemia, which should suppress glucagon secretion. Elevated concentrations of glucagon stimulate HGP and oppose the effect of insulin in suppressing HGP. There also is enhanced sensitivity to the stimulatory effect of glucagon on HGP.[30] In type 2 diabetes, when glucagon secretion is inhibited by somatostatin, fasting plasma glucagon levels decline in association with a marked reduction in basal HGP.[29]

Septicidal septet
With a normal glomerular filtration rate of ~ 180 liters/day and a mean day-long plasma glucose concentration of 100 mg/dl, the kidney of healthy subjects filters ~ 180 g/day of glucose.[31] In healthy individuals, 90% of the filtered glucose is reabsorbed by the high-capacity, low-affinity sodium glucose co-transporter 2 (SGLT-2) in the proximal convoluted renal tubule,

and the remaining 10% is reabsorbed by the high-affinity, low-capacity SGLT-1 transporter in the straight segment of the descending proximal tubule.[31,32] In nondiabetic subjects, no glucose appears in the urine until the plasma glucose concentration exceeds ~ 180–200 mg/dl, at which level all of the excess filtered glucose is excreted. In people with poorly controlled diabetes, either type 1 or type 2, the threshold (~ 180–200 mg/dl) at which glucose appears in the urine, as well as the maximum renal tubular glucose reabsorptive capacity (TmG), is markedly increased,[31–34] thereby contributing to the maintenance of hyperglycemia. Cultured human proximal renal tubular cells from patients with type 2 diabetes demonstrate increased SGLT-2 messenger RNA and protein concentrations, with a fourfold increase in the uptake of the nonmetabolizable glucose analog α-methyl-D-glucopyranoside (AMG).[35] In patients with diabetes, it would be desirable for the kidney to excrete the excessive filtered load of glucose in an attempt to restore normoglycemia. In contrast, the diabetic kidney responds to the ambient hyperglycemia by enhancing glucose reabsorption,[31–34] thereby contributing to the pathogenesis of glucose intolerance.

Ominous octet

Lastly, neurotransmitter dysfunction in the CNS plays a key role in the etiology of type 2 diabetes.[2,36] Under normal circumstances, insulin signals the brain to stop eating and decrease energy intake. Obese nondiabetic patients and obese patients with type 2 diabetes are markedly resistant to insulin, and their β-cells respond to the insulin resistance with a compensatory increase in insulin secretion. Despite the hyperinsulinemia, which should suppress appetite, obese people continue to overeat, indicating that the appetite centers also must be resistant to insulin, and, indeed, this has been demonstrated with functional magnetic resonance imaging.[36] There also is marked resistance to the appetite-suppressant effect of leptin in obese people with type 2 diabetes. Low dopamine levels in the hypothalamus and increased catecholamine levels in the CNS also contribute to the dysregulation of appetite and may directly cause insulin resistance in liver and peripheral tissues (muscle).[37,38]

Summary: pathophysiological disturbances

Recognition that multiple pathophysiological disturbances comprise the ominous octet has provided new insight into novel approaches for the treatment of patients with type 2 diabetes. In the following sections, we will review antidiabetic agents that have shown promise for the treatment of type 2 diabetes. Some of these are well along in phase 3 trials, whereas others are still in the preclinical phase of development. New rapid- and long-acting insulin preparations will not be discussed, except where they have been used in combination with GLP-1 receptor agonists.

GLP-1 Receptor Agonists

GLP-1 receptor agonists have many clinical benefits. They effectively reduce A1C, augment insulin secretion and preserve β-cell function, inhibit glucagon secretion by the α-cell, reduce the elevated basal rate of HGP, promote weight loss through their appetite-suppressant effect, delay gastric emptying,[26,39,40] and improve many cardiovascular risk factors, including dyslipidemia, hypertension, and endothelial dysfunction.[41] Not surprisingly, there exists considerable interest in the development of new agents in this class.

Lixisenatide (Sanofi) is a once-daily prandial GLP-1 receptor agonist that was approved by the European Medicines Agency (EMA) in February 2013[42,43] and, like exenatide, has its primary effect in lowering the postprandial rise in plasma glucose concentration.[43] A 13-week randomized, double-blind, placebo-controlled, dose-ranging study found that lixisenatide 20 µg administered once daily provided the best efficacy-to-tolerability ratio, with no additional benefits with any of the twice-daily doses.[44] Lixisenatide 20 µg once daily significantly improved glycemic control with low rates of hypoglycemia and beneficial weight effects when administered as monotherapy,[45] as add-on therapy to oral agents,[44,46–48] and in combination with basal insulin with or without oral antidiabetic therapy.[49,50] In a recent study, exenatide twice daily had a slightly better effect on glucose control than lixisenatide once daily within the established noninferiority margin of 0.3%.[51] Combination therapy with lixisenatide plus insulin glargine in a

fixed-combination administered as a single daily injection in an easy-to-use pen is in phase 2 development. Sanofi withdrew its lixisenatide application in the United States, citing the possibility that its ongoing cardiovascular study data could be shared publically, but it plans to resubmit the application when that trial is completed.

