Abstract

Diabetes

Diabetes mellitus is a very common disorder caused by high levels of sugar in the bloodstream. It is caused by problems with the hormone named insulin and also be affected or precipitated by other hormones. It has long been known that several peptide hormones have significant impact on the regulation of glucose homeostasis. Hormone-based therapies effectively lead to prevent or slow the progression of diabetes. Here we summarize the roles of metabolic hormones such as insulin, GLP-1, leptin, FGF21, adiponectin, ghrelin, nesfatin, etc. in glucose metabolism and therapies of diabetes.

Introduction

Diabetes is a metabolic disorder that human body does not produce or properly uses insulin, a hormone that is required to convert sugar, starches, and other food into energy. Diabetes mellitus is characterized by constant high levels of blood glucose (sugar). Human body has to maintain the blood glucose level at a relatively steady range, which is related to insulin, glucagon and other hormones [1]. Acute, life-threatening consequences of uncontrolled diabetes are hyperglycemia with ketoacidosis or the nonketotic hyperosmolar syndrome. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of different organs, especially the eyes, kidneys, nerves, heart, and blood vessels. Symptoms of marked hyperglycemia include polyuria,
polydipsia, weight loss, sometimes with polyphagia, and blurred vision. Impairment of growth and susceptibility to certain infections may also accompany chronic hyperglycemia. Moreover, long-term complications of diabetes include retinopathy with potential loss of vision; nephropathy leading to renal failure; peripheral neuropathy with risk of foot ulcers, amputations, and charcot joints; and autonomic neuropathy causing gastrointestinal, genitourinary, and cardiovascular symptoms and sexual dysfunction. Patients with diabetes have an increased incidence of atherosclerotic cardiovascular, peripheral arterial, and cerebrovascular disease. Hypertension and abnormalities of lipoprotein metabolism are also often found in people with diabetes [2].

Diabetes can be classified into the following general categories:

1. Type 1 diabetes, formerly called insulin-dependent diabetes or juvenile diabetes (due to β-cell destruction, usually leading to absolute insulin deficiency).

2. Type 2 diabetes (due to a progressive insulin secretory defect on the background of insulin resistance).

3. Gestational diabetes mellitus (GDM) (diabetes diagnosed in the second or third trimester of pregnancy that is not clearly overt diabetes).

4. Specific types of diabetes due to other causes, e.g., monogenic diabetes syndromes (such as neonatal diabetes and maturity-onset diabetes of the young [MODY]), diseases of the exocrine pancreas (such as cystic fibrosis), and drug- or chemical-induced diabetes (such as in the treatment of HIV/AIDS or after organ transplantation) [2-4].

Diabetes epidemic imposes a significant health burden on international society. There are currently 382 million people living with diabetes worldwide; by 2035 this will rise to 592 million. The number of people with type 2 diabetes is increasing in every country. 74% of people with diabetes live in low- and middle-income countries. The greatest number of people with diabetes are between 40 and 59 years of age. 179 million people with diabetes are undiagnosed. Diabetes caused 4.9 million deaths in 2014, every seven seconds a person dies from diabetes [5].

The global pandemic of diabetes induces searches for adjunctive drugs to reinforce the basic treatment typical for the specific type of this disease. These agents are meant to stimulate insulin secretion, increase insulin sensitivity or inhibit the antagonists of the hormone. It has long been known that several peptide hormones have significant impact on the regulation of glucose metabolism, which have been found to increase insulin secretion, and thus hormone-based therapies have emerged as new modalities for the treatment of diabetes [6]. Here we summarize the roles of metabolic hormones such as insulin, GLP-1, leptin, FGF21, adiponectin, ghrelin, nesfatin, etc. in patho-
genesis and treatments of diabetes.

**Insulin**

**The Role of Insulin in Glucose Metabolism**

Insulin is a peptide hormone produced by beta cells in the pancreas, which consists of A- and B-polypeptide chains, these two chains linked together by disulfide bonds [7]. It is first synthesized as a single polypeptide named preproinsulin in pancreatic β-cells. Preproinsulin contains a 24-residue signal peptide which directs the nascent polypeptide chain to the rough endoplasmic reticulum (RER). The signal peptide is cleaved as the polypeptide which transported into lumen of the RER, forming proinsulin [8]. Insulin regulates the metabolism of carbohydrates and fats by promoting the absorption of glucose from the blood to skeletal muscles and fat tissue and by causing fat to be stored rather than used for energy [9].

**Insulin secretion**

The stimulation of insulin release, which is required for the disposal of nutrients at the time of food intake, appears to be the result of a joint excitation of the pancreatic β cell by metabolic, hormonal and neural stimuli [10]. Among all nutrients, glucose is the major stimulant of insulin release, insulin in turn is required for the major peripheral tissues to utilize glucose [11]. Moreover, individual amino acids also stimulate the release of insulin.

The most effective essential amino acid for insulin release is arginine, histidine is least effective [12]. Besides, free fatty acids (FFAs) provide an important energy source as nutrients, and they also act as signalling molecules in various cellular processes, including insulin secretion. FFAs are thought to promote insulin secretion in an acute phase [13,14].

When plasma glucose concentrations rise, β-cell glucose uptake increases mainly via insulin-independent glucose transporters. Intracellularly, glucose is metabolized resulting in an increase in the ATP-to-ADP ratio and the closure of ATP-sensitive potassium channels ($K_{ATP}$ channels) [15]. As a result, the cell membrane depolarizes, leading to the opening of voltage-dependent calcium channels and the influx of extracellular calcium. The elevation of intracellular calcium triggers the exocytosis of insulin (and C-peptide) granules to the portal vein [16]. Although species dependent, glucose-stimulated insulin secretion (GSIS) at supraphysiological levels (ie, during a glucose tolerance test) is biphasic, with a first phase or triggering phase lasting 5 to 6 min, which represents the secretion of the readily releasable pool of insulin granules; and a second phase or amplification phase lasting over 60 min, which represents the replenishment of the readily releasable pool by the reserve pool of insulin granules [17].
**Insulin signaling**

Insulin receptor (IR) is a transmembrane dimer that belongs to the tyrosine kinase superfamily. Biochemically, the insulin receptor is encoded by a single gene INSR, from which alternate splicing during transcription results in either IR-A or IR-B isoforms [18,19]. Downstream post-translational events of either isoform result in the formation of a proteolytically cleaved α and β subunit. The α-subunit is extracellular, whereas the β-subunit comprises extracellular, transmembrane, and intracellular regions. The latter contains the tyrosine kinase domain and regulatory regions [19,20]. On insulin binding, the receptor is activated and undergoes autophosphorylation, which initiates a signaling cascade [21]. The current information concerning insulin signal transduction on protein ser/thr kinase cascades as signalling intermediates, and their status as participants in insulin regulation of energy metabolism [22]. Two canonical signaling pathways are well established: the phosphatidylinositol 3-kinase (PI3K)/Akt pathway, responsible for insulin's metabolic effects; and the Ras/mitogen-activated protein kinase pathway, accountable for insulin's effects on cell growth and proliferation [23,24]. In the PI3K/Akt pathway, the activated receptor phosphorylates tyrosine residues of insulin receptor substrate (IRS), creating binding sites for the Src homology 2 domain of PI3K [25]. The active (phosphorylated) PI3K is translocated to the membrane where it catalyzes the conversion of phosphatidylinositol 4,5-bisphosphate to phosphatidylinositol 3,4,5-trisphosphate. The latter activates phosphatidylinositol 3,4,5-trisphosphate-dependent protein kinase, which in turn activates protein kinase B or Akt by phosphorylation of serine and threonine residues [24,25]. Activated Akt leads to the phosphorylation of multiple substrates that ultimately results in the metabolic effects of insulin, including glucose uptake, via activation of AS160 and subsequent translocation of glucose transporter 4 to the plasma membrane; glycogen synthesis by inactivating glycogen synthase kinase-3; protein synthesis by regulation of the mammalian target of rapamycin; lipolysis [26].

