Current and Emerging Treatment Options in Diabetes Care

Christoffer Clemmensen, Timo D. Müller, Brian Finan, Matthias H. Tschöp, and Richard DiMarchi

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References
Abstract

Diabetes constitutes an increasing threat to human health, particularly in newly industrialized and densely populated countries. Type 1 and type 2 diabetes arise from different etiologies but lead to similar metabolic derangements constituted by an absolute or relative lack of insulin that results in elevated plasma glucose. In the last three decades, a set of new medicines built upon a deeper understanding of physiology and diabetic pathology have emerged to enhance the clinical management of the disease and related disorders. Recent insights into insulin-dependent and insulin-independent molecular events have accelerated the generation of a series of novel medicinal agents, which hold the promise for further advances in the management of diabetes. In this chapter, we provide a historical context for what has been accomplished to provide perspective for future research and novel emerging treatment options.

Keywords

Co-agonist · Combination therapies · Diabetes · Glucose · Insulin · Metabolism · Obesity · Pharmacology · Therapeutics

1 Introduction

Globally, diabetes affects more than 387 million people and is an escalating threat to personal health and national economies (Guariguata et al. 2014; IDF 2014). In 2014 alone, ca. 5 million patients died as a consequence of diabetes (IDF 2014). As a result, the development of safe and effective treatment options has become an international enterprise. Type 1 diabetes (T1D, representing ca. 10% of diabetes cases) and type 2 diabetes (T2D, representing ca. 90% of diabetes cases) constitute the majority of the disease and are generally viewed as two different, yet biologically related disorders. T1D is an autoimmune disease with a prominent genetic component, and T2D is an age- and lifestyle-related disease associated with obesity and inactivity (Kahn et al. 2006; van Belle et al. 2011). Despite having different etiologies, T1D and T2D lead to similar metabolic dysfunctions and long-term complications. One hallmark of diabetes is an absolute or relative lack of insulin, which leads to an increase in plasma glucose levels. If left uncontrolled, diabetes induces multiple acute and chronic complications such as ketoacidosis, kidney failure, heart disease, retinopathy, and various vascular complications (Kahn et al. 2006; van Belle et al. 2011).

T2D currently accounts for ~90% of diabetic cases (Scully 2012) and most T2D patients will eventually require insulin replacement therapy at a later stage of the disease. A deeper molecular understanding of T2D pathophysiology has facilitated a number of medicinal strategies that hold promise to prevent, intervene in, or halt the progression of the disease. Substantial evidence implicates insulin-independent mechanisms with an array of circulating factors, as well as the brain’s powerful...
glucoregulatory control in glucose disposal as part of the disease (Schwartz et al. 2013). These insights, combined with a deeper understanding of insulin-dependent and insulin-independent molecular events, have accelerated the generation of novel pharmacotherapies for the treatment of T2D. The aim of this chapter is to present a mechanism-based analysis of the therapeutic benefits and pitfalls associated with different classes of medicines for both types of diabetes and an orientation to novel emerging treatment options.

2 Regulation of Glucose Metabolism

2.1 Peripheral Control of Glucose Metabolism

For almost a century, research on glucose homeostatic processes has predominantly focused on the role of peripheral control mechanisms, most notably the role of pancreatic islets as the key organ for regulating glycemic control (Weir and Bonner-Weir 2004). The prevailing dogma is that a meal-induced rise in blood glucose stimulates beta cells in the endocrine pancreas to secrete insulin. Insulin lowers this postprandial glucose surge by acting on the energy-storing organs, such as skeletal muscle and adipose tissue, to facilitate uptake of glucose and to suppress glucose output via inhibition of hepatic gluconeogenesis (Fig. 1a). Conversely, in fasted and hypoglycemic states, the pancreatic alpha cells secrete glucagon, which stimulates hepatic glucose production and opposes the actions of insulin. Under non-diseased physiological conditions, these processes efficiently maintain blood glucose levels within a relatively narrow and stable range (Unger and Cherrington 2012).

Half a century ago, it was discovered that oral ingestion of glucose elicits an enhanced insulin response relative to that of an intravenous glucose infusion (Elrick et al. 1964; McIntyre et al. 1964). This observation, subsequently termed “the incretin effect,” introduced the gut as a metabolically relevant endocrine organ and led to the identification and glucoregulatory impact of many gut-derived peptides (Baggio and Drucker 2007). Thus, in the 1970s and 1980s, the most prominent incretin hormones glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) were identified and their ability to augment glucose metabolism delineated (Dupre et al. 1973; Schmidt et al. 1985). Both GIP and GLP-1 are secreted from the gut in response to ingested nutrients and exhibit insulinotropic actions at pancreatic beta cells, contributing to postprandial glucose homeostasis (Fehmann et al. 1995).