Liraglutide (Novo Nordisk), a once-daily GLP-1 receptor agonist, has been combined with insulin degludec, a long-acting basal insulin that is available in Europe, Japan, and many other countries. The combination, known as IDegLira, is administered once daily, reduces FPG and postprandial plasma glucose (PPG) levels, and lowers A1C by 1.9% in patients with type 2 diabetes with a starting A1C of 8.7%.[52,53] The decrement in A1C with IDegLira was greater than that with liraglutide alone (1.3%) or that with degludec alone (1.4%). Eighty-one percent of patients with type 2 diabetes treated with IDegLira achieved an A1C < 7.0% with weight loss and a reduced rate of hypoglycemia compared to those treated with insulin degludec. IDegLira currently is under review by the EMA.

Albiglutide (GlaxoSmithKline) is a GLP-1 receptor agonist developed by fusing a human GLP-1 dimer to recombinant human albumin.[54] Because of its long half-life, albiglutide is administered once weekly. In a 32-week trial in patients with type 2 diabetes, albiglutide reduced A1C by 0.78% from a starting A1C of 8.16% and decreased body weight by 0.64 kg.[55] These reductions were less than those observed with liraglutide, which decreased A1C by 0.99% and body weight by 2.19 kg. The drug's A1C-lowering and weight-reducing efficacy do not appear to be as robust as liraglutide, possibly because of albiglutide's inability to penetrate the CNS because of fusion with the large albumin molecule.

Despite their efficacy and durability in reducing A1C and promoting weight loss, new prescriptions for GLP-1 receptor agonists compromise < 5% of the U.S. market. This low market penetrance is accounted for by two factors: injection barrier and cost. To circumvent the injection barrier, Intarcia has developed a small, matchstick-sized osmotic pump (known as the ITCA 650) that is inserted subcutaneously just beneath the skin and delivers a slow, constant

rate of exenatide for up to 1 year. In a 48-week study, ITCA 650 delivering exenatide in doses of 20, 40, 60, and 80 µg/day reduced A1C by 1.0, 1.0, 1.5, and 1.4%, respectively, with weight loss of 6.0, 10.8, 7.7, and 7.9%, respectively.[56]

Dulaglutide (Eli Lilly) is a once-weekly GLP-1 analog fused with a human Fc antibody fragment. In a 52-week study, dulaglutide was more effective than exenatide twice daily, sitagliptin, and metformin.[57,58] Semaglutide (Novo Nordisk) is a once-weekly GLP-1 receptor agonist that is in phase 3 trials and preliminarily has been reported to have superior A1C-lowering efficacy compared to liraglutide at the 1.8 mg/day dose.[59]

Long-Acting DPP-4 Inhibitors
Currently, five DPP-4 inhibitors are approved in the United States and/or Europe: sitagliptin, saxagliptin, alogliptin, linagliptin, and vildagliptin. All but vildagliptin (administered twice daily) are administered once daily and cause 24-hour inhibition of the enzyme DPP-4, which degrades both GLP-1 and GIP. A once-weekly DPP-4 inhibitor, omarigliptin (MK-3105; 25 mg), is in development by Merck Sharp & Dohme[60] and, in a 12-week study, lowered A1C by a placebo-adjusted 0.71%.[61]

Insulin Secretagogues: TAK-875
Free fatty acid receptor 1 (FFAR-1, also called G protein coupled receptor 40 [GPR-40]) is a member of a superfamily of cell surface receptors whose expression is highest in pancreatic β-cells. Ligand binding (unsaturated medium- and long-chain fatty acids) of FFAR-1 activates a subunit of the Gq class of G proteins (Gαq), causing hydrolysis of the plasma membrane phospholipid, phosphatidylinositol bisphosphate, to generate diacylglycerol and inositol trisphosphate. Activation of FFAR-1 by fatty acids or synthetic ligands stimulates insulin secretion, but only in the presence of elevated glucose concentrations and via a pathway distinct from other glucose-dependent insulin secretagogues such as GLP-1 receptor agonists.[62]

In a phase 2 randomized, double-blind, placebo- and active-comparator–controlled, 12-week trial, TAK-875 (Takeda Pharmaceuticals) in doses ranging from 50 to 200 mg/day reduced A1C by 1.0–1.1% compared to 1.0% with glimepiride (4 mg once

daily) and 0.1% with placebo.[63] The incidence of hypoglycemia was similar in the TAK-875 and placebo groups. TAK-875 significantly increased the insulinogenic index (ΔCP0-30/ΔG0-30, in which CP = C-peptide and G = glucose) of β-cell function during the OGTT, whereas glimepiride had no effect on this index. Body weight increased slightly with TAK-875 (~ 0.3 kg) compared to glimepiride (~ 1.0 kg). Although demonstrating clinical efficacy, trials with TAK-875 recently were stopped because of concerns about hepatotoxicity. However, other GPR-40 agonists are in preclinical development.[64] Studies with some[65–67] but not with other[68,69] GPR-119 agonists, which act directly on the β-cell and enteroendocrine K- and L-cells to increase insulin and incretin secretion, respectively, have shown promise.