**Major effects of insulin on glucose homeostasis**

Insulin is the primary anabolic endocrine signal, and it plays a critical role in carbohydrate metabolism. Insulin increases cellular glucose uptake, stimulates glycolysis, and promotes the synthesis of hepatic and muscle glycogen, adipose triglycerides, and skeletal muscle protein; while simultaneously preventing their degradation [27,28].

The major effects of insulin on carbohydrate metabolism are:

1. It increases the rate of glucose transport across the cell membrane in skeletal muscle and adipose tis-
sue. An increase in insulin promotes glucose uptake by activating a complex cascade of signaling events. In brief, binding of insulin to the insulin receptor leads to down stream tyrosine phosphorylation of protein substrates that then engage and activate PI3K. This leads to downstream signaling through PKB/Akt and PKC-λ/ζ, which results in GLUT4 translocation from its intracellular pool to the plasma membrane and glucose transport into the cell [28].

2. It stimulates the rate of glycolysis by increasing hexokinase and 6-phosphofructokinase activity in the liver, decreases the release of glucose from the liver by inhibiting the expression of key gluconeogenic enzymes [29].

3. It upregulates the rate of glycogen synthesis and inhibits the rate of glycogen breakdown [29].

**Treatment of Diabetes**

For many decades, it has been accepted that insulin injection is most used for diabetes therapy. Many forms of insulin treat diabetes. They’re grouped by how fast they start to work and how long their effects last [30].

**Rapid-Acting insulin**

Rapid-acting insulins such as insulin lispro and insulin aspart do not self-aggregate in solution as human (regular) insulin does, and these insulins are rapidly absorbed. Insulin lispro differs from human insulin by an amino acid exchange of lysine and proline at positions 28 and 29. The substitution of aspartic acid for proline at position 28 created insulin aspart. Rapid-acting insulins peak at 40 to 60 minutes after injection. They were effective in decreasing the postprandial glucose concentration when administered 5 min before a meal to women with GDM [31,32].

**Short-Acting insulin**

Regular insulin has a delay to onset of action of 30 to 60 minutes. Patients are instructed to inject regular insulin 20 to 30 minutes prior to meals (ie, lag time is the time between injecting insulin and eating) to match insulin availability and carbohydrate absorption. Regular insulin acts almost immediately when injected intravenously. What is more, regular insulin has a duration of action of more than 8 h in some patients, three mealtime injections during the day can compensate for the insulin waning effect of a single Neutral protamine Hagedorn injection at night [30].

**Intermediate-Acting insulin**

The most widely used intermediate-acting human insulin is Neutral Protamine Hagedorn (NPH) insulin, which also has to be administered twice daily in many cases to provide a 24-h basal insulinemia. NPH insulin is slowly absorbed due to the addition of protamine to regu-
lar insulin [30].

**Long-Acting insulin**

A modified human insulin that forms a microprecipitate in the subcutaneous tissue, is released slowly with a peakless delivery of about 20 to 24 hours in most patients. More specifically, the novel recombinant insulin analog insulin glargine is a modification of human insulin with a very long duration of action in which two arginines are added to the B-chain and glycine is substituted for aspartagine at the A21 position of the insulin molecule [33,34]. Glargine gained approval from the United States Food and Drug Administration in April 2000, for use in treating type 1 and type 2 diabetes in humans. In patients with type 2 diabetes, once-daily bedtime insulin glargine is as effective as once- or twice-daily NPH in improving and maintaining glycemic control. In addition, insulin glargine demonstrates a lower risk of nocturnal hypoglycemia and less weight gain compared with NPH insulin [35].

**Ultra-long acting insulin**

Insulin degludec (IDeg) is a new-generation ultra-long-acting basal insulin. IDeg is primarily a result of the slow release of IDeg monomers from soluble multihexamers that form after subcutaneous injection, resulting in a long half-life and a smooth and stable pharmacokinetic profile at steady state [36]. A clinical trial showed that IDeg, which used in combination with mealtime insulin aspart (IAsp), is a well-tolerated and efficacious treatment when used in people with type 1 diabetes, providing comparable glycemic control to insulin glargine at comparable doses, but with lower rates of hypoglycemia [37].

**Several Adverse Effects of Insulin**

Although insulin is the most effective drugs for diabetes treatment, there are still some major adverse effects.

**Hypoglycemia**

Hypoglycemia is the most common adverse effect of insulin therapy. In the type 1 DM and type 2 DM, intensive therapy increased the risk of severe hypoglycemia [30,37,38]. Severe hypoglycemia was reported by 26% of patients with a mean of 1.9 episodes per patient per year, and 43% of episodes occurred nocturnally in type 1 DM. While 1% to 2% more type 2 DM receiving insulin reported at least 1 episode of severe hypoglycemia per year than those patients receiving other therapies. Thus intensive therapy, with oral medications or insulin, has been shown to increase the risk of episodes of hypoglycemia [30,38].

**Weight gain**

Generally, patients receiving insulin gain weight. Patients with type 1 DM receiving intensive insulin therapy gained 4.75 kg more than patients receiving conventional therapy during the 3.5- to 9-year study period [39]. Patients with type 2 DM receiving intensive insulin therapy gained significantly more weight (1.4-2.3 kg) than those patients treated with sulfonylureas or metformin [40].
Proliferative retinopathy

Rapid improvement in diabetes control results in progressive worsening of retinopathy in approximately 5% of patients [41-44].

Risk of cancer

Carstensen et al. pay attention that cancer is more frequent among diabetes patients, but it is unknown how this excess varies with duration of diabetes and insulin use. A cohort’s analysis suggested that diabetic patients have elevated cancer incidence rates compared with the non-diabetic population, highest in the first year after diagnosis and the first year after initiation of insulin treatment [45].