In addition to insulin, glucagon, and the incretin hormones, other humoral factors including epinephrine (adrenaline), glucocorticoids, and growth hormone can impact glucose homeostasis (Gerich 1993). More recently, the field has enlarged with the realization of the glucoregulatory role of an array of more recently discovered factors including fibroblast growth factors (FGFs) (Kharitonenkov et al. 2005), cytokines (Fernandez-Real et al. 1998), and peptides...
Fig. 1 Schematic overview of normal and pathological glucose homeostasis. Plasma glucose levels are regulated by coordinated interactions between brain- and islet-related mechanisms, involving both insulin-dependent and insulin-independent pathways. (a) Under normal conditions,
secreted from muscle (Steensberg et al. 2000), fat (Hotta et al. 2001), and bone (Booth et al. 2013).

### 2.2 Central Control of Glucose Metabolism

A growing body of evidence has established that the brain directly affects glucose homeostasis through both insulin-dependent and insulin-independent mechanisms (Fig. 1a) (Kleinridders et al. 2014; Schwartz et al. 2013). The mechanisms underlying the ability of centrally acting hormones to lower blood glucose in diabetic animal models are still under investigation but hypothesized to implicate lowering of hepatic glucose production while increasing glucose uptake in skeletal muscle and brown adipose tissue (Rojas and Schwartz 2014; Schwartz et al. 2013). Thus, glucose homeostasis is likely controlled by complex and coordinated interactions between brain-, gut-, and islet-related biological systems. Importantly, as indicated above, our understanding of how factors secreted from other peripheral tissues feed into the major glucoregulatory systems is now starting to be revealed.

### 3 Pathogenesis and Pathophysiology of Diabetes

#### 3.1 Type 1 Diabetes

T1D is an autoimmune disorder in which the insulin-producing beta cells of the pancreas are selectively destroyed by autoreactive T cells (van Belle et al. 2011). The autoreactive T cells have been shown to recognize islet autoantigens including insulin, glutamic acid decarboxylase (GAD), and zinc transporter 8 (ZnT8) (Bluestone et al. 2010). Eventually, the depleted pancreatic beta-cell function cannot sustain sufficient insulin to maintain euglycemia, and the patients ultimately require insulin replacement therapy. The etiology and pathophysiology of the autoimmunity preceding the diagnosis of T1D are influenced by a combination of genetic and environmental factors (van Belle et al. 2011). Despite a growing understanding of T1D pathogenesis, the driving immune triggers orchestrating the attack of the beta cells remain enigmatic. Autoantibodies can be detected before the clinical onset of T1D. However, the gap between early biochemical alterations and the clinical manifestation complicates the elucidation of causative environmental triggers (van Belle et al. 2011). Until now, environmental triggers proposed to be involved...
in the disease pathogenesis include viruses, bacteria, and nutrients (Knip et al. 2005). Unraveling how these stimuli might interact with specific molecular targets to initiate the autoimmune cascade is crucial for intervening as early as possible in order to preserve functional beta-cell mass.

3.2 Type 2 Diabetes

Historically, T2D was considered an age-related disease linked to a sedentary lifestyle and hypercaloric diet. It is now acknowledged that genetic factors also play a prominent role for the onset and progression of the disease (Kahn et al. 2012). T2D is a progressive disorder with a pathogenesis that involves a reciprocal interplay of persistent increases in insulin demand and its subsequent production. Insulin resistance is the most well-defined pathological gateway to T2D (Martin et al. 1992) and frequently coincides with excess adipose tissue mass and ectopic lipid deposition in tissues involved in glucose disposal (Kahn et al. 2006).

Insulin resistance results from a reduced response of cells in adipose tissue and skeletal muscle to stimulate insulin-mediated glucose uptake as well as a blunted response of cells in the liver to shut down hepatic glucose production. Under normal circumstances, pancreatic beta cells balance the loss of insulin sensitivity by increasing insulin production and release (Fig. 1b). This compensation by pancreatic beta cells often prevents hyperglycemia despite the prevailing insulin-resistant state. However, it is only upon failure of beta cells to fully compensate for the increased insulin demand that hyperglycemia and T2D ensue (Fig. 1c) (Kahn 2003). This loss of beta-cell plasticity is not solely a consequence of cellular loss but also reflects reduced functionality and an impaired response to insulin secretagogues (Kahn 2003). In parallel, without insulin to act as a brake on glucagon secretion from pancreatic alpha cells, elevated glucagon levels and hepatic insulin resistance lead to uncontrolled hepatic glucose production (Fig. 1c). These reciprocal events intensify the metabolic rearrangements and an ever-escalating glucotoxicity that eventually exhausts beta-cell function to amplify the disease cascade (D’Alessio 2011). Additionally, the altered islet biology may impact the glucoregulatory capacity of the brain, which may be further deranged in obese subjects in which central leptin resistance coincides with hampered insulin control (Morton and Schwartz 2011). Ultimately, late-stage, insulin-deficient T2D patients require insulin supplementation to maintain euglycemia.