SGLT-2 and SGLT-1 Inhibitors
Recently, canagliflozin (Janssen), an SGLT-2 inhibitor with some, but clinically insignificant, SGLT-1 inhibitory action, was approved by the U.S. Food and Drug Administration (FDA). In a 52-week trial, canagliflozin was shown to be more effective than glimepiride[70] and sitagliptin.[71]

Dapagliflozin (AstraZeneca), a highly selective SGLT-2 inhibitor, is approved in Europe and, on 8 January 2014, was also approved in the United States by the FDA. In people with type 2 diabetes, dapagliflozin increases urinary excretion of glucose by ~ 70–80 g/day, similar to that observed with canagliflozin.[72,73] Dapagliflozin reduces the TmG in people with type 2 diabetes, but most importantly, it reduces the renal threshold at which glucose spills into the urine to ~ 40 mg/dl.[74] Like canagliflozin, dapagliflozin is effective in lowering both FPG and PPG concentrations, resulting in an A1C reduction of ~ 0.7–0.8% with a starting A1C of ~ 8.0–8.2%.[73,75] Reduction in the mean day-long plasma glucose concentration resulted in improved tissue sensitivity to insulin by 25–30% and enhanced β-cell function by 90–100%,[76] from correction of glucotoxicity. Like canagliflozin, dapagliflozin is equally effective in new-onset versus longstanding type 2 diabetes patients[77] and in severely insulin-resistant, as well as insulin-deficient, individuals treated with insulin.[78] Dapagliflozin can be added to the therapeutic regimen of patients with type 2 diabetes who are treated with metformin, pioglitazone, a DPP-4

inhibitor, a sulfonylurea (SU), or any combination thereof.[73,75] Dapagliflozin also can be added to insulin in patients with type 2 diabetes.[79]

Because sodium and glucose reabsorption are coupled in the proximal tubule, all SGLT-2 inhibitors, including dapagliflozin, reduce blood pressure by ~ 5–6/1–2 mmHg due to their mild natriuretic effect. The loss of glucose calories (70–80 g × 4 kcal/g = 280–320 kcal/day) in the urine is associated with a 2.5- to 3-kg weight loss after 12 months, and the weight loss persists for > 2 years.

The most common side effect observed with dapagliflozin and other SGLT-2 inhibitors is vulvovaginitis in female patients and balanitis primarily in uncircumcised males.[73,75] The incidence of urinary tract infection was slightly increased in dapagliflozin-versus placebo-treated patients with type 2 diabetes (4.3 vs. 3.7%). Volume depletion–related side effects (dizziness and hypotension) can occur and are more common in elderly patients and individuals treated with a diuretic. Hypoglycemia is uncommon with SGLT-2 inhibitors unless they are combined with an SU or insulin. Because of reduced efficacy, dapagliflozin is not approved for use in patients with an estimated GFR < 60 ml/min/1.73 m². By comparison, the efficacy of canagliflozin is modestly reduced in patients with an estimated GFR of 45–60 ml/min/1.73 m² and is not approved with an estimated GFR < 45 ml/min/173 m².

Empagliflozin (Boehringer Ingelheim/Eli Lilly) will be reviewed by the FDA in the first quarter of 2014, and, because of efficacy similar to canagliflozin and dapagliflozin and a paucity of side effects,[80,81] the FDA has waived review by an Endocrine Advisory Committee. Other SGLT-2 inhibitors in phase 2–3 trials include tofogliflozin (Chugai), ipragliflozin (Astellas), luseogliflozin (Taisho), and ertugliflozin (Pfizer/Merck).