Glucagon-like peptide 1 (GLP-1)

Glucagon-like peptide 1 (GLP-1) is a 29-amino acid peptide hormone mainly produced in the intestinal epithelial endocrine L-cells [46]. GLP-1 was first identified following the cloning of cDNAs and genes for proglucagon in the early 1980s [47], which is a selective cleavage of the proglucagon molecule by PC1/3 [48]. The biologically active forms of GLP-1 are: GLP-1-(7-37) and GLP-1-(7-36) amide [49, 50]. As an anorectic hormone, GLP-1 is released by the distal intestine in response to ingested nutrients [46,51], which is extremely rapidly metabolized and inactivated by the enzyme dipeptidyl peptidase IV even before the hormone secretion [46,52]. The main actions of GLP-1 are to enhance insulin secretion and to inhibit glucagon secretion, thereby contributing to limit postprandial glucose excursions [46]. The insulinotropic activity of GLP-1 in type 2 diabetes mellitus therefore offers great potential for treatment of hyperglycemia without causing hypoglycemia [53,54].

Effects of GLP-1 on Islet Function

Classically, GLP-1 is secreted from intestinal L cells in response to nutrient ingestion, and signals through the GLP-1 receptor (GLP-1R), which is abundantly expressed in pancreatic islets [55]. The most well characterized role of GLP-1 action is its effects in pancreatic islets to lessen post-prandial glucose excursion through the glucose-sensitive stimulation of insulin release from β cells. In addition to the direct insulinotropic effects, GLP-1 also inhibits glucagon secretion from pancreatic α cells in a glucose-dependent manner. Fasting blood glucose reduction may also be achieved via the effects of GLP-1 in the induction of satiety and gut motility delay, leading to decreased glucose absorption [54]. Furthermore, GLP-1-treatment stimulates insulin biosynthesis and secretion from pancreatic beta cells and also somatostatin release from delta cells [56].

Effects of GLP-1 on Skeletal Muscle Insulin Resistance

Approximately 80-90% of exogenous glucose infusion is taken up by skeletal muscle. Skeletal muscle insu-
lin resistance is the primary defect in diabetes, preceding the failure of beta cell function and overt hyperglycemia. GLP-1 receptor has been identified in skeletal muscle tissue [57]. Its activation has potent effects on glycogenesis, glycolysis and glucose oxidation independent of its insulinotropic effect [58]. In vitro studies have shown that exenatide, like GLP-1 and insulin, enhances glucose uptake in skeletal muscle, which is mediated by certain kinases (PI3K/PKB, p70s6k and MAPKs) through GLP-1 receptors in skeletal muscle [59]. In vivo expriments, the average glucose uptake rates of gastrocnemius in exenatide-treated diabetic rats were approximately 65 percent of the uptake in the nondiabetic control rats and were 41 percent higher than in the vehicle-treated diabetic rats, suggesting skeletal muscle insulin resistance (IR) was improved by exenatide [60]. Exenatide can significantly alleviate the ultrastructural damage of cells in skeletal muscles through a protective effect on the mitochondria and myofibers of T2DM rats [60]. Therefore, exenatide remarkably increase the glucose uptake of peripheral muscle tissues to improve the IR of T2DM rats.

Effects of GLP-1 on Glucose Production

Peripheral adipose tissue degradation is the main source of glycerol during fasting. Because of the lack of glycerokinase in adipose tissue, the glycerol released by lipolysis cannot be resynthesized into adipose tissue, and therefore glycerol appearance rates in the blood are also a reliable indicator for lipolysis [61]. It appears that lipolysis in the diabetic rats was partially inhibited by both GLP-1 and exenatide [62]. Gluconeogenesis is a metabolic pathway that results in the generation of glucose from noncarbohydrate carbon such as glycerol, it is one of the major sources of fasting endogenous glucose production (EGP), which maintains the body’s fasting blood glucose within normal levels [63]. However, the hepatic insulin resistance seen in diabetes is a major cause of the high level of gluconeogenesis in diabetes. Exenatide does significantly inhibit hepatic gluconeogenesis and increases glucose uptake in the peripheral muscle tissues to improve hepatic and extra hepatic insulin resistance in diabetic rats [57].

Incretin-based Therapies

Modified gastric bypass surgery has been applied to the treatment of the type 2 diabetes mellitus (T2DM) patients in the 1990s. It is reported that Roux-en-Y gastric bypass (RYGB) rapidly reverses symptoms of diabetes via a GLP-1-mediated mechanism suggesting that GLP-1 can be used as diabetes therapy [64]. Actually, it has long been known that peptide hormones from the gastrointestinal tract have significant impact on the regulation of glucose metabolism. Among these hormones, incretins have been found to increase insulin secretion, and thus incretin-based therapies have emerged as new modalities for the treatment of type 2 diabetes [65].
GLP-1 receptor agonists

The development of GLP-1R agonists for the treatment of type 2 diabetes with improved glycemic control combined with a sustained weight loss, is a major breakthrough in the medical treatment of type 2 diabetes. GLP-1 receptor agonists are effective agents for the treatment of type 2 diabetes, offering many advantages over other agents, including weight loss, potential beta-cell protection, and low risks of hypoglycemia. They also have positive effects on cardiovascular parameters, including reductions in blood pressure, lipids, and weight, although the clinical relevance of this remains to be determined. Overall, GLP-1 receptor agonists are effective and innovative agents for patients with type 2 diabetes. As of early 2015, there are five GLP-1 analogs either approved by the U.S. Food and Drug Administration (FDA) or the European Commission for the treatment of type 2 diabetes: exenatide (Byetta), lixisenatide (Lyxumia), liraglutide (Victoza), dulaglutide (Trulicity), and albiglutide (Tanzeum) [66,67].

Dipeptidyl Peptidase 4 (DPP-4) inhibitors

GLP-1 is rapidly degraded by the enzyme DPP-4 and it is no longer available in active form. Thus DPP-4 inhibition has the potential to be a novel, competent, acceptable approach to treat type 2 diabetes [68]. The effects of GLP-1 can also be exploited by protecting endogenous GLP-1 from degradation by the enzyme DPP-4. Oral administration of inhibitors of this enzyme increase the circulating levels of active GLP-1 which is associated with anti-diabetic effects. DPP-4 inhibitors are small molecules that are active upon oral administration. They have shown a clinically significant and sustained effect on glycemic control. However, DPP-4 inhibitors have little effect on body weight, presumably because the plasma concentrations of active GLP-1 are not elevated sufficiently to exert this effect. Several DPP-4 inhibitors are undergoing clinical development. Currently four of them sitagliptin, vildagliptin, saxagliptin, and linagliptin have been approved as medications for type 2 diabetes [65,68].

Leptin

Leptin is a 167-amino acid peptide with a four-helix bundle motif similar to that of a cytokine, which is produced predominantly in the adipose tissue but is also expressed in a variety of other tissues, including placenta, ovaries, mammary epithelium, bone marrow, and lymphoid tissues [69,70]. In addition, it has close relationship with physiology and pathophysiology of energy homeostasis, reproductive, endocrinology, immune, and metabolism [71]. Leptin binds to leptin receptors (ObRs) located throughout the central nervous system and peripheral tissues, with at least six receptor isoforms identified (ObRa, ObRb, ObRc, ObRd, ObRe, and ObRf) [72,73]. Studies of genetically obese mice serendipitously found in the Jackson Laboratories revealed that their phenotypes derive from homozygous mutations of either the obese (ob)
or diabetic (db) genes that result in obesity and insulin resistance or diabetes as well as endocrine and immune dysfunction [74-78].

