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Chapter

Emerging Role of Pancreatic β-Cells during Insulin Resistance

Alpana Mukhuty, Chandrani Fouzder, Snehasis Das and Dipanjan Chattopadhyay

Abstract

In today's world, type 2 diabetes has become a part of every household and leads to various complications including high blood sugar level, diabetic retinopathy, diabetic foot, diabetic nephropathy and diabetic neuropathy. Yet people lack awareness about this disease and its detrimental effects. For a better understanding of this disease we must know about the causes and preventive measures since the medications used in treating type 2 diabetes have moderate to severe side effects. Type 2 diabetes is characterized by loss of insulin receptor activity in skeletal muscle and adipocytes, compensatory insulin secretion from pancreatic β-cells, β-cell dysfunction and death. The proper functioning of β-cells is a major criterion for preventing advent of type 2 diabetes. The different natural or physiological insulin secretagogues include glucose, amino acids and fatty acids, which stimulate insulin secretion under the influence of various hormones like incretins, leptin, growth hormone, melatonin and estrogen. However, excess of nutrients lead to β-cell dysfunction and dearth of insulin involving various signal molecules like SIRT1, PPARγ, TLR4, NF-KB, Wnt, mTOR, inflammasomes, MCP1, EGFR, and Nrf2. A deeper insight into the functioning of these signaling molecules will also create new avenues for therapeutic interventions of curing β-cell dysfunction and death.

Keywords: insulin resistance, pancreatic β-cell dysfunction, lipotoxicity, glucotoxicity, type 2 diabetes

1. Introduction

Changing food habits, sedentary lifestyle and obesity has made type 2 diabetes (T2D) a global epidemic. T2D has various characteristic features such as insulin resistance caused when peripheral tissues such as liver, muscle and adipocytes have a decreased response to insulin. The progression from normal glucose tolerance to type 2 diabetes involves several transitional stages of impaired fasting glucose and impaired glucose tolerance which is known as prediabetes. The mechanism leading to the development of these glucose metabolic alterations is multifactorial. The most prevalent factor of T2D is insulin resistance that occurs when peripheral tissues such as liver, muscle and adipocytes, the main target organs of Insulin hormone, loses the ability to respond to insulin [1]. Generally in the obese patients without T2D and initially in people who develop insulin resistance, pancreatic β-cells are able to compensate for insulin resistance by increasing insulin secretion by increasing β-cell mass via increased proliferation and hypertrophy [2, 3].

Increasing of β-cells in a compensatory mechanism to avoid the complications caused due to insulin resistance and henceforth prevents diabetes [4]. This unique mechanism of β-cell mass expansion has been observed in normal individuals during physiological growth [5] as well as in insulin resistant patients, especially pregnant women [6] and obese people [7]. In patients having T2D the initial stage of β-cell compensation is followed by dysfunction or failure of β-cells due to less proliferation and increased apoptosis [1, 8].

Pancreatic β-cell dysfunction plays a critical role in progression of T2D. Insulin is produced as preproinsulin and then processed to proinsulin. Proinsulin is then converted to insulin and C-peptide and stored in secretory granules. Synthesis of insulin is regulated at both transcription and translational level. Several transcription factors in the cis-acting sequences within the 5′ region and trans-activators regulate insulin gene transcription. These transcription factors are paired homeobox gene 6 (PAX6), pancreatic and duodenal homeobox-1 (Pdx-1), MafA and B-2/Neurogenic differentiation 1 (NeuroD1). Insulin secretion from β-cells contains a series of events and is controlled by variety of factors and signaling pathways that ultimately leads to the fusion of secretory granules with the plasma membrane. The various stimulants that regulate insulin secretion are glucose, free fatty acids, amino acids, also various hormones like melatonin, estrogen, leptin, growth hormone and glucagon like peptide-1 [9].

2. Structure of insulin

The monomeric structure of insulin is made up of "A" chain with 21 amino acids and "B" chain with 30 amino acids, which are bound by disulfide bonds. Actually three disulfide bonds are present in the structure of insulin monomer, two in between the A and B chains (A7–B7, A20–B19) and one within the A chain (A7–A11) [10]. The secondary structure of the A chain is made up of two antiparallel α-helices in between A2–A8 and A13–A19 residues. Also the helices are connected by residues at A9–A12. As a result of this particular arrangement the two ends remains in close proximity to each other and side by side [11].