All of the above inhibitors of renal glucose reabsorption are highly specific for SGLT-2. It is widely believed that SGLT-1 is responsible for the reabsorption of only ~ 10% of the filtered glucose load.[82] Within the GI tract, SGLT-1 is the transporter responsible for glucose absorption, and subjects genetically deficient in SGLT-1 develop glucose-galactose malabsorption associated with diarrhea. Furthermore, SGLT-1 is the transporter in the L-cell

that is responsible for GLP-1 release. For these reasons, pharmaceutical companies have been reluctant to develop a combined SGLT-2/SGLT-1 inhibitor. However, recent studies in combined SGLT-1/SGLT-2 knockout mice suggest that SGLT-1 is responsible for a much greater reabsorption of the filtered glucose load than previously appreciated.[83]

Studies in mice treated with the nonabsorbable SGLT-1 inhibitor LX 2761 (Lexicon) demonstrated reductions in FPG and PPG and a reduction in A1C of 0.7% with no GI side effects, no increase in glucosuria, and an increase in circulating levels of GLP-1 and peptide YY (PYY), hormones that suppress the appetite.[84] With respect to the increase in GLP-1, reduced GI absorption of glucose leads to increased distal delivery of glucose and short-chain fatty acids (produced by bacterial metabolism of glucose in the GI tract), both of which enhance GLP-1 and PYY secretion by the L-cell.

In humans, the combined SGLT-1/SGLT-2 inhibitor LX4211 (Lexicon) has been shown to increase urinary glucose excretion, delay intestinal glucose absorption, and increase circulating GLP-1 levels.[85,86] In a 28-day study in subjects with type 2 diabetes, LX 4211 produced modest glucosuria (less than typically seen with selective SGLT-2 inhibitors), yet decreased the FPG concentration by 52–68 mg/dl, suggesting a significant inhibitory effect on gut glucose absorption.[87] In a phase 2, 12-week study involving 299 patients with type 2 diabetes on metformin monotherapy, LX 4211 (400 mg) reduced A1C by 0.92% from a baseline of 8.1%.[88] These results, although preliminary, suggest that combined SGLT-1/SGLT-2 inhibitors may have advantages over selective SGLT-2 inhibitors.

NEW MET (Metformin-Delayed Release)
Metformin is the number-one prescribed oral antidiabetic agent in the United States and worldwide, yet its mechanism of action remains poorly understood.[89] Bioavailability of metformin is ~ 40–60%, and the biguanide is mainly absorbed in the upper small intestine. In diabetic rats, metformin lowers blood glucose levels acutely when given orally or intraportally, but not intravenously.[90] Plasma metformin levels correlate poorly

with the drug's glucose-lowering effect. Metformin is concentrated in the cells of the distal small intestine and has been shown to increase GLP-1 and PYY.[91] Collectively, these observations suggest that the glucose-lowering effect of metformin, at least in part, results from a pre-systemic effect on the enteroendocrine L-cells in the small intestine to release gut hormones.

Using a delayed-release formulation that escapes absorption in the upper small bowel, 20 healthy subjects and 24 patients with type 2 diabetes were treated with NEW MET (Elcelyx) for 5 days. NEW MET, 500 mg twice daily, was as effective in lowering plasma glucose concentrations as 2,000 mg of metformin immediate release and metformin extended release, despite a 45–68% reduction in plasma metformin exposure. All metformin preparations similarly increased plasma GLP-1 and PYY levels. In a recently completed 12-week phase 2 dose-finding trial, NEW MET (600, 800, and 1,000 mg/day) was compared to extended-release metformin (1,000 and 2,000 mg/day) in 240 patients.[92] NEW MET, 1,000 mg/day, was 50% more effective in reducing A1C than metformin extended release, 1,000 mg/day, despite plasma metformin levels that were 65% lower. These results demonstrate that NEW MET, which targets the lower bowel, effectively lowers A1C while minimizing metformin exposure. The lower plasma exposure may allow the use of NEW MET in patients with diabetes who have reduced renal function, and the small tablet size will facilitate double and triple combination antidiabetic preparations.

Insulin Sensitizers
The only insulin-sensitizing drugs available for the treatment of patients with type 2 diabetes are the thiazolidinediones (TZDs), which improve both muscle and hepatic insulin sensitivity.[2] Although metformin often is classified as an insulin sensitizer, we have shown that, in the absence of weight loss, it does not increase insulin-mediated glucose disposal in muscle.[93] Therefore, there is great interest in the development of novel insulin-sensitizing agents that are not associated with weight gain and fluid retention.

Mitochondrial target of TZDs
Emerging evidence suggests that the insulin-sensitizing, glucose-lowering

action of TZDs can be separated from their effect to serve as a ligand for peroxisome proliferator–activated receptor (PPAR)-γ.[94] MSDC-0160 and MSDC-0602 (Metabolic Solutions Development Company) have been shown to improve insulin resistance in multiple tissues, suppress hepatic gluconeogenesis and lipogenesis, reduce plasma glucose and insulin levels, and increase plasma adiponectin concentration in wild-type and PPAR-γ knockout mice.