4 Current Treatments for Diabetes

The primary goal of antidiabetic treatment is to restore or improve glucose control. Hemoglobin A1c (HbA1c) is a biochemical marker that reflects chronic improvements in plasma glucose levels and is frequently employed for the clinical evaluation of therapeutic efficacy (Bonora and Tuomilehto 2011). As outlined above, T2D manifests in numerous states of impaired insulin function, and it is
the failure of the beta cells to secrete sufficient insulin to compensate for the defect that results in hyperglycemia. Accordingly, drugs that can enhance insulin sensitivity as well as compounds that can amplify insulin secretion may serve to improve glycemic control (Cefalu 2007). Current antidiabetic pharmacotherapy primarily consists of insulin, biguanides, sulfonylureas, thiazolidinediones, alpha-glucosidase inhibitors, incretin enhancers, GLP-1 analogs, amylin analogs, sodium-glucose co-transporter 2 inhibitors (SGLT2 inhibitors), and bile acid sequestrants. This multitude of antidiabetic therapeutics allows for a degree of personalized treatment that can be tailored to the glycemic status of each patient. However, each class of drugs is associated with specific efficacy shortcomings and safety concerns that need to be accounted for when selecting a pharmacotherapy. Furthermore, diabetics (in particular T2D) frequently suffer from comorbidities such as cardiovascular disease and obesity, which may complicate treatment and limit therapeutic options.

Insulin replacement therapy is indispensable for T1D patients. Also, patients suffering from T2D may eventually require exogenous insulin to maintain glycemic control (Fonseca and Haggar 2014). Much progress has been made since the initial discovery of insulin. Insulin analogs with diverse pharmacokinetic properties are now available and employed to tailor individualized regimens in personalizing glycemic control (Fonseca and Haggar 2014). Insulin-induced hypoglycemia is typically not a risk factor for diabetics suffering from insulin resistance, and for T1D patients, the development of insulin analogs with more “peakless” profiles has helped to lower the risk of treatment-induced hypoglycemia (Fonseca and Haggar 2014). Insulin is frequently employed to support the therapeutic efficacy of other antidiabetic compounds including metformin, TZDs, and incretin-based therapies (Barnett 2013; Wulffele et al. 2002). The pharmacological efficacy of these compounds may be significantly hampered if sufficient insulin is not available to support their independent molecular action.

Having the highest benefit-risk profile compared to other available medications, metformin is the most frequently used biguanide and the first-in-line oral therapy for treating T2D (Bennett et al. 2011). Metformin reduces fasting glucose levels by inhibiting hepatic glucose output and stimulating uptake and utilization of glucose in skeletal muscle (Bailey and Turner 1996; Viollet et al. 2012). The underlying cellular mechanisms of action are being investigated but remain somewhat elusive to date (Viollet et al. 2012). Metformin is often used in combination with drugs that can complement its pharmacological profile, such as insulin secretagogues or insulin sensitizers (Bennett et al. 2011). Interestingly, diabetics treated with metformin have a relatively lower risk of developing cancers as compared to patients treated with insulin or sulfonylureas (Bowker et al. 2006). This protective effect is sustained in combination therapies involving metformin (Currie et al. 2009). The most common adverse effects associated with metformin treatment are dose-related gastrointestinal disturbances.

Thiazolidinediones (TZDs) bind to and activate the peroxisome proliferator-activated receptor gamma (PPARγ) to enhance insulin sensitivity and reduce hyperglycemia (Hauner 2002; Saltiel and Olefsky 1996). TZDs exert a number of pleiotropic effects, such as reducing circulating levels of pro-inflammatory cytokines...
and increasing adiponectin levels, which may add to the insulin-sensitizing effects associated with their usage (Defronzo et al. 2013; Hauner 2002; Tonelli et al. 2004). However, PPARγ is abundantly expressed in fat cells (also in the muscle and liver), and activation by TZDs initiates a lipogenic transcriptional signaling and the most common adverse effect associated with TZDs – weight gain (Fonseca 2003; Smith et al. 2005). Further, an increased risk of congestive heart failure has been associated with the use of TZDs (Hernandez et al. 2011). The FDA has approved adjunctive therapy with TZDs in combination with metformin, insulin, sulfonylureas, and glinides (Derosa and Sibilla 2007; Fuchtenbusch et al. 2000).