**The Role of Leptin in Glucose Metabolism**

**Regulation of islet secretion by leptin**

The pancreatic beta-cell has been shown to be a key peripheral target of leptin, with leptin suppressing insulin synthesis and secretion from beta-cells both in vitro and in vivo [79]. Leptin (1-100 nmol/l) also produced a dose-dependent inhibition of glucose-stimulated insulin secretion by isolated islets from ob/ob mice. In contrast, leptin at maximum effective concentration (100 nmol/l) did not inhibit glucose-stimulated insulin secretion by islets from db/db mice [80]. These results provide evidence that a functional leptin receptor is present in pancreatic islets and suggest that leptin overproduction, particularly from abdominal adipose tissue, may modify directly both basal and glucose-stimulated insulin secretion.

**Effects of leptin on skeletal muscle metabolism**

Skeletal muscle is a key metabolic tissue for insulin-stimulated glucose disposal and for energy metabolism. Skeletal muscle resistance to the key metabolic hormones, leptin and insulin, is an early defect in obesity. Leptin stimulates the oxidation of fatty acids and the uptake of glucose, and prevents the accumulation of lipids in non-adipose tissues, which can lead to functional impairments known as “lipotoxicity” [81]. Leptin increases glucose uptake in skeletal muscle via the hypothalamic–sympathetic nervous system axis and β-adrenergic mechanism, while leptin stimulates fatty acid oxidation in muscle via AMP-activated protein kinase (AMPK) [82]. Sáinz N et al. found leptin enhances the intracellular GLUT4 transport in skeletal muscle of ob/ob animals by reducing the expression and activity of the negative regulators of GLUT4 traffic TBC1D1 and TBC1D4 [83].

**Effects of leptin on hepatic insulin sensitivity**

The liver plays a vital role in integrating and controlling glucose homeostasis. Thus, it is important that the liver receive and respond to signals from other tissues regarding the nutrient status of the body. Leptin appears to act as a negative regulator of insulin action in the liver. In contrast to impaired glucose homeostasis induced by a complete deficiency of leptin action, Hepatic specific deletion of leptin increases hepatic insulin sensitivity and protects against age- and diet-related glucose intolerance [84].

**Leptin and Diabetes**

Association between serum leptin levels and diabetes mellitus were restricted to specific racial/ethnic groups and were not consistent in previous findings [85]. Some studies reported that there is no association between plasma leptin levels and diabetes [86-88], whereas others sug-
gest that leptin levels are closely related to body fatness [89-91]. Higher leptin levels, conjunct with obesity and weight gain are probably involved in the subsequent development of diabetes [82]. Besides fat mass and gender, the main determinants for leptin levels in type 2 diabetic subjects as in healthy subjects is insulin secretion and the degree of insulin resistance also seem to contribute significantly to leptin levels [92].

**Leptin-based Therapeutics**

Leptin can correct diabetes in animal models of both diabetes mellitus type 1 (T1DM) and type 2 (T2DM). Interestingly, leptin exerts potent anti-diabetic actions that are independent of its effects on body weight and food intake. In addition, long-term leptin-replacement therapy is well tolerated and dramatically improves glycemic control, insulin sensitivity, and plasma triglycerides in patients with severe insulin resistance due to lipodystrophy. Together, these results have spurred enthusiasm for the use of leptin therapy to treat humans suffering from diabetes mellitus [93].

**Type 1 diabetes**

Leptin suppress the apoptosis of beta cells in Kilham rat virus induced rodent model of type 1 diabetes [94]. Leptin therapy ameliorated STZ-induced hyperglycemia and hyperketonemia in mice [95]. In nonobese diabetic mice with uncontrolled type 1 diabetes, leptin administration have multiple short- and long-term advantages over insulin monotherapy for type 1 diabetes [96]. Another new area for leptin therapeutics is its potential for achieving better glucose control with lower insulin dosage in type 1 diabetes patients; a clinical trial evaluating these effects is currently ongoing and is based on previous studies showing improved glucose metabolism in type 1 diabetes in rodents after combinatorial treatment with insulin and leptin [97].

**Type 2 diabetes**

Plasma leptin is reduced in untreated type 2 diabetes probably as a consequence of reduced insulin secretion [98]. Leptin has metabolic effects on peripheral tissues including muscle, liver, and pancreas, and it has been successfully used to treat lipodystrophic diabetes, a leptin-deficient state. Leptin administration to the type 2 diabetes mice (MKR mice) resulted in correction of diabetes. The main effect of leptin therapy was enhanced hepatic insulin responsiveness possibly through decreasing gluconeogenesis without an effect that reduced food intake. In addition, the reduction of lipid stores in liver and muscle induced by enhancing fatty acid oxidation and inhibiting lipogenesis leads to an improvement of the lipotoxic condition. In brief, leptin could be a potent antidiabetic drug in cases of type 2 diabetes that are not leptin resistant [99].

**Fibroblast Growth Factor 21 (FGF21)**

Tetsuya Nishimura et al. firstly isolated cDNA encoding a novel FGF (210 amino acids) from mouse embryos.
As it is the 21st documented FGF, Tetsuya Nishimura et al. tentatively termed it FGF-21 [100]. Fibroblast growth factor 21 (FGF21) is an atypical member of the FGF family, which responds to the PPARα transcription factor, regulating lipolysis in adipose tissues, fatty acid oxidation and ketogenesis in livers. FGF21 is thought to act on its target tissues, including liver and adipose tissue, to improve insulin sensitivity and reduce adiposity associated with diabetes and obesity [101,102].

**The Role of FGF21 in Glucose Metabolism**

**Regulation of islet function by FGF21**

Growing evidence shows that FGF21 is a potential therapeutic agent for treatment of T2DM, obesity, and their complications [103,104]. Notably, FGF21 has also been reported to improve pancreatic β-cell function and preserve islet and β-cell mass [105]. Hyperglycemia in type 2 diabetes mellitus may lead to FGF21 resistance in pancreatic islets, probably through reduction of PPARγ expression, which provides a novel mechanism for glucose-mediated islet dysfunction [106]. In islets isolated from healthy rats, FGF-21 increased insulin mRNA and protein levels but did not potentiate glucose-induced insulin secretion. Islets and INS-1E cells treated with FGF-21 were partially protected from gluelipotoxicity and cytokine-induced apoptosis in islets isolated from diabetic rodents, FGF-21 treatment still increased islet insulin content and glucose-induced insulin secretion, thus preservation of β-cell function and survival by FGF-21 may contribute to the beneficial effects of this protein on glucose homeostasis observed in diabetic animals [105].