Ongoing studies indicate that MSCD-0602 targets a previously uncharacterized mitochondrial complex (mitochondrial target of TZDs [mTOT]), which contains two well-conserved mitochondrial proteins (Mpc1 and Mpc2) that appear to modulate pyruvate entry into the mitochondria and regulate pyruvate oxidation.[95] In a 12-week phase 2b trial with 258 patients with type 2 diabetes, doses of 100 and 150 mg/day of MSDC-0160 were as effective as pioglitazone (45 mg/day) in reducing A1C and were associated with less fluid retention and weight gain.[96] Developers of a second mTOT-modulating compound recently have completed a phase 2a trial in patients with type 2 diabetes with similar results.[96]

Pyruvate dehydrogenase kinase inhibitors
The pyruvate dehydrogenase complex (PDC) catalyzes the irreversible oxidation of pyruvate, generating acetyl-CoA and carbon dioxide, and is a key enzyme controlling the rate of oxidative glycolysis. In its dephosphorylated form, PDC is active.[97] There are four pyruvate dehydrogenase kinase (PDHK) isoenzymes with tissue-specific distribution. Inhibition of PDHK-4 in muscle increases pyruvate oxidation in muscle and decreases the supply of gluconeogenesic precursors (lactate and alanine) to the liver, whereas inhibition of PDHK-2 in the liver decreases gluconeogenesis and the excessive rate of HGP that is characteristic of type 2 diabetes. Two PDHK inhibitors, AZD 2545 (Roche) and leelamine, have proven effective in lowering blood glucose levels in diabetic rodent models,[98] and JTT-251 (Japan Tobacco and Akros Pharma) shows promise in preclinical trials as a PDHK inhibitor for the treatment of type 2 diabetes.

Protein tyrosine phosphatase 1B inhibitors

Insulin initiates its stimulatory action on glucose metabolism by causing phosphorylation of three tyrosine residues on the insulin receptor.[2,99] This sets into motion a series of phosphorylation-dephosphorylation reactions whereby insulin receptor substrate 1 (IRS-1) translocates to the cell membrane, where it undergoes phosphorylation on contiguous tyrosine molecules.[2] This results in activation of phosphoinositol-3-kinase, Akt, and other insulin-signaling molecules, leading to glucose transport into the cell and subsequent metabolism. Mutagenesis of any of the three tyrosine residues on the insulin receptor impairs insulin action and mutagenesis of all three tyrosine residues simultaneously renders the insulin receptor inactive.

Because insulin receptor tyrosine phosphorylation is reduced in people with type 2 diabetes,[2,20] it makes sense to increase tyrosine phosphorylation with protein tyrosine phosphatase 1B inhibitors.[100,101] In mice, genetic ablation of protein tyrosine phosphatase 1B (PTP-1B) results in enhanced insulin sensitivity.[102] ISI-113175 (ISIS Pharmaceuticals), an antisense oligonucleotide PTP-1B inhibitor (100–200 mg injected weekly), has completed a phase 2 trial in patients with type 2 diabetes on stable, maximal doses of SU. After 13 weeks, the 200 mg/week cohort reported a 25 mg/dl decrease in average weekly fasting self-monitoring of blood glucose values ($P = 0.026$ vs. placebo) and a 25 µmol/l decrease in serum fructosamine ($P = 0.009$ vs. placebo). A significant 65% increase in adiponectin was noted with ISI-113175.[103]

Fibroblast growth factor-21

Fibroblast growth factor (FGF)-21 is a secreted protein that is produced in liver and adipose tissue and has been shown to enhance insulin sensitivity, reduce plasma glucose levels, and improve the lipid profile in preclinical models of diabetes and obesity. FGF-21 links FGF receptors to the Ras/mitogen-activated protein (MAP) kinase pathway and stimulates glucose uptake into adipocytes.[104] In a recent dose-finding study, an analog of FGF-21, LY 2405319 (Eli Lilly), was administered to 46 obese patients with type 2 diabetes for 28 days. FPG and insulin concentrations declined significantly, total LDL cholesterol and triglycerides decreased by 10–20%, HDL cholesterol increased significantly,[105,106] and plasma adiponectin, an insulin-sensitizing adipocytokine, increased. Weight decreased by 1.5–1.7 kg, although the decrease was not significant. Although the precise mechanisms via which FGF-21 exerts its beneficial effects on glucose and lipid metabolism in type 2 diabetes remain to be established, the drug appears to have a novel mechanism of action and may prove effective as a glucose- and lipid-lowering drug.