Sulfonylureas and glinides improve glycemia by enhancing insulin secretion (Blickle 2006; Proks et al. 2002). Both compounds bind to an ATP-dependent K+ channel, albeit at different sites, expressed on the pancreatic beta-cell membrane. This leads to a membrane depolarization and calcium-mediated insulin secretion (Melander 2004; Proks et al. 2002). The major adverse risk associated with their usage is hypoglycemia (Melander 2004). Moreover, as with TDZs, sulfonylureas and glinides stimulate adiposity and lead to weight gain (Liu et al. 2012).

Inhibitors of dipeptidyl peptidase-IV (DPP-IV), the enzyme responsible for degrading GLP-1, are referred to as incretin enhancers, whereas incretin mimetics refers to the group of synthetic analogs of GLP-1. GLP-1 signals through its receptor on pancreatic beta cells to promote glucose-stimulated insulin secretion. Unlike sulfonylureas, which cause nonspecific insulin secretion, there is little hypoglycemic risk with treatment of incretin-based therapies. They only promote glucose-stimulated insulin secretion, thus offering an internal buffering capacity due to their mechanism of action. While GLP-1 analogs promote clinically relevant, albeit modest, weight loss, DPP-4 inhibitors present a weight-neutral profile (Foley and Jordan 2010; Nathan et al. 2009). GLP-1R agonists may improve cardiovascular risk factors; however, dose-dependent adverse gastrointestinal events and nausea are linked to their usage (Aroda and Ratner 2011; Kanoski et al. 2012).

Alpha-glucosidase is an enzyme involved in the intestinal degradation of complex carbohydrates. Specific enzyme inhibitors protect against postprandial hyperglycemia by delaying carbohydrate absorption in the proximal gut (Lebovitz 1997). However, the interference with nutrient absorption induces gastrointestinal side effects, which have limited their usage. Further, the impact on HbA1c levels is modest, and the alpha-glucosidase inhibitors are less effective in lowering glycemia than metformin and sulfonylureas (Bolen et al. 2007; van de Laar et al. 2005).

The peptide amylin is synthesized in the pancreatic beta cells and co-secreted with insulin in response to a meal (Butler et al. 1990; Moore and Cooper 1991). The administration of amylin analogs is purported to inhibit glucagon secretion from the islet alpha cells leading to a decrease in postprandial glucose excursions (Kruger and Gloster 2004). The reduction in glucagon secretion assists in attenuating hepatic glucose production. Further, amylin analogs slow gastric emptying, elicit hypophagia, and are associated with weight loss (Roth 2013). The effect of amylin-based therapy as measured by HbA1c lowering is modest (Ratner et al. 2004). Consequently, amylin has been approved as adjunctive therapy with insulin for patients who have not achieved glycemic control with insulin monotherapy (Ryan et al. 2005;
Amylin decreases body weight in both diabetics and nondiabetics and is currently being investigated for its antiobesity potential (Inzucchi and McGuire 2008; Sadry and Drucker 2013).

Recently, pharmacological inhibitors of sodium-glucose co-transporter 2 (SGLT2) were approved for the treatment of T2D (Elkinson and Scott 2013). Blocking SGLT2 lowers the reabsorption of renal glucose excretion and thus reduces circulating glucose levels (Ferrannini and Solini 2012). Chronic administration lowers HbA1c levels by 0.5–1.5% without the risk of causing hypoglycemia (Nauck 2014). The somewhat distinctive mechanism of action of SGLT2 inhibitors implies a therapeutic opportunity for adjunctive administration with an insulin secretagogue or sensitizing agent. Common adverse events include genital and urinary tract infections; however, more serious safety concerns pertaining to increased cancer risk have recently been raised (Nauck 2014).

Bile acid sequestrants (BASs) were originally developed for treating dyslipidemia (Handelsman 2011). Importantly, BASs were shown to reduce hyperglycemia in patients with coexisting diabetes and dyslipidemia (Garg and Grundy 1994). The glucose-lowering mechanism of BASs remains elusive but seems to involve increasing the circulating bile acid pool, subsequent activation of bile acid receptors such as the farnesoid X receptor (FXR) or Takeda G protein-coupled receptor 5 (TGR5), and the resulting endogenous release of GLP-1 and/or FGF19 (Hylemon et al. 2009). The efficacy of BASs to concurrently improve HbA1c and LDL cholesterol makes them an attractive add-on to the existing glucose-lowering agents. Thus far, reported adverse events associated with their usage primarily relate to mild gastrointestinal discomfort (Handelsman 2011).