**Effects of FGF21 on glucose uptake**

A potential role as a metabolic regulator emerged when FGF21 was shown to increase glucose uptake in adipocytes. FGF21 enhances glucose uptake by inducing the expression of glucose transporter-1 (GLUT1) in adipocytes. Ge X et al. investigated the signaling pathways that mediate FGF21-induced GLUT1 expression and glucose uptake in vitro and in vivo, suggesting FGF21 induces GLUT1 expression and glucose uptake through sequential activation of ERK1/2 and transcription factors serum response factor (SRF) and Ets-like protein-1 (Elk-1), which in turn triggers the transcriptional activation of GLUT1 in adipocytes [107]. Moyers et al. describe the early signaling events triggered by FGF-21 treatment of 3T3-L1 adipocytes and reveal a functional interplay between FGF-21 and peroxisome proliferator-activated receptor gamma (PPARγ) pathways that leads to a marked stimulation of glucose transport [108].

Besides as a potent regulator of glucose uptake in adipocytes, FGF21 also has direct effects on enhancing skeletal muscle glucose uptake, providing additional points of regulation that may contribute to the beneficial effects of FGF21 on glucose homeostasis. FGF21 has a direct effect on skeletal muscle to enhance insulin-stimulated glucose
uptake, which increases glucose uptake in primary human myotubes and isolated adult mouse skeletal muscle. FGF21 increased glucose uptake in the absence or presence of insulin, whereas the signalling mechanisms by which FGF21 regulates glucose metabolism in skeletal muscle remain to be determined [109].

Effects of FGF21 on hepatic glucose production

FGF21 functions physiologically as an insulin sensitizer under conditions of acute refeeding and overfeeding [110]. During starvation, FGF21 expression in lean rodents is strongly induced in liver by prolonged fasting through a mechanism that involves the nuclear receptor peroxisome proliferator-activated receptor α. FGF21, in turn, induces the transcriptional coactivator protein peroxisome proliferator-activated receptor γ coactivator protein 1α and stimulates hepatic gluconeogenesis, fatty acid oxidation, and ketogenesis [111]. In fed statue, rats treated with intracerebroventricular FGF21 displayed a robust increase of insulin sensitivity due to increased insulin-induced suppression of both hepatic glucose production and gluconeogenic gene expression, with no change of glucose utilization [112]. Berglund et al. also discovered that chronic FGF21 ameliorated fasting hyperglycemia in diabetic ob/ob mice via increased glucose disposal and improved hepatic insulin sensitivity [113].

FGF21 Level in Diabetic Animals and Patients

Circulating fibroblast growth factor 21 (FGF21) levels are elevated in diabetic subjects and correlate directly with abnormal glucose metabolism, while pharmacologically administered FGF21 can ameliorate hyperglycemia [103]. Hojman et al. found muscular FGF-21 expression was associated with hyperinsulinemia in men but not in women [114]. FGF21 expression in the liver and white adipose tissue is increased in diabetic rodents, but these increases occur in the context of impaired glucose tolerance and increased hepatic lipid content, suggesting that the ability of endogenous FGF21 to exert beneficial effects on glucose homeostasis and lipid oxidation is impaired in the diabetic state [115,116].

Treatment of Diabetes

FGF21 is a novel metabolic regulator that exerts potent antidiabetic effect in animal models of type 2 diabetes mellitus. Positive metabolic actions of FGF21 without the presence of apparent side effects make this factor a hot candidate to treat type 2 diabetes and accompanying metabolic diseases [117]. Metformin is widely used as a glucose-lowering agent in patients with type 2 diabetes (T2D), which is a potent inducer of hepatic FGF21 expression and that the effect of metformin seems to be mediated through AMPK activation. As FGF21 therapy normalizes blood glucose in animal models of type 2 diabetes, the induction of hepatic FGF21 by metformin might play an important
role in metformin’s antidiabetic effect [118]. Moreover, treatment of obese/diabetic animals with FGF21 also reduces blood glucose levels and increases glucose tolerance and insulin sensitivity [103,113,119]. Kharitonenko et al. evaluated its bioactivity in diabetic nonhuman primates. When administered daily for 6 weeks to diabetic rhesus monkeys, FGF-21 caused a dramatic decline in fasting plasma glucose, fructosamine, triglycerides, insulin, and glucagon. FGF-21 administration also led to significant improvements in lipoprotein profiles, including lowering of low-density lipoprotein cholesterol and raising of high-density lipoprotein cholesterol, beneficial changes in the circulating levels of several cardiovascular risk markers/factors, and the induction of a small but significant weight loss. These data support that FGF-21 can be used for the treatment of diabetes and other metabolic diseases [120].

As an alternative to native FGF21, LY2405319 (LY), a variant of FGF21, LY treatment produced significant improvements in dyslipidemia. Favorable effects on body weight, fasting insulin, and adiponectin were also detected [121]. Another antidiabetic strategy using agonistic anti-FGFR1 (FGF receptor 1) antibodies (R1Mabs) that mimic the metabolic effects of FGF21 induced sustained amelioration of hyperglycemia, along with marked improvement in hyperinsulinemia, hyperlipidemia, and hepatosteatosis [122].

In sum, FGF21 is one of the most promising candidates given its outstanding pharmacologic benefits for nearly each and every abnormality of a metabolic disease and lack of apparent side effects in a variety of animal models. Thus, FGF21 represents a novel and appealing therapeutic reagent for Type 2 diabetes mellitus, obesity, dyslipidemia, cardiovascular and fatty liver diseases.

**Adiponectin**

Adiponectin is a collagen-like circulating protein secreted by adipocytes which can regulate energy homeostasis and glucose and lipid metabolism [123]. The discoveries of adiponectin were breakthroughs in the field of metabolic diseases because the beneficial metabolic effects of adiponectin which convey insulin-sensitizing and antidiabetic effects are well established [124,125]. Yamauchi T et al. found that administration of adiponectin causes glucose-lowering effects and ameliorates insulin resistance in mice. Conversely, adiponectin-deficient mice exhibit insulin resistance and diabetes [126]. In addition, decreased concentrations of adiponectin are seen in patients with type 2 diabetes and in those who do not have diabetes but are resistant to insulin [127,128]. Here, we summarize the important roles of adiponectin in glucose metabolism in closely related to organs and tissues.
The Role of Adiponectin in Glucose Homeostasis

Regulation of islet function by adiponectin

The effects of adiponectin on β-cell function are still speculative. Following the discovery of adiponectin, two adiponectin receptors (AdR-1 and AdR-2) were cloned [129]. The adiponectin receptors AdR-1 and AdR-2 are expressed in pancreatic islets, specifically, on the beta cells. Although both subtypes are present, AdR-1 is the predominant form, at least in the mouse [130]. Given that globular adiponectin has a stronger affinity for AdR-1, the globular domain of adiponectin might be a potent and effective fragment affecting β-cell function [131]

The direct effect of adiponectin on insulin secretion in β-cells has been examined in several studies but with variable and inconsistent results. Although adiponectin stimulates insulin secretion by enhancing exocytosis of insulin granules, expressions of the insulin gene and its transcription factors, it apparently has a dual effect on insulin secretion that is dependent on the prevailing glucose concentration and status of insulin resistance [131]. Beyond affecting the insulin secretion in β-cells, several investigations have demonstrated that adiponectin has anti-apoptotic effects on beta cells, both in cell culture and islet preparations [130]. The antiapoptotic properties of adiponectin are mediated by activation of PI3K-Akt and MEK-ERK1/2 pathways [132], ERK had a delayed response to adiponectin, whereas Akt activity was enhanced by both acute and chronic treatment. Typically, adiponectin-induced Akt phosphorylation is suggested to be downstream of AMP-activated protein kinase (AMPK) activation [133]. However, it remains unclear whether adiponectin directly activates AMPK in β-cells because experiments with isolated mouse islets report that adiponectin does not affect the phosphorylation of AMPK at 5.6 mmol/L of glucose [134], indicating that adiponectin may not be able to activate AMPK under basal glucose concentrations because AMPK may already be activated by glucose itself [135].