11-β-Hydroxysteroid dehydrogenase-1 inhibitors

11-β-Hydroxysteroid dehydrogenase-1 (11-β-HSD-1) enhances the conversion of cortisone (inactive) to cortisol (active) in the liver and adipose tissue without disturbing the pituitary (ACTH)-adrenal axis. In genetically obese hyperglycemic mice, 11-β-HSD-1 inhibitors improve insulin sensitivity, hyperglycemia, and the plasma lipid profile. In the past decade, many 11-β-HSD-1 inhibitors have been designed, synthesized, and tested in clinical trials.[107,108] The glucose-lowering effect of this class of antidiabetic agents has been modest. In a 28-day phase 2b trial with INCB 13739 (Incyte), there was a trend for the FPG concentration to decline (–19.5 mg/dl), and insulin-mediated glucose disposal and suppression of HPG (euglycemic insulin clamp technique) demonstrated a tendency to increase.[109] However, in another study, no improvement in insulin sensitivity was observed in diet-treated patients with type 2 diabetes treated with carbenoxolone.[110] In a phase 3 trial in 80 patients with type 2 diabetes and metabolic syndrome, MK-0916 (Merck) reduced A1C modestly ($P < 0.05$) without significant reduction in fasting or 2-hour plasma glucose concentrations during OGTT.[111] Two new 11-β-HSD-1 inhibitors, RO151 and RO838 (Hoffman-LaRoche), showed a tendency for A1C to improve without change in any lipid parameters.[112] Currently, Boehringer Ingelheim also has an 11-β-HSD-1 inhibitor in active clinical trials.

Diacylglycerolacyl Transferase-1 Inhibitors

There are two isoenzymes of diacylglycerolacyl transferase (DGAT). DGAT-1 catalyzes the formation of triglycerides from diacylglycerol (DAG) and acyl-CoA, the terminal and committed step in triglyceride synthesis. By inhibiting DGAT-1 in the GI tract, postprandial hyperlipidemia can be reduced and has been shown to be associated with insulin sensitization, reduction in liver triglycerides, and weight loss in preclinical studies.[113] In a 1-week, randomized, placebo-controlled study in 62 obese male subjects, AZD 7687 (Roche) produced a consistent dose-dependent reduction in postprandial plasma triglyceride excursion, indicating inhibition of gut DGAT-1 activity.[114] However, marked GI side effects, mainly diarrhea, occurred at drug doses that inhibited triglyceride excursions by ≥ 250%. Further concern about this approach is the observation that DGAT-1 inhibition increases muscle levels of DAG and ceramide, two fatty acid derivatives shown to cause insulin resistance.[115] Moreover, DGAT overexpression in skeletal muscle lowered levels of lipotoxic fatty acid derivatives, inhibited triglyceride synthesis, enhanced fatty acid oxidation, and improved insulin-mediated muscle glucose disposal.[115]

Anti-Inflammatory Therapies

In type 2 diabetes, adipose tissue is in a state of chronic inflammation,[116] and adipose tissue hypoxia plays a central role in this inflammatory process.[117] In addition to adipose tissue hypoxia, metabolites of FFA and glucose, including DAG, ceramide, and reactive oxygen species (ROS), contribute to the chronic inflammation in obesity by directly activating signaling kinases (protein kinase C, c-Jun N-terminal kinase [JNK], and insulin receptor kinase) and stimulating cell membrane receptors (TLR4, CD36) involved in inflammation and by inducing endoplasmic reticulum stress.[118,119] Thus, inhibition of these inflammatory pathways has been suggested as a strategy to improve insulin sensitivity, lower plasma glucose levels, and prevent or slow the atherosclerotic process in people with type 2 diabetes. Of the anti-inflammatory agents, high-dose salicylates have been the most extensively studied.

The IKKβ/NF-κB (inhibitor of NF-κB kinase subunit β/nuclear-factor κβ) pathway is a potent inflammatory pathway that is activated by FFA, lipotoxic metabolites, ROS, and endoplasmic reticulum stress. IKKβ causes

NF-κB activation by phosphorylating the inhibitor of κβα (Iκβα), leading to its dissociation from NF-κB in the cytosol. NF-κB is a transcription factor that then translocates into the nucleus where it activates genes controlling the synthesis of tumor necrosis factor-α and other serine kinases that inhibit insulin signaling and cause insulin resistance.[119–121] High-dose salicylates inhibit the activity of IKKβ[122] and ameliorate muscle insulin resistance and reduce HGP in rodent models of diabetes.[123,124]

In a large National Institutes of Health (NIH)-sponsored, randomized trial (Targeting Inflammation Using Salsalate in Type 2 Diabetes) involving 286 patients with type 2 diabetes, salsalate (3.5–4 mg/day) lowered A1C by 0.33% ($P < 0.01$ vs. baseline and placebo).[125] Although promising, the reduction in A1C was not sufficiently great to warrant continuation of the study. It should be emphasized, however, that many inflammatory pathways are activated in diabetes and obesity, and inhibition of a single pathway may not be sufficient to produce a clinically meaningful reduction (≥ 0.5%) in A1C. Thus, combined inhibition of the IKKβ/NF-κB beta pathway with simultaneous inhibition of the MAP kinase, JNK, TLR4, or other pathways[119] may be required to produce a greater reduction in A1C.