As a function of time, the majority of T2D patients receive more than one type of medication (Bailey 2013; Bennett et al. 2011), and designing an individual medicinal strategy entails a multitude of factors for consideration. These include beta-cell functionality and insulin sensitivity but also the ease of use, financial costs, tolerability, disease comorbidities, and the history of diabetes (Bennett et al. 2011; Nathan et al. 2009). Whereas parallel administration of two or more drugs may exhibit additive or synergistic glucose-lowering effects, it may also amplify adverse events, complicating overall medical care. A frequently employed antidiabetic combination therapy is insulin and metformin, which efficaciously lowers hyperglycemia without introducing a concomitant weight gain (Makimattila et al. 1999; Nathan et al. 2009). Conversely, it has been shown that combining insulin therapy with sulfonylureas instead of metformin is associated with increased mortality (Mogensen et al. 2015), underscoring the complexity of prescribing safe and efficacious antidiabetic pharmacotherapies.

5 Novel Avenues for Treating Diabetes

Research programs aiming to illuminate the molecular underpinnings of diabetic pathologies have increased exponentially in recent years. This effort is being directed increasingly toward the development of novel drugs for the treatment of
diabetes and the comorbidities. In addition to the broadened scope of basic discovery research and exploratory pharmacology, investment continues to refine, supplement, and optimize the therapeutic utility of current treatment options. Although there is a broad set of quality options for patients and the prescribing physician, glycemic control in both T1D and T2D remains suboptimal. Additionally, many current medicines possess dose-limiting adverse effects and are of narrow therapeutic index. In the following sections, some of the more prominent and promising preclinical strategies for treating diabetes are reviewed.

5.1 Next-Generation Insulin Analogs

Insulin is a miraculous substance but a dangerous drug. It is the first-in-line treatment for T1D and advanced stages of T2D. Throughout the last decade, we have witnessed a steady progression in the production and quality of insulin to a point where biosynthesis can produce virtually unlimited amounts of insulin in the highest chromatographic purity. Biosynthesis has also been employed to refine the pharmacokinetics of the hormone where site-specific mutations have been introduced to either accelerate or to postpone insulin action (Hirsch 2005). Consequently, the primary objective of cutting-edge research has advanced from pharmacokinetics to pharmacodynamics. The discovery of an insulin that is glucose sensitive is a primary target, much in the manner that an incretin only operates in hyperglycemia. Such an insulin analog or novel formulation would provide for more aggressive treatment of hyperglycemia with less risk of life-threatening hypoglycemia. Simultaneously, the perfection of pump-infused insulin is being attempted through the development of novel glucagon formulations and structural analogs, coupled with continual glucose monitoring (Chabenne et al. 2014; Wu et al. 2011). It is not inconceivable that in the not-so-distant future, a much improved approach to insulin-dependent control of glycemia could emerge. Separately, attempts to minimize body weight in concert with insulin therapy have reached an advanced development state. Obesity is a common feature of advanced, insulin-dependent T2D, and it serves to accelerate pancreatic failure while promoting weight gain. Combination basal insulin therapy with GLP-1 agonism has proven clinically that improved glycemic control, with less hypoglycemia and weight gain, can be achieved (Balena et al. 2013; Garg 2010; Vora 2013). It represents a paradigm shift where it is likely that increased effort will be devoted to further minimize the use of insulin through the identification of additional mechanisms to restore insulin sensitivity and endogenous beta-cell function.

5.2 Pancreatic Transplantation

Although pancreatic transplantation is not a new procedure (Kelly et al. 1967), recent progress in the development and success rate of both pancreatic and islet transplantation procedures have made these invasive therapies increasingly appealing.
The surgeries can be curative and are often employed in T1D patients who are undergoing a renal transplantation or in patients with poorly controlled glycemia or with recurrent hypoglycemia (Gruessner and Sutherland 2005; Gruessner and Gruessner 2013). Improvements in transplantation surgery and immunosuppressive therapy are reflected in a >95% 1-year survival rate and graft survival of close to 85% (Gruessner and Gruessner 2012). Importantly, a successful transplant is more efficient in lowering HbA1c levels and maintaining glycemic control than insulin therapy (Dieterle et al. 2007). An alternative to pancreatic transplantation is the less invasive islet transplants. Despite the obvious appeal of a less invasive procedure, a pancreatic transplant typically has better long-term glycemic outcomes than islet transplants (Gruessner and Gruessner 2013). Sourcing sufficient human islets remains a constant challenge and stem cell technology possesses huge potential to address this need (Bouwens et al. 2013). There still remain sizable issues to scaling the technology for commercial application while addressing a host of safety concerns pertaining to the potential for uncontrolled proliferation and insulin release that might evolve to be non-glucose regulated.