The epidemiologic evidence demonstrates a close association between adiponectin and β-cell dysfunction [136]. Considering the therapeutic potential of adiponectin on β-cells as well as insulin-resistant peripheral tissues, it is crucial to develop adiponectin as a new medication available for human use. Although β-cell dysfunction is by no means the sole pathophysiological feature of type 2 diabetes mellitus, studies to elucidate the mechanisms by which adiponectin improve β-cell function would provide a means to preserve β-cells in humans and thereby contribute toward understanding, preventing, and controlling diabetes [137].
Effects of adiponectin on skeletal muscle metabolism

Being a major source of glucose uptake, skeletal muscle plays a key role in insulin sensitivity [130]. The antidiabetic effects of adiponectin are well characterized and regulation of skeletal muscle metabolism is an important contributory mechanism. Early work in cultured mouse or rat skeletal muscle cells found that adiponectin increased glucose uptake and regulated the subsequent metabolic fate [138-141]. Similar findings were made in primary human skeletal muscle cells [142] and muscle strips from human patients [143].

AdR-1 is also the major adiponectin receptor found in skeletal muscle [130]. The AdipoR isoforms and APPL1 (adaptor protein containing pleckstrin homology domain, phosphotyrosine binding domain and leucine zipper motif)-dependent downstream signaling events play a vital role in adiponectin's metabolic effects in muscle [144]. APPL1 mediates adiponectin-stimulated phosphorylation of AMPK and p38 MAPK in muscle cells. Coexpression of either kinase-inactive AMPK or kinase-inactive p38 MAPK with HA-tagged GLUT4 only partially suppressed adiponectin-stimulated GLUT4 membrane translocation. These results suggest that an AMPK and p38 MAPK-independent pathway may also be involved in adiponectin-stimulated GLUT4 membrane translocation. Interaction between APPL1 and Rab5 (a small GTPase) mediates adiponectin-stimulated phosphorylation of AMPK and p38 MAPK in muscle cells [127]. Therefore, when circulating adiponectin levels fall or skeletal muscle becomes resistant to adiponectin action, the lack of proper glucose and fatty acid homeostasis in muscle contributes to the development of diabetes [144].

Effects of adiponectin on hepatic glucose production

Adiponectin has several effects on the hepatic glucose production. One of the most prominent of these is the inhibition of hepatic glucose output, lowering systemic glucose levels. Adiponectin acts to improve the hepatic insulin sensitivity, thus glucose synthesis is significantly suppressed for any given dose of insulin in the presence of physiological doses of adiponectin [130]. On the other hand, adiponectin induces fatty acid oxidation and glucose uptake, and suppresses gluconeogenesis in muscle and liver, thereby improving peripheral insulin sensitivity [145]. Adiponectin acts to suppress the expression and activity of key regulators in gluconeogenesis, such as phosphoenolpyruvate carboxykinase and glucose-6-phosphatase [146]. Whereas murine euglycaemic clamp experiments have shown no difference in rates of glucose disappearance, glycolysis or glycogen synthesis in the presence or absence of intravenous adiponectin infusion [147], again highlighting adiponectin's main effect, which is to lower blood sugar by suppressing hepatic glucose output rather than disposal [130,148].
Adiponectin Level in Diabetic Animals and Patients

Recent data strongly supports that adiponectin plays a pivotal role in the pathogenesis of type 2 diabetes. The adiponectin gene is located on chromosome 3q27, which has been reported to be linked to type 2 diabetes and the metabolic syndrome [149-151]. Therefore, the adiponectin gene appears to be a promising candidate susceptibility gene for type 2 diabetes. Among the SNPs (single nucleotide polymorphism) in the adiponectin gene, 1 SNP located 276 bp downstream of the translational start site (SNP 276) was concomitantly associated with decreased plasma adiponectin level, greater insulin resistance, and an increased risk of type 2 diabetes [152].

For the animal model, the plasma levels of adiponectin were decreased in parallel to the progression of insulin resistance in obese and diabetic monkeys [153]. And also for ob/ob diabetic mice, there is a decrease in adiponectin levels when compared with age-matched lean animals [154]. For clinical patients, plasma adiponectin concentrations are decreased in obese subjects and type 2 diabetic patients and other insulin-resistant states [155]. In sum, the decreased plasma adiponectin concentrations can be found in diabetic animals and patients.

Treatment of Diabetes

The clinical significance of our current understanding of adiponectin biology have two aspects; Firstly, adiponectin can be regarded as a robust biomarker for identifying individuals with metabolic syndrome; Secondly, adiponectin is an attractive therapeutic target because the well documented widespread beneficial physiological actions of adiponectin spanning diabetes, inflammation, cardiovascular diseases and cancer have provided much impetus for discovery and development of adiponectin-based therapeutics [156].

The discovery of adiponectin has contributed to the understanding of metabolic disorders, because substantial data have revealed its role in the development of insulin resistance, T2D, and cardiovascular disease (CVD). Currently, intensive lifestyle modifications and several agents (e.g., PPAR-γ or PPAR-α agonists, some statins, angiotensin converting enzymes inhibitors, angiotensin II receptor blockers, some calcium channel blockers, mineralocorticoid receptor, new β-blockers, and several natural compounds) have been demonstrated to be effective in increasing circulating adiponectin levels to prevent metabolic syndrome, T2D, and CVD. In sum, identifying new agents that have adiponectin-raising properties are important. Recombinant adiponectin will be a challenging therapeutic strategy for these diseases in the future despite some studies that have shown no effect of recombinant adiponectin in animals [157].
Ghrelin

Ghrelin is the endogenous ligand of the G protein-coupled growth hormone secretagogue receptor, which was discovered from stomach by Masayasu Kojima and colleagues in 1999. They named it “ghrelin” for the reason that after the word root “ghre” in Proto-Indo-European languages meaning “grow,” since ghrelin has potent growth hormone (GH) releasing activity [158]. Ghrelin mainly secreted from the stomach mucosa but it is also expressed widely in different tissues such as small intestine, brain, cerebellum, pituitary, heart, pancreas, salivary gland, adrenal, ovary, and testis. It is initially produced within neurocrine cells as a 117 amino-acid preproghrelin and then processed by preprotein convertase 1/3 to a 28-amino-acid peptide. This 28-amino-acid peptide is a peptide hormone in which the third amino acid, usually a serine but in some species a threonine, is modified by an octanoic acid; this modification is essential for ghrelin’s activity [159]. In 2008, two independent groups reported that ghrelin O-acyl transferase (GOAT) account for this acylation. Actually, majority of circulating ghrelin exists as des-acyl ghrelin, identical to acyl-ghrelin except that the third amino acid serine is not acylated [160,161].