The B chain is made up of α-helices and β-pleated sheets [11] and in the T state it exists in two different conformations in crystallized form [12]. The α-helix exists between B9 and B19, a β-turn between B20 and B23 and the chain folds in a "V" due to Gly20 and Gly23. An extended β-strand structure in between residues B24 and B30 which allows the chain to be in close proximity to form a β-sheet with PheB24 and TyrB26 which are in close contact with B11 and B15 leucine residues of α-helix. There is a continuous α-helix from B1 to B19 in the R state. The stability of the native insulin structure is due to the disulfide bonds in between Cys residues A7–B7 and A20–B19. The affinity of insulin towards the insulin receptor is determined by the side chain interactions in between A chain and B chain. These disulfide bonds between the A and B chain provide the tertiary structure of insulin monomer which is very highly organized. The various amino acid interactions in the side chain also contribute to the stable tertiary structure of the insulin monomer molecule. These interactions are also responsible for the interaction or affinity of insulin towards its receptor [11].

The hydrophobic inner core of the insulin monomer is composed of the following amino acids residues: A6–A11 and Leu A11, B1 and B15, Ile A2, Phe B24, Val A3, Ile A13, Val B18 and Val B12. The amino acid residues from B20 to B23 are necessary for stabilizing the β-turn thereby leading to the folding of the β-sheet in between B23 and B30 towards the α-helix and hydrophobic inner core. In the dimeric form of insulin these non-polar amino acids remain in the inner side. The insulin subunits

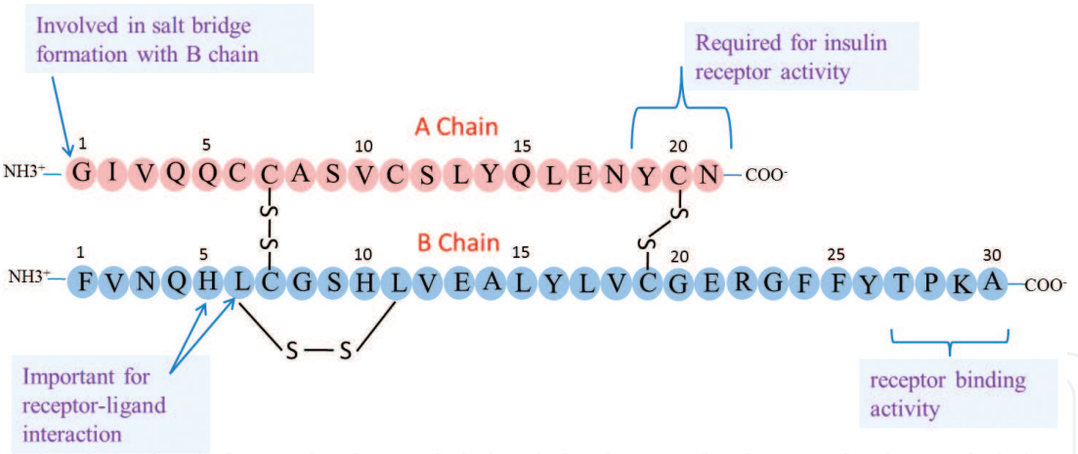

Figure 1.
Structure of insulin [10, 11, 12, 20].

generally remain as dimers [12]. The dimeric form of insulin is stabilized by the antiparallel β-sheets at the carboxy terminals of the B chains which remain expose on the surface of the dimeric structure. The hydrophobic core of the insulin dimer is composed of non-polar residues [11].

There are three dimers made up of six molecules of insulin peptide to make a hexamer. Some differences in the side chain like in the 25th residue (Phe) in the B chain, which is arranged to be inside the hydrophobic core of the peptide chain on one side of the dimer, deforms the perfect two-fold symmetry [11]. Also there are two zinc atoms with the imidazole groups in three histidine residues in the B chain along with two water molecules in the insulin hexamer [12].

The knowledge about the structure of insulin is necessary to understand its interaction with insulin receptor. The amino acids in the specific regions of the insulin molecule that facilitate its binding with the receptor are located at the amino terminal of the A chain: GlyA1, IleA2, ValA3, GluA4: carboxy terminal of the A chain: TyrA19, CysA20, AsnA21; and carboxy terminal of the B chain: GlyB23, PheB24, PheB25, TyrB26. These residues have are denoted as the "cooperative site" of the insulin due to their negative cooperativity [13, 14].