Glucagon Receptor Antagonists

It is well known that plasma glucagon levels are elevated in type 2 diabetes and that the liver is hypersensitive to glucagon.[28,29] Moreover, reduction of plasma glucagon concentration with somatostatin, while maintaining basal plasma insulin levels, has been shown to normalize the elevated basal rate of HGP and FPG concentration in hyperglycemic patients with type 2 diabetes.[27] Inhibition of glucagon secretion with resultant reduction in HGP represents a major mechanism via which both DPP-4 inhibitors and GLP-1 receptor agonists improve glycemic control in type 2 diabetes. This has led to the development of glucagon receptor antagonists, which, in diabetic animal models, have been proven to effectively lower the elevated basal rate of HGP and FPG concentration.[126]

A number of orally administered glucagon receptor antagonists have been synthesized. A major concern about this class of drugs is the resultant pancreatic α-cell hyperplasia and chronically elevated plasma glucagon levels. However, glucagon receptor antagonists that lower blood glucose levels without severe α-cell hypertrophy and only a moderate increase in plasma glucagon concentration have been developed.[127] In phase 2 studies, both MK-0893 and MK-3577 (Merck) have been shown to have robust A1C-lowering efficacy,[128] but studies with these agents have been discontinued because of a rise in LDL cholesterol. In a 24-week study, LY 2409021 (Eli Lilly) 20 mg/day reduced A1C by 0.92%, but elevation in hepatic aminotransferases, although modest, may limit the drug's clinical usefulness.[129]

Glucokinase Activators

Glucokinase is the enzyme that mediates the phosphorylation of free glucose after entry into the cell. Because of its high Km, the enzyme can rapidly respond to an increase in plasma glucose concentration. In the β-cell, a specific glucokinase is the rate-limiting step for glucose metabolism and thus for insulin secretion, whereas in the liver, a different glucokinase responds to an increase in ambient glucose levels by augmenting glycogen synthesis and inhibiting HGP. The clinical importance of glucokinase is highlighted by inactivating mutations, which are responsible for maturity-onset diabetes of the young type 2. The unique features of glucokinase and its central role in the regulation of insulin secretion and HGP have led to a search for activators of the enzyme in β-cells, hepatocytes, or both.[130]

More than 100 patents for glucokinase activators have been filed, but results to date have been disappointing. Initial encouraging results were observed with Roche and Merck glucokinase activators, but the efficacy waned over time, leading to discontinuation of the clinical development programs. A similar waning of efficacy has been observed with AZ D1656 (AstraZeneca) in a 6-month trial and with AMG 151 (Amgen; previously Bio Array-403). A novel, hepatic-specific activator, TTP 399 (Trans Tech Pharm), which does not interfere with binding of glucokinase to the glucokinase regulatory protein, has shown promise in a 6-week phase 2a study in people with type 2 diabetes, reducing A1C by 0.92% versus baseline and 0.53% versus placebo.[131] However, the treatment period was short, and the results of longer-term studies are awaited.

Despite these largely negative results, it is anticipated that the development of novel glucokinase activators will continue because of the pivotal role of the enzyme in the regulation of glucose homeostasis. Two recent studies[132–134] in patients with type 2 diabetes with hepato-specific glucokinase activators (GKM-001 [Advinus Therapeutics] and PF-04991532 [Pfizer]) have shown glucose-lowering efficacy, but the studies were of short duration (14 days) and contained a small number of subjects.

Fructose-1,6-Bisphosphatase Inhibitors

The bidirectional enzyme fructose 1,6-biphosphatase (FBPase) catalyzes the conversion of fructose-1, 6-bisphosphate to fructose-6-phosphate and back to fructose-1,6-bisphosphate and plays a central role in the regulation of glycolysis (forward reaction) and gluconeogenesis (reverse reaction). When Ser32 of the bifunctional protein is phosphorylated, the negative charge causes a conformational change of the enzyme to favor FBPase activity; otherwise, phosphofructokinase 2 activity is favored.[135] In patients with type 2 diabetes, the basal rate of HGP is increased because of an accelerated rate of gluconeogenesis.

In animal models of type 2 diabetes, inhibition of FBPase effectively lowers HGP from a variety of gluconeogenic substrates without causing hypoglycemia.[136,137] Preliminary results with MB07803 (Metabasis Therapeutics) in a 14-day study in 42 patients with type 2 diabetes demonstrated a modest reduction in FPG concentration.[138] Safety concerns about hypoglycemia and lactic acidosis may limit the clinical usefulness of FBPase inhibitors or other drugs that block gluconeogenesis in hepatoctyes.