The Functions of Ghrelin

Orexigenic hormone, ghrelin, which secreted from the stomach into the bloodstream under fasting conditions, it transmits a hunger signal from the periphery to the central nervous system. Ghrelin exerts wide physiological actions throughout the body, including growth hormone secretion, appetite and food intake, gastric secretion and gastrointestinal motility, glucose homeostasis, cardiovascular functions, anti-inflammatory functions, reproductive functions, and bone formation [162]. In recent years, many scholars focus on the research about the role of ghrelin in glucose metabolisms. However, there are with large controversies and mechanisms need further explored.

The Relationship Between Ghrelin and Insulin Secretion

Studies show that ghrelin is highly expressed in pancreases. Yukart Date et al. reported that ghrelin is present in pancreatic α-cells which increased the cytosolic free Ca2+ concentration in β-cells and stimulated insulin secretion [163]. In contrast, Wierup et al. regard that ghrelin is expressed in a novel endocrine islet cell type named ε-cell [164]. The direct effect of ghrelin on insulin secretion in β-cells has been examined in several studies but with variable and inconsistent results. Martina Kvist Reimer et al. found high does of ectogenic acylated ghrelin (150 nmol/kg) induced a rapid rise in glucose and insulin levels, while lower dose of 5 nmol/kg and only slightly inhibited insulin secretion, which show that the effect of ghrelin on insulin release is dependent on the dose and elicited on distal signaling steps in islet cells [165]. Other studies demonstrated that ghrelin is able to suppress in-
sulin secretion in several in vitro experimental models, including rodent islets, pancreatic cell lines perfused rat pancreas and human subjects [166-168]. Ghrelin receptor antagonism or neutralization of endogenous ghrelin significantly increases insulin release from perfused pancreas [166]. Ghrelin attenuates glucose-induced insulin release via PTX-sensitive Gαι2-mediated activation of Kv channels and suppression of [Ca2+]i in β-cells, representing the unique signaling of ghrelin distinct from that for growth hormone release [167].

The Relationship Between Ghrelin and Glucose Uptake

An investigation suggests that ghrelin appears to directly potentiate insulin-stimulated glucose uptake in adipocyte. Therefore, ghrelin may play a role in adipocyte regulation of glucose homeostasis [168]. Besides, ghrelin may also have direct insulin-sensitizing effects on skeletal muscle. Muscle expresses the putative ghrelin receptor GHS-R1b, although a function for this receptor remains to be described [169]. Wylie W Vale et al. found that ghrelin enhanced glucose uptake in C2C12 cells, induced GLUT4 translocation to the cell surface [170]. While our experiments show that ghrelin contributes to derangements of glucose metabolism induced by rapamycin via altering the expression and translocation of GLUT4 in muscles [171].

Effects of Ghrelin on Hepatic Glucose Production

Ghrelin was shown to activate the insulin-signaling cascade and to independently stimulate expression of glucogenic genes in cultured hepatocytes. Sustained ghrelin treatment was associated with hyperglycemia and increased transcript levels of the key enzyme of the gluconeogenic pathway, glucose-6-phosphatase, in keeping with in vitro findings [172]. Changes in phosphorylated AMP-activated protein kinase (AMPK) and total and phosphorylated acetyl-CoA carboxylase (ACC) further support the involvement of altered AMPK signaling in hepatic effects of ghrelin treatment and indicate a link between ghrelin and AMPK in vivo [173]. In conclusion, ghrelin induced a lipogenic and glucogenic pattern of gene expression and AMP-activated protein kinase in liver [174].

In addition, ghrelin hampers insulin’s capacity to suppress endogenous glucose production, whereas it reinforces the action of insulin on glucose disposal, independently of food intake and body weight. These metabolic effects are unlikely to be mediated by the GHS receptor. Furthermore, simultaneous administration of des-ghrelin abolishes the inhibitory effect of ghrelin on hepatic insulin action. Glucose output by primary hepatocytes is time- and dose-dependently stimulated by acylated ghrelin and inhibited by unacylated ghrelin [175]. Moreover, unacylated ghrelin counteracts the stimulatory effect of acylated ghrelin on glucose release. These actions might
be mediated by a different receptor than GHS-R1a, and apparently, acylated ghrelin and unacylated ghrelin must be considered as separate hormones that can modify each other’s actions on glucose handling, at least in the liver [176].

Ghrelin and Diabetes

Shinya Ishii et al. found that plasma ghrelin concentrations in untreated diabetic rats were significantly higher than in control rats and were normalized by insulin treatment, the elevated plasma ghrelin levels could contribute to the diabetic hyperphagia in part by increasing hypothalamic (neuropeptide Y) NPY [177]. While recent studies have shown that ghrelin concentration in the patients with diabetes mellitus type 2 is lower than normal, higher BMI in subjects with lower ghrelin levels [162]. Total plasma ghrelin as well as unacylated ghrelin concentrations are lower in obese patients with metabolic syndrome compared to nonobese counterparts [178]. Furthermore, among obese subjects, plasma ghrelin levels are lower in insulin resistant persons compared to insulin sensitive persons [175]. Circulating ghrelin concentrations are also reduced in healthy offspring of type 2 diabetic patients indicating the presence of possible genetic component in the regulation of ghrelin plasma levels [179].

The ghrelin Arg51Gln mutation is associated with low plasma ghrelin concentrations. Pöykkö et al. found that the ghrelin 51Gln allele could increase the risk for Type 2 diabetes and hypertension [180].

Therapy of Diabetes

In type 1 diabetes a decreased ghrelin level can be found, which is probably a compensating mechanism for hyperglycemia. Lowering of the ghrelin level was also seen in insulin resistant adolescents with diabetes risk factors. The hormone inhibits apoptosis and takes part in the promotion of the β-cells proliferation and regeneration [162]. In addition, discovery of the new cells producing ghrelin in pancreas (ε-cells) opens new perspectives in the field of the glucose metabolism control [164]. Possibly, ghrelin producing cells or their precursors might become, in the future, a source of β-cells to transplant them to the patients with diabetes [181]. While Shin et al. found that the ghrelin agonist RM-131 accelerates gastric emptying of solids and reduces symptoms in patients with type 1 diabetes mellitus [182]. Moreover, administering the antibodies against ghrelin or the ghrelin receptors antagonists prevented the active energetic balance caused by this hormone and improved the glucose tolerance in type 2 diabetes [162].