5.3 Leptin

Leptin is an adipocyte-derived hormone that serves to inform the brain of peripheral fuel availability (Zhang et al. 1994). Circulating leptin induces catabolic actions and weight loss by activating specific leptin receptors in the hypothalamus and the hindbrain (Myers et al. 2008). In addition, hypothalamic leptin receptor activation prominently regulates glucose metabolism and can correct diabetes in animal models of both T1D and T2D (Morton and Schwartz 2011). Infusion of leptin into the lateral cerebral ventricle in rats with uncontrolled insulin-deficient diabetes reduces hyperglycemia and improves glucose tolerance, purportedly by inhibiting hepatic glucose production and stimulating glucose uptake (German et al. 2011). Furthermore, leptin therapy corrects hyperglycemia in humans with coexisting lipodystrophy and T1D (Park et al. 2008). Leptin is currently being studied in clinical trials for its ability to improve glycemic control and reduce the requirements for insulin replacement therapy in T1D (NCT01268644).

Despite the capacity of leptin to enhance insulin sensitivity and reduce hyperglycemia in animal models of T2D, clinical trials investigating the efficacy of leptin to correct clinical parameters in obese T2D subjects have been discouraging (Mittendorfer et al. 2011; Moon et al. 2011). Whether the failure of leptin to ameliorate glycemic control in T2D coincides with leptin resistance and excess body weight needs further investigation. Notably, an increasing number of preclinical studies have demonstrated that several agents (FGF21, amylin, exendin-4, and a GLP-1/glucagon co-agonist) can restore leptin sensitivity in diet-induced leptin-resistant models to harvest additional weight-lowering and glycemic benefits of leptin therapy (Clemmensen et al. 2014; Muller et al. 2012; Roth et al. 2008). These studies have spurred new enthusiasm for leptin as an agent in novel combinatorial pharmacotherapies for the treatment of metabolic disorders. However, exogenous
leptin administration has been associated with adverse effects including increased blood pressure and immunogenicity (Kim et al. 2014). These limitations must be resolved before leptin can progress further in the clinic as a drug candidate.

5.4 FGF21

FGF21 is a hormone with profound effects on glucose and lipid metabolism and is currently being investigated as a potential therapy for the treatment of T2D (Kharitonenkov and Adams 2014). It is expressed in multiple tissues including liver, pancreas, adipose, and muscle tissue. Glucagon appears to regulate hepatic FGF21 production (Habegger et al. 2013) as well as PPARalpha agonists (Galman et al. 2008). Fasting (Galman et al. 2008) and dietary macronutrient composition (Laeger et al. 2014) influence circulating levels in a circadian manner (Andersen et al. 2011). Experimental studies have demonstrated that the administration of recombinant FGF21 improves insulin sensitivity in multiple species ranging from rodents to monkeys to man (Kharitonenkov and Adams 2014). The insulin-sensitizing efficacy of FGF21 is associated with an inhibition of hepatic glucose output, increased circulating adiponectin, and a reduction in body fat (Kharitonenkov and Adams 2014). The molecular mechanisms responsible for the metabolic effects of FGF21 are still being investigated, and studies using FGF receptor-mutated mice imply that the majority of the effects are linked to FGF receptor 1 activation in adipose tissue (Adams et al. 2012a). Recently, a novel FGF21 analog was tested in obese subjects with T2D (Gaich et al. 2013), and it was observed to improve an array of metabolic parameters. Discouragingly, no significant improvements in hyperglycemia were observed through the course of 28 days of daily treatment. This may reflect differences in pharmacological properties between native FGF21 and the analog clinically tested or consequential to the short treatment duration and the small sample size tested in the study. Future clinical trials are needed to confirm these observations and, if validated, to determine the molecular basis.

Despite the wealth of preclinical literature supporting a novel role for FGF21 in treatment of metabolic disease, rodent studies have reported that FGF21 negatively regulates bone metabolism and that such therapy may impose skeletal fragility (Wei et al. 2012). Conversely, a positive relationship between circulating FGF21 levels and bone mineral density has been reported for healthy human subjects (Lee et al. 2013). It is a conundrum that requires additional study, and it is warranted that a balanced analysis of the benefits to metabolism is carefully assessed in the context of bone mineral metabolism.