Acetyl-CoA Carboxylase Inhibitors

Acetyl-CoA carboxylase (ACC) catalyzes the irreversible carboxylation of malonyl-CoA for the biosynthesis of fatty acids. Circulating FFAs and increased levels of intracellular lipotoxic metabolites of fatty acids (FACoAs, DAG, and ceramides) cause insulin resistance in liver and skeletal muscle and inhibit insulin secretion.[2] Not surprisingly, the ACC inhibitor NDI-630 (Nimbus) has been shown to enhance insulin sensitivity, lower

plasma FFA and glucose levels, and correct dyslipidemia in animal models of obesity and type 2 diabetes.[139]

Other Oral Antidiabetic Therapies

A variety of other oral antidiabetic therapies have shown some promise in improving glycemia in type 2 diabetes, including bile acid sequestrants,[140] activators of the bile acid farnesoid X receptor,[141] AMPK activators,[142–144] modulators of the gut microbiota,[145] activators of glycogen synthase,[146] inhibitors of glycogen phosphorylase,[147] and ranolazine.[148] Ranolazine currently is approved by the FDA as an antianginal drug that works by inhibiting the late sodium current in cardiac myocytes. How this is related to the decrease in A1C observed in patients with type 2 diabetes is unclear, although, at higher doses than achieved clinically, ranolazine has been shown to inhibit fatty acid oxidation. In vitro studies have demonstrated that ranolazine inhibits glucagon secretion by the pancreatic α-cells by inhibiting sodium channels.[149,150]

In preclinical studies, activation of the protein deacetylase SIRT1 with SRT3025 has been shown to promote weight loss, inhibit hepatic gluconeogenesis and lipogenesis, and enhance insulin sensitivity.[151] Whether similar results will be observed in humans remains to be seen. Most recently, obeticholic acid (OCA) has been shown to be effective in treating nonalcoholic fatty liver disease (NAFLD) in an NIH-sponsored trial and to improve insulin sensitivity in people with type 2 diabetes and NAFLD. This has raised interest in the use of OCA to treat patients with type 2 diabetes.

Anti-Obesity Medications

The current diabetes epidemic is being driven by the obesity epidemic, which represents a state of tissue fat overload. Accumulation of lipotoxic metabolites in the β-cell inhibits insulin secretion, whereas increased levels of FACoA, DAG, and ceramides in the liver and muscle cause insulin resistance.[2,119] Recently, Qsymia (combination phentermine/topiramate XR) and Belviq (lorcaserin) have been approved by the FDA as treatments for weight loss in obese individuals. Lorcaserin is a selective 5-hydroxytryptamine 2C (serotonin) agonist that decreases food intake through the proopiomelanocortin system. Phentermine is a sympathomimetic appetite-suppressing drug, whereas topiramate is a γ-aminobutyric acid receptor modulator, although its mechanism of action in promoting weight loss is poorly understood.

In the Behavioral Modification and Lorcaserin for Obesity and Overweight Management in Diabetes Mellitus trial,[152] lorcaserin reduced body weight by ~ 5% and mean A1C by ~ 1.0%, even though the use of diabetes medications was decreased. In the 2-year SEQUEL study,[153] phentermine/topiramate reduced body weight by ~ 10%, and, in the subset of obese patients with type 2 diabetes, it decreased A1C more than placebo with fewer increases in diabetes medications. Progression to type 2 diabetes was significantly reduced (0.9 vs 3.7%, $P < 0.001$) in nondiabetic patients treated with phentermine/topiramate.[153]

At present, it is unclear whether either lorcaserin or combination phentermine/topiramate have antidiabetic actions beyond their weight loss effect. Nonetheless, these weight loss medications are effective in improving glycemic control in obese patients with type 2 diabetes.

Conclusion

Multiple pathophysiological disturbances comprise type 2 diabetes. It is imperative that agents continue to be developed as the epidemic of diabetes continues and is likely to worsen during the next several decades. Promising agents have been, and continue to be, developed. Some are variations on therapeutic classes already available (GLP-1 receptor agonists, DPP-4 inhibitors, SGLT-2 inhibitors, metformin, TZDs/mTOTs modulators, and bile acid sequestrants), some are anti-obesity drugs that may hold promise for type 2 diabetes (phentermine/topiramate and lorcaserin), and others are unique classes that may or may not come to fruition for the treatment of diabetes in the future (PDHK inhibitors, PTP-B inhibitors, FGF-21 analogs, 11-β-HSD-1 inhibitors, DGAT-1 inhibitors, glucagon receptor antagonists, glucokinase activators, FBPase inhibitors, ACC inhibitors, anti-inflammatory medications, AMPK activators, and modulators of gut microbiota). Time will illuminate the potential for each drug candidate, although it is clear that the pipeline for diabetes pharmacotherapies is robust.

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