- Out of the two chains in the structure of insulin, the A chain has more significant role for binding to the receptor. Acetylation of the amino terminal reduces binding to receptor by 30% which makes a free amino terminus necessary for binding to receptor [15].
- Gly1 deletion reduces binding to receptor by 15% which may be due to some salt bridge formation between Gly1 and B chain carboxy terminus [16].
- Also TyrA19, CysA20 and AsnA21 in the carboxy terminus of the A chain are also necessary for insulin receptor activity [16].
- The carboxy terminal of the B chain has also a significant role in the receptor binding activity, specially the first four residues, whose deletion reduces receptor binding activity by 30% [17, 18].
- Fifteen percent of the receptor binding activity is detained when HisB5 is deleted and 1% of binding activity is reduced when LeuB6 is deleted [19].
- For the maintenance of disulfide bonds between A and B chain, CysB7 is critical [20].

- HisB10 is necessary for activity because when substituted with AspB10, proinsulin is not converted to insulin [21].

- However, synthetic insulin containing AspB10 has 500% greater binding affinity than normal insulin [22].

- PheB24 forms hydrogen bonds important for dimer formation and PheB25 is important for conformation of the native insulin structure [16].

- GlyB23, PheB24, PheB25 and TyrB26 in the B chain carboxy terminus are evolutionarily conserved residues needed for receptor binding [16] (**Figure 1**).

3. Insulin synthesis

The various stimulants in blood that lead to insulin secretion are glucose, monosaccharide, amino acid and fatty acid.

3.1 Glucose stimulated insulin secretion

Glucose acts as the main stimulus for insulin secretion in rodents as well as human beings because it is one of the major constituents of their diet and enters the circulation immediately after digestion of food. Glucose transporter 2, i.e., GLUT2 is the main glucose sensor found in the plasma membrane of β-cells. Translocation of GLUT2 to plasma membrane is dependent on insulin and it bears low substrate affinity, hence leading to high uptake of glucose. Upon entry into β-cell glucose is phosphorylated to glucose-6-phosphate by glucokinase, a type of hexokinase. Glucokinase is the rate-limiting step in the glucose metabolism in β-cells [23]. Since pyruvate dehydrogenase is not found in β-cells, pyruvate is metabolized to produce metabolic coupling factors via two pathways: (a) pyruvate is metabolized to acetyl-coA and thereby it enters glucose oxidation: the main signaling pathway couple to pyruvate oxidation through the tricarboxylic acid cycle (TCA) by mitochondria "ATP-sensitive potassium (K_{ATP}) channel-dependent insulin release." The other pathway is anaplerosis where pyruvate, like other TCA cycle intermediates is replenished. However, some of the products of these processes can act as signals stimulating release of insulin, like malonyl-CoA, NADPH, and glutamate. These products are known to amplify K_{ATP} channel-dependent insulin secretion [24, 25].

Formation of glycerol-3-phosphate (Gly3P) is the third glucose signal. Glucokinase phosphorylates glucose into glucose-6-phosphate (G6P), G6P then enters glycolysis to produce pyruvate. Gly3P can also be produced by G6P via dihydroxyacetone phosphate (DHAP) pathway. These compounds stimulate insulin secretion. Gly3P also promotes β-cell glycolysis via the mitochondrial Gly3P NADH shuttle process, which activates mitochondrial energy metabolism and augments insulin secretion [26, 27]. Dysfunction of β-cells after prolonged exposure to elevated levels of glucose has been linked to changes in glucose detection and metabolism, apoptosis, and calcium handling. Now it has already been reported that glucotoxicity impedes final steps in insulin secretion, i.e., exocytosis [28].

3.2 Fatty acids and insulin secretion

Free fatty acids (FFAs) exert both positive and negative effects on β-cell survival and insulin secretory function, depending on concentration, duration, and glucose abundance. Insulin secretion from β-cell is also stimulated by free fatty acids (FFAs).