5.5 Bariatric Surgery

Bariatric surgery provides unquestionably superior body weight and glycemic outcomes when compared to drug therapy in obese patients with poorly controlled
T2D (Schauer et al. 2014). Reports indicate that 60–80% of the patients receiving a Roux-en-Y gastric bypass show a profound reversal of their diabetes (Adams et al. 2012b; Buchwald et al. 2009). The molecular basis of the glycemic improvement constitutes a subject of intense interest as an appreciable degree of it occurs before there is a meaningful difference in body weight. Clinical studies have highlighted changes in multiple gut-secreted peptides such as GLP-1 and ghrelin as a mechanistic explanation for the glycemic benefit of such surgeries (Cummings et al. 2005; Falken et al. 2011; Karamanakos et al. 2008). Studies using genetic animal models have indicated that neither factor alone is crucial for the metabolic benefits (Chambers et al. 2013; Wilson-Perez et al. 2013). Recent, preclinical reports imply that coordinated alteration in multiple systems including bile homeostasis, microbiota, and gut-brain communication functions in concert with humoral alterations to mediate the metabolic effects of surgery (Berthoud et al. 2011; Furet et al. 2010; Lutz and Bueter 2014; Ryan et al. 2014). Identification of these mechanisms could lead to the development of a pharmacological strategy that may reproduce the glycemic control of surgery and render such invasive surgical procedures obsolete.

5.6 Multi-hormone Combination Therapies

It has become increasingly evident that adjusted enteroendocrine responses contribute to the massive and rapid metabolic improvements achieved by bariatric surgeries. Additionally, recent clinical and preclinical advances highlight that parallel targeting of more than one biological mechanism yields superior metabolic efficacy and fewer adverse events compared to traditional monotherapies (Sadry and Drucker 2013). Simultaneous targeting of multiple metabolic pathways can be achieved by coadministration of two distinct hormones (Cegla et al. 2014; Fonseca et al. 2010; Morrow et al. 2011; Muller et al. 2012; Neschen et al. 2015) or through the application of unimolecular polyagonists. These multifunctional hormones combine to embellish certain hormone action profiles but, more importantly, serve to recruit distinct pharmacology that leads to enhanced efficacy and safety (Day et al. 2009; Finan et al. 2012, 2013, 2015; Pocai et al. 2009; Schwenk et al. 2014).

In 2009, the discovery of co-agonist peptides possessing action at the glucagon and the GLP-1 receptors was reported to spectacularly lower body weight and improve glucose metabolism in animal models of obesity and glucose intolerance (Day et al. 2009; Pocai et al. 2009). A follow-up study revealed that GLP-1/glucagon co-agonism reverses leptin resistance in DIO animals (Clemmensen et al. 2014). This observation is provocative and sets the stage for future clinical studies with a central question being at what percent body weight reduction does leptin action return in human subjects. Of note, a recent human study exploring the efficacy of parallel glucagon and GLP-1 receptor agonism showed promising metabolic improvements (Cegla et al. 2014).
While the development of GIP agonists for diabetes has been clouded by the prospect of promoting weight gain, a novel dual incretin co-agonist (GLP-1/GIP) was recently reported to improve glycemic control and enhance insulin secretion in rodents and nonhuman primates (Finan et al. 2013). Furthermore, the enhanced insulinotropic effect of the co-agonist was found in clinical study to substantially reduce HbA1c levels in a dose-dependent improvement (1.1% from baseline) at the highest dose within just 6 weeks. Importantly, the treatment with the co-agonist was not associated with altered gut motility or vomiting, implying that the co-agonist can be dosed to improve efficacy while maintaining a robust safety profile. Follow-up clinical studies are ongoing to probe the efficacy and safety of these unimolecular co-agonists.

The concept of employing multi-agonists or the coadministration of several compounds with complementary mechanisms of action can be expanded to include a multitude of novel treatment protocols. The approach may thus significantly advance the possibility for individualized treatments to finally close the performance gap between drug therapy and surgical procedures.

5.7 Antiobesity Pharmacotherapies

It is well established that excess body fat mediates multiple metabolic disturbances that contribute to insulin resistance and pancreatic secretory defects (Kahn and Flier 2000; Kahn et al. 2006), rendering obesity a prominent role in escalating the diabetes epidemic. Accordingly, several antiobesity pharmacotherapies may have potential in the prevention and management of T2D. Equally, antidiabetic medications display modest antiobesity activity as well (e.g., GLP-1R agonists, amylin analogs, and SGLT2 inhibitors) (Scheen and Van Gaal 2014). Of note, the FDA recently approved the antidiabetic incretin mimetic liraglutide for the treatment of obesity. In contrast to the doses used for treating T2D (1.2 mg or 1.8 mg), the dose for treating obesity is 3.0 mg.