Nesfatin-1

Nestfatin, an 82 amino acids peptide, is discovered by Oh-I S et al. as a satiety molecule that is associated with melanocortin signalling in the hypothalamus. As an anorexir nucleobindin-2 (NUCB2)-derived hypothalamic peptide, nesfatin controls appetite and energy metabolism
NUCB2 mRNA was predominantly expressed in the pituitary and at lower levels in the hypothalamus, spleen, thymus, heart, liver, and muscle of both male and female mice. Expression was much higher in reproductive organs, such as the testis, epididymis, ovary, and uterus, than in the hypothalamus, suggesting that nesfatin-1/NUCB2 have widespread physiological effects in endocrine and non-endocrine organs [184]. NUCB2/nesfatin-1’s physiological property is to reduce food intake and also gave rise to an involvement in the long term regulation of body weight, especially under conditions of obesity. In addition, studies indicated the involvement of NUCB2/nesfatin-1 in other homeostatic functions as follow: glucose homeostasis, water intake, gastrointestinal functions, temperature regulation, cardiovascular functions, puberty onset and sleep. Recently, the involvement of NUCB2/nesfatin-1 in glucose homeostasis has been investigated giving rise to the speculation that NUCB2/nesfatin-1 represents a peptidergic link between eating and diabetes [185].

**Regulation of islet function by Nesfatin**

Gonzalez R et al. found pronesfatin immunopositive cells exclusively in the pancreatic islets, insulin producing beta cells colocalize pronesfatin in the islets of both mice and rats. No colocalization of glucagon and pronesfatin was found in mice, while some glucagon positive cells were positive for pronesfatin in rat islets. The abundant presence of pronesfatin immunoreactivity and its colocalization with insulin suggests a potential role for pronesfatin-derived peptides in islet biology and glucose homeostasis in rodents [186]. NUCB2/nesfatin-1 is locally released from rat pancreatic islets following stimulation with glucose supporting a regulatory action of nesfatin-1 secretion in response to increasing glucose levels [187-189]. The expression of NUCB2 in the endocrine pancreas is regulated by the glycemic state with a reduced protein expression in type 2 diabetic Goto-Kakizaki rats compared to normoglycemic Wistar rats [187] and in human islets of type 2 diabetic subjects obtained from an islet transplantation center [190]. Functional in vitro studies using rat or mouse isolated islets or cultured MIN cells demonstrated that nesfatin-1 stimulates the expression of pre-proinsulin mRNA expression and increases the glucose-induced insulin release through stimulation of calcium influx involving L-type channels [188,191,192]. Whereas, another study using isolated mouse islets or INS-1 (832/13) cells did not observe an increase in insulin secretion but showed a stimulation of glucagon release. Matteo R et al. reported that nesfatin-1 is a novel glucagon-stimulatory peptide expressed in the beta cell and its expression is decreased in T2D islets [190].

**Nesfatin and Glucose Uptake**

Continuously infusing the nesfatin-1 via osmotic pumps into twelve-week-old male C57BL/6J lean mice, high fat diet-induced obese mice, which increase insulin...
secretion and insulin sensitivity via altering AKT phosphorylation and GLUT 4 membrane translocation in the skeletal muscle, adipose tissue and liver [193]. This observation was further confirmed in diabetic animal model, intravenous injection of nesfatin-1 reduces blood glucose levels in hyperglycemic db/db mice indicating an insulino-notropic effect [194]. In vitro experiments, R. Gonzalez et al. found insulin-stimulated glucose uptake in L6 muscle cells was inhibited by nesfatin-1 pretreatment, basal and insulin-induced glucose uptake in adipocytes from nesfatin-1-treated rats was significantly increased [188]. Furthermore, nesfatin-1 induce glucose uptake and mobilize glucose transporter GLUT-4 in human and murine cardiomyocytes [195], podocytes [196].

Nesfatin and Glucose Production

Infusion of nesfatin-1 into the third cerebral ventricle markedly inhibited hepatic glucose production (HGP), promoted muscle glucose uptake, and was accompanied by decreases in hepatic mRNA and protein expression and enzymatic activity of phosphoenolpyruvate carboxykinase (PEPCK) in both standard diet- and HFD-fed rats through a neural-mediated pathway [197].

Nesfatin and Diabetes

Dong et al. observed that nesfatin-1 secretion was significantly increased while expression of nesfatin-1 neurons were decreased in hypothalamus in diabetes group compared to only high-calorie diet control group; whereas blood glucose and insulin resistance coefficient decreased with treatment of nesfatin-1 in diabetes mice [198]. Not only the mouse experiments, circulating levels of NUCB2/nesfatin-1 show an inverse relationship with circulating glucose in Goto-Kakizaki rats [186], a finding also confirmed in type 2 diabetic human subjects, fasting nesfatin-1 was significantly lower in T2 DM patients compared to healthy subjects, indicating the reduction in fasting nesfatin-1 may be one of the appetite-related hormones involved in diabetic hyperphagia [199]. Furthermore, intravenous administration of nesfatin-1 decreased the blood glucose level significantly in hyperglycemic db/db mice (mimics of Type 2 diabetes model) but not in streptozotocin-mediated diabetes model, suggesting effect of nesfatin-1 is insulin-dependent [200].

In addition, nesfatin-1 levels were found lower in patients with gestational diabetes mellitus (GDM) compared with control pregnant women. Maternal serum and cord blood nesfatin-1 levels correlated negatively with the gestational age, but there was no correlation with the birth weight [201].

In sum, most studies are consistent with lower NUCB2/nesfatin-1 levels as an underlying mechanism contributing to the glucose intolerance under conditions of diabetes. However, an investigation reported enhanced plasma NUCB2/nesfatin-1 levels in Chinese patients with newly diagnosed type 2 diabetes mellitus or impaired glucose tolerance compared to healthy subjects [202,203].
The reasons for these divergent results still need further exploration and should take into account potential specific racial and genetic factors [188].

Because of its effect on increasing insulin secretion, nesfatin-1 may be used as an anti-diabetic agent. Studies suggested that nesfatin-1 plays a role type 2 diabetes mellitus (T2DM) via stimulating free acid utilization [199]. However, in another study nesfatin-1 has been described as a novel stimulatory agent for glucagon secretion in beta cells. Additionally, they showed decreased expression level of nesfatin-1 in type-2-diabetes islets which may provide a compensatory mechanism to overcome hyperglycaemia [190]. Therefore the precise physical and pathophysiological effects of nesfatin-1 on glucose and energy mechanism still remain unknown [198].

Conclusion

The prevalence of obesity and diabetes has grown to epidemic proportions over the past thirty years, principally as a consequence of prolonged high carbohydrate- and high fat- containing diet in combination with decreased physical activity, and with this an alarming increase in the incidence of type 2 diabetes has emerged [123,204]. Diabetes mellitus is a common and costly chronic medical illness while lack of adherence to diabetic self-management regimens is associated with a high risk of diabetes complications such as loss of vision, renal failure, foot ulcers, cardiovascular disease, stroke or even cancer, etc. [1-4,45,205]. Diabetes actually is, in a sense, a consequence of hormonal imbalance. All of body’s hormones work together and affect each other, so imbalances of other hormones can lead to insulin imbalances or insulin resistance. So far most hormones are not available to diabetes treatments, further researches are needed to investigate the safety and efficiency of hormonal basis therapy. Although many findings break new ground, none of the currently available medications are successful as long-term monotherapy and none of them have effectively halted the continuous decline in beta-cell mass [206]. So there is still room for additional mechanisms of action and hopefully that in the next couple of years investigators will yield a more complete picture of how these hormones have function on diabetes.

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