The FFAs can also upregulate glucose stimulated insulin secretion (GSIS) from β-cells. In total absence of FFAs the β-cells lose their insulin secreting capability which can again be restored when exogenous fatty acids are added [29–31]. The FFAs act upon β-cells through free fatty acid receptor (FFAR)-1, hence controlling β-cell function [32, 33]. The intracellular metabolism of FFA leads to the production of lipid signal molecules like long-chain acyl-CoA and DAG [34]. DAG in turn activates protein kinase C (PKC), which in turn tales part in insulin secretion [35]. The effect of fatty acids on pancreatic islet insulin release depends mainly on degree and time of exposure. Circulating low levels of free fatty acids in the range of physiologic postprandial values actually aids in enhancing glucose-induced insulin secretion. However, excessive accumulation of lipids within islets impairs insulin secretion [36].

3.3 Amino acid stimulated insulin secretion

At individual concentrations amino acids found in physiological concentrations are poor insulin secretagogues. Some combinations of amino acids at physiological concentrations are capable of enhancing GSIS [37], like that of, glutamine cannot stimulate insulin secretion or enhance GSIS alone, but in combination with leucine, glutamine is capable of stimulating insulin secretion from β-cells and enhancing GSIS [38]. Leucine activates glutamate dehydrogenase, and glutamate dehydrogenase can convert glutamate to α-ketoglutarate, leading to production of ATP and stimulating insulin secretion [37]. Two important incretin hormones secreted from K-cells and L-cells in the gastrointestinal tract, Glucose dependent insulinotropic peptide (GIP) and glucagon-like peptide-1 (GLP-1), are stimulated to be secreted after ingestion of nutrients like glucose and amino acids. These hormone levels rise in the circulation after feeding food rich in protein and carbohydrates. Then they directly trigger insulin secretion from β-cells by binding to their specific cell-surface receptors, hence enhancing GSIS [39–41].

4. Regulation of insulin secretion

4.1 Neural and hormone regulation

4.1.1 GLP-1

GLP-1 is an incretin hormone secreted from small intestinal L-cells along with GIP when the nutrient content in blood is high generally after ingestion [42, 43]. Nutrient load from oral route triggers more insulin secretion than intravenous nutrient load [44]. GLP1-agonists and analogues are already used as an effective therapy for type 2 diabetes that are safe due to the glucose dependent effect on the insulin secretion and large randomized clinical trials proved their additional cardiovascular benefits [45]. GLP-1 acts upon β-cells due to the presence of GLP-1 receptor (GLP-1R). Activation of GLP-1R leads to activation of adenylyl cyclase, which in turn generates cAMP. Elevated level of cAMP in the cytosol enhances GSIS. Hence GLP-1 secretion is dependent on high blood glucose levels [45, 46].

4.1.2 Leptin

Leptin, secreted from adipocytes, regulates function of insulin upon the glucose storing fat and liver cells [47, 48]. However, in absence of leptin, hyperinsulinemia leads to drop in blood glucose levels [47, 49]. The inhibitory action of leptin has been well known in clonal β-cells [50], cultured rodent islets [51], perfused rodent

pancreas [50, 52], human islets [51, 53, 54] and mice islets [51]. Leptin inhibits insulin secretion by antagonizing the action of elevated intracellular cAMP [55]. 3-isobutyl-1-methylxanthine (IBMX) induces leptin, elevating cAMP content by inhibiting phosphodiesterases (PDEs) [56], the enzymes which catalyze hydrolysis of cAMP. GLP-1-induced insulin secretion is also inhibited by leptin, and GLP-1 which augments insulin secretion by activation of the cAMP signaling pathways [52].

4.1.3 Estrogen

In the "classical" mechanism of action of estrogen, the estrogen molecules diffuse into cell and bind to the estrogen receptor ER located in the nucleus. Rapid or "nongenomic" effects of estrogen are thought to occur through the ER located in or adjacent to the plasma membrane and may require presence of "adaptor" proteins, which target the ER to the membrane. Activation of the membrane ER leads to a rapid change in cellular signaling molecules and stimulation of kinase activity, which in turn may affect transcription [57].

β-cells are not general estrogen targets but the presence of estrogen receptor in islets makes the effect of 17β-estradiol on β-cells noteworthy [58, 59]. 17β-estradiol enhances insulin secretion from β-cells [60] and in humans, it is known to increase insulin secretion in postmenopausal women [61, 62], thus it augments glucose-stimulated insulin secretion (GSIS) [63]. Two types of are present in β-cells: (1) the estrogen receptors in the nucleus, i.e., nuclear ERs (ERα and ERβ) and (2) the estrogen receptors in the membrane, i.e., the membrane ER (ERγ) [64]. 17β-estradiol significantly decreases activity of K_{ATP} channel [60], causing membrane depolarization and opening of voltage-gated Ca^{2+} channels, thereby potentiating glucose-induced intracellular [Ca^{2+}] oscillations, in a reversible manner.

4.1.4 Melatonin

Melatonin, a hormone secreted by pineal gland, helps in maintaining circadian rhythm and biological clock [65]. However, melatonin receptors are found on clonal β-cells [66, 67] and human islets [68]. Melatonin shows both stimulatory [69] and inhibitory effects [70, 71], as well as neutral effects [72] on insulin section. However a decent number of reports have been found in literature about the inhibitory effect of melatonin in clonal β-cells [66, 68, 69, 73]. Melatonin inhibits glucose- and KCl-stimulated insulin secretion in rat islets [74]. Long term melatonin administration enhances hyperinsulinemia in vivo [75]. The signaling pathway of melatonin shows that melatonin receptor is coupled to Gi, which inhibits G protein [76]. Melatonin mediates stimulatory effect on insulin secretion through its receptor MTNR1A, by activation of Gq/11 which provokes release of IP3 by activating PLC-ε to augment insulin secretion [69, 77, 78].

4.1.5 Growth hormone

Growth hormone (GH) stimulates production of insulin-like growth factor-I (IGF-I) and its binding proteins [79]. Human IGF1 and IGF2 show high sequence similarity with insulin. Insulin receptor (IR) has two isoforms, IRA and IRB. IRB only binds insulin with high affinity while IRA binds both insulin and IGF2 with equal affinity. The IGF1 receptor (IGF1R) has high affinity towards both IGF1 and IGF2 but it binds insulin with very low affinity. According to the conventional view regarding the actions of insulin and IGF-1 in mammals, insulin mediates mainly a metabolic response, and IGF-1 mediates growth promoting effects in vivo [80]. Recombinant human IGF-I decreases serum levels of insulin and C-peptide in

human [81]. IGF-1 also suppresses insulin secretion in isolated rat islets [82]. This inhibitory activity of growth hormone is mediated through PDE3B activation [83], which is responsible for breaking down cAMP in β-cells.

4.1.6 Adrenergic and cholinergic agents

Adrenergic drugs (epinephrine, norepinephrine and isoproterenol) are known to inhibit insulin secretion by binding to alpha receptors present in rat pancreas. On the other hand cholinergic drugs (acetylcholine and carbamylcholine) stimulate insulin secretion but this effect is suppressed by simultaneous addition of atropine. Thus the autonomic nervous system regulates insulin secretion under physiological conditions [84] (**Figure 2**).

4.2 Regulation by signaling pathways

4.2.1 SIRT1

SIRT1, mammalian sirtuin homolog, plays a key role in energy homeostasis and extends a cell lifespan by calorie restriction [85]. Glucose metabolism is tightly coupled to the regulation of insulin secretion and β-cell function [86]. Till now there are two reports showing SIRT1 positively regulates glucose-stimulated insulin secretion in pancreatic β-cells [87, 88]. In β-cells, FoxO1 is constitutively phosphorylated in cytoplasm, and activates insulin receptor signaling [89]. Accumulation of FoxO1 in the nucleus of insulin-secreting cells is triggered by palmitate during induction of lipotoxicity and impairs insulin secretion [90, 91]. Increased expression of SIRT1 in pancreatic β cells in mice improves glucose tolerance by enhancing insulin secretion [87]; deletion of SIRT1 can impair glucose-stimulated insulin secretion [88]. In both these reports, SIRT1 enhances insulin secretion by transcriptional repression of uncoupling protein 2 (UCP2) [92]. Activation of SIRT1 gives

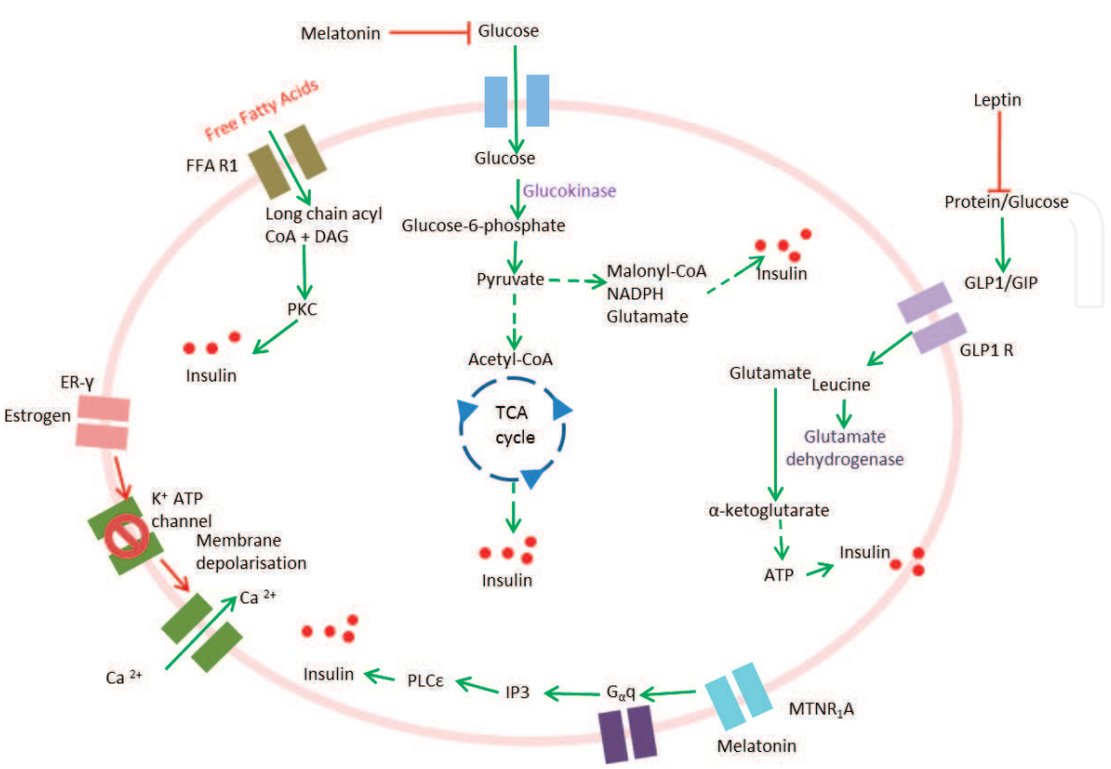

Figure 2.
Hormonal and nutrient regulation of insulin secretion [23, 26, 27, 32–35, 45, 46, 55, 57, 60, 64, 72].

protection from high-fat-induced obesity and insulin resistance [92–94], and slight overexpression of SIRT1 has a protective role from high-fat induced glucose intolerance [95–97]. If SIRT1 is inhibited then insulin promoter activity is suppressed, insulin regulatory genes such as v-maf musculoaponeurotic fibrosarcoma oncogene homolog A (MafA) and NK6 homeodomain 1 (NKX6.1) mRNA expressions are down regulated leading to decreased insulin secretion. On the contrary, activation or overexpression of SIRT1 antagonizes reduced insulin transcriptional activity by exerting negative effect on pancreatic and duodenal homeobox 1 (PDX1)-stimulated insulin promoter activity and also abolishes forkhead box O1 protein (FOXO1)-insulin transcriptional activity [98].

4.2.2 PPARγ

PPAR-γ regulates the major β cell genes involved in glucose sensing, insulin secretion and insulin gene transcription and protects from glucose, lipid, cytokine and islet amyloid polypeptide (lAPP)-induced stress pathways [99]. PPAR-γ is a member of nuclear hormone receptor superfamily of ligand-activated transcription factors and TZDs are oral agents that are high-affinity activators of PPAR-γ [100]. PPARγ ablation protects mice from high fat diet induced insulin resistance [101] and isolated islets from these mice show blunted TZD response towards GSIS [102]. Mice with PPAR-γ ablated pancreas show glucose intolerance at baseline with downregulated Pdx-1 and GLUT2 expression in their isolated islets [103]. Chronic high glucose can decrease PPAR-γ mRNA levels in mouse islets [104]. PPAR-γ is upregulated after 60% pancreatectomy procedure in rats changing to pro differentiation state from proliferative state [105]. Promoters of GLUT2 and glucokinase have functional PPREs that bind PPAR-γ/RXRα heterodimer, and lead to transcriptional upregulation of these genes in β cell [106, 107]. The expression of these genes is impaired in diabetic rodent models [108, 109].

PPARγ agonists modulate IAPP-induced ER stress [110]. The islet-specific KO of the ATP-binding membrane cassette transporter protein A1 (ABCA1) and PPAR-γ KO model both show increased intra-islet triglyceride accumulation and lowered GSIS [101, 111]. Rosiglitazone restores GSIS and decreases apoptosis in isolated human lipotoxic islets with a reduction in intra-islet triglyceride accumulation and reduced inducible nitric oxide synthase (iNOS) expression [112, 113]. PPAR-γ agonists also inhibit cytokine-induced activation of JNK in insulinoma cell lines [114]. PPAR-γ agonists have been shown to increase AKT phosphorylation in the setting of both IAPP-and lipid-inducted toxicity. These effects were blocked by PI3 kinase inhibitors and associated with increased levels of insulin receptor substrate 2 (IRS2) proteins [115].

Activation of PPAR-γ inhibits IL-1β and IFN-γ stimulated nuclear translocation of p65 subunit of NF-KB and DNA binding activity leading to reduced inducible nitric oxide synthase and cyclooxygenase-2 expression [116].

PPAR-γ activation also increases intracellular calcium mobilization, insulin secretion, and β-cell gene expression through GPR40 and GLUT2 gene upregulation [117]. Thus PPAR-γ agonists not only improve insulin sensitivity in the target tissues, but also act within the β-cells.

4.2.3 Wnt

Wnt signaling stimulates β-cell proliferation, specifically Wnt3a promotes expression of Pitx2, a direct target of Wnt signaling, and Cyclin D2, an essential regulator of cell cycle progression [118]. Single nucleotide polymorphisms (SNPs) in TCF7L2 are linked to etiology of T2D [119]. Expression of three Tcf genes

(Tcf7, Tcf7l1, Tcf7l2) in pancreas is reduced by treatment with insulin or high fat diet feeding [120]. A significant elevation of TCF7L2 mRNA expression occurs in pancreatic islets along with impaired insulin secretion [121]. TCF7L2 depletion in isolated human or mouse pancreatic islets results in significant increased β-cell apoptosis and decreased proliferation with attenuated GSIS. Over-expression of TCF7L2 protects islets from glucose- and cytokine-mediated apoptosis [122]. These findings suggest that β-cell function and survival are positively regulated by the expression of Tcf7l2 in type 2 diabetes.

4.2.4 mTOR

Rapamycin, an mTORC1 complex inhibitor, reduces the number and proliferation of pancreatic and endocrine progenitors. Mice lacking mTOR in pancreatic progenitors suffer from hyperglycemia in neonates, hypoinsulinemia and pancreatic agenesis/hypoplasia with pancreas rudiments containing ductal structures lacking differentiated acinar and endocrine cells [123].

AMP-activated protein kinase (AMPK) is a controller of β-cell function. Inhibition of AMPK in β-cells by high glucose inversely correlates with activation of the mammalian Target of Rapamycin (mTOR) pathway. Glucose and amino acid sensing ability of AMPK is important in regulation of insulin secretion [124]. Rapamycin also induces fulminant diabetes by increasing insulin resistance and reducing-cell function and mass [125].

Obesity induced by excess nutrient intake leads to the upregulation of mTORC1/S6K1 signaling in insulin-sensitive tissues, including β-cells [126–128]. mTORC1 activation play an initial role in adaptation to nutrient excess and obesity, but chronic and persistent hyperactivation could lead to development of insulin resistance by a negative feedback loop on IRS signaling [129].

4.2.5 MCP1

Monocyte chemoattractant protein-1 (MCP-1) a chemokine that regulates migration and infiltration of monocytes/macrophages, is constitutively present in normal human islet β-cells in the absence of an inflammatory infiltrate and plays a key role in monocyte recruitment [130]. NF-kappaB plays an important role for MCP-1 expression in β-cells [131]. MCP-1 also induces amylin expression through ERK1/2/JNK-AP1 and NF-κB related signaling pathways independent of CCR2. Amylin upregulation by MCP-1 may contribute to elevation of plasma amylin in obesity and insulin resistance [132].

4.2.6 Nrf2

The Keap1-Nrf2 signaling plays an important role in oxidative stress response and metabolism. Nrf2 prevents reactive oxygen species ROS mediated damage in pancreatic β-cells [133]. β-cells have low expression levels of antioxidant enzymes, making them susceptible to damage caused by ROS. GLP-1 effectively inhibits oxidative stress and cell death of β-cells induced by the pro-oxidant tert-butyl hydroperoxide (tert-BOOH) [134]. NOX activation through Src signaling plays an important role in ROS overproduction and impaired GSIS caused by lipotoxicity [135].

4.2.7 EGFR

Epidermal growth factor receptors are crucial regulators of β-cell proliferation and β-cell mass regulation. Partial tissue-specific attenuation of EGFR signaling in

islets leads to significantly reduced beta-cell proliferation [136]. Phosphorylation of ribosomal S6 kinase, a mammalian target of rapamycin (mTOR) target, is upregulated in islets from glucose and interleukin injected 6-month-old rats. β-cell mass expansion occurs in presence of chronic nutrient excess EGFR signaling, mTOR activation, and FOXM1-mediated cell proliferation [137].

4.2.8 ER stress

In pancreatic β-cells, the endoplasmic reticulum (ER) is an important cellular compartment involved in insulin biosynthesis. ER stress elicits a signaling cascade known as the unfolded protein response (UPR) which regulates both function and survivability of β-cells [138]. Chronic high glucose leads to insulin mRNA degradation by IRE1α activation, profuse XBP-1 splicing, and induction of pro-apoptotic effectors, such as Jun N-terminal kinase (JNK) and C/EBP homologous protein (CHOP), causing β-cell dysfunction and death [139–142]. Free fatty acids (FFAs) and inflammatory cytokines also induce ER stress in β-cells through upregulation of the proapoptotic effector CHOP, and JNK and caspase-12 activation by UPR [143–146].

4.2.9 Inflammasome

ER stress, oxidative stress and high glucose concentrations activates NLRP3 inflammasome leading to interleukin (IL)-1β production and caspase-1 dependent pyroptosis. Whether IL-1β or intrinsic NLRP3 inflammasome activation contributes to β-cell death is disputed [147].

The Nlrp3 inflammasome plays important role in obesity-induced insulin resistance and β-cell failure. Endocannabinoids contribute to insulin resistance through activation of peripheral CB_1 receptors (CB_1Rs) promoting β-cell failure [148]. *NLRP3*-knockout mice showed improved glucose profiles after a high-fat diet, due to attenuated IL-1β release from islet cells. Hyperglycemia-induced IL-1β release leads to increased ROS, dissociation of TXNIP from thioredoxin and its binding to NLRP3 and activation of NLRP3 [149].

4.2.10 TLR4

Toll-like receptor 4 (TLR4), a pattern recognition receptor, is a crucial element in the triggering of innate immunity, which binds to pathogen-associated molecules such as Lipopolysaccharide (LPS), and initiates a cascade of pro-inflammatory events [150]. TLR4 is also known to occur in pancreatic β-cells but its function is yet to be clearly established. β-cells respond to palmitate via TLR4/MyD88 pathway and produce chemokines that recruit M1-type proinflammatory monocytes/macrophages to the islets [151]. High fat diet-induced obesity stimulates TLR4 up-regulation in pancreatic β-cells, and lead to the recruitment of macrophage into pancreatic islet, which finally results in pancreatic β-cell dysfunction [152].

Fetuin-A, a secreted glycoprotein, can promote lipotoxicity in β-cells through the TLR4-JNK-NF-κB signaling pathway [153]. Later it was also discovered that pancreatic β-cells are capable of secreting fetuin-A under free fatty acid stimulation which ultimately leads to inflammation [154].

4.2.11 G-proteins

Medium- to long-chain fatty acids activate FFAR1/GPR40 and it is predominantly coupled to $G\alpha_q$ which signals through PLC-mediated hydrolysis of