The antiobesity agent orlistat inhibits gastrointestinal lipases and serves to lower the availability of fatty acids for absorption (Hadvary et al. 1988). Orlistat has been shown to improve glycemic control in obese T2D subjects (Hollander et al. 1998) and to exhibit additive glycemic properties when coadministered with metformin (Miles et al. 2002). Similarly, combination therapy of the sympathomimetic amine phentermine and the anticonvulsant agent topiramate results in ~10% weight loss in obese subjects (when provided in conjunction with lifestyle modification) (Rueda-Clausen et al. 2013). Notably, the combination of phentermine and topiramate (± parallel metformin treatment) administered to T2D patients enhances weight loss and improves glycemic control relative to placebo (SEQUEL trial) (Garvey et al. 2012). Lorcaserin is a selective serotonin 2C agonist that lowers body weight in overweight and obese adults (Smith et al. 2010). Coadministration of lorcaserin with metformin and/or a sulfonylurea can improve HbA1c and fasting glucose levels in obese subjects with T2D (O’Neil et al. 2012). Recently, co-treatment with the antidepressant bupropion and the opioid receptor antagonist naltrexone...
was approved by the FDA for the treatment of obesity, and this combination therapy may also exhibit meaningful glycemic improvements in obese subjects with T2D (Hollander et al. 2013). Thus, marketed antiobesity therapies may serve as valuable adjuncts in polypharmaceutical treatment options for overweight diabetics.

Evidence supporting the prospect that melanocortin 4 receptor (MC4R) agonism may constitute an effective therapy or co-therapy for diabetes and obesity is accumulating. MC4R is acknowledged to play a seminal role in energy metabolism and MC4R agonism decreases feeding and increases energy expenditure (Tao 2010). Notably, MC4R stimulation also enhances insulin sensitivity and improves glucose tolerance in rodents and nonhuman primates (Kievit et al. 2013; Obici et al. 2001). Currently, MC4R agonists are being evaluated in clinical trials for the treatment of obesity (NCT01749137). Future studies investigating the antidiabetic virtues of MC4R agonism, either as monotherapy or in combination with other agents, seem warranted.

### 6 Perspectives and Future Directions

Diabetes is a disease that was identified thousands of years ago. How ironic it is that we are currently experiencing a global epidemic of disease. The increased prevalence is associated with enhanced urbanization and increased body weight. Fortunately, through the second half of the last century, a number of effective antidiabetes drugs emerged, and recombinant DNA technology emerged to provide human insulin in virtually unlimited quantity. In concert with advances in glucose monitoring and the full appreciation of hyperglycemic danger, these drugs have been used to provide much improved glycemic control and patient outcomes. Nonetheless, there is much that still needs to be addressed. Insulin remains a drug of exceedingly narrow therapeutic index and the prospect of life-threatening hypoglycemia remains the largest impediment to normalizing plasma glucose. The epidemic of obesity represents a huge challenge, as currently registered antiobesity drugs are only fractionally effective in normalizing body weight. Bariatric surgeries have emerged to address the most advanced forms of obesity, and they are very effective in providing sizable decreases in weight and eliminating diabetes in a sizable percent of patients. However, what is needed is a less invasive approach to manage obesity and preferably one that can be used in adolescents and young adults where T2D has now made its appearance.

There is reason for optimization. Our knowledge of the molecular basis of T2D and obesity has never been greater. The emergence of multiple new antidiabetic medicines demonstrates what can be accomplished when translational research is focused on a specific disease. The first-generation antiobesity drugs have established a foundation from which more effective therapies, and combinations with these first-generation drugs, can be developed to provide more meaningful reductions in body weight with the ultimate goal eliminating the current performance difference relative to gut surgery. Separately, insulin therapy is destined to improve with the renewed emphasis to discover a more glucose-sensitive approach.
to therapy. The simultaneous advances in biotechnology, material sciences, synthetic chemistry, and information technology are integrating to provide novel approaches to insulin-dependent diabetes that were impossible as recent as a decade ago. While it is impossible to predict the future with certainty, especially against such lofty goals as outlined in this chapter, the discovery of next-generation medicines with greater transformative impact are certainly plausible. While it is not uncommon for technology to fail in delivering near-term solutions to large medical challenges, when it is viewed over a longer period, it is likely to exceed expectations. If we can maintain the level of interest in addressing diabetes and obesity across academic, biotechnology, and large pharmaceutical companies, then we remain optimistic for the future.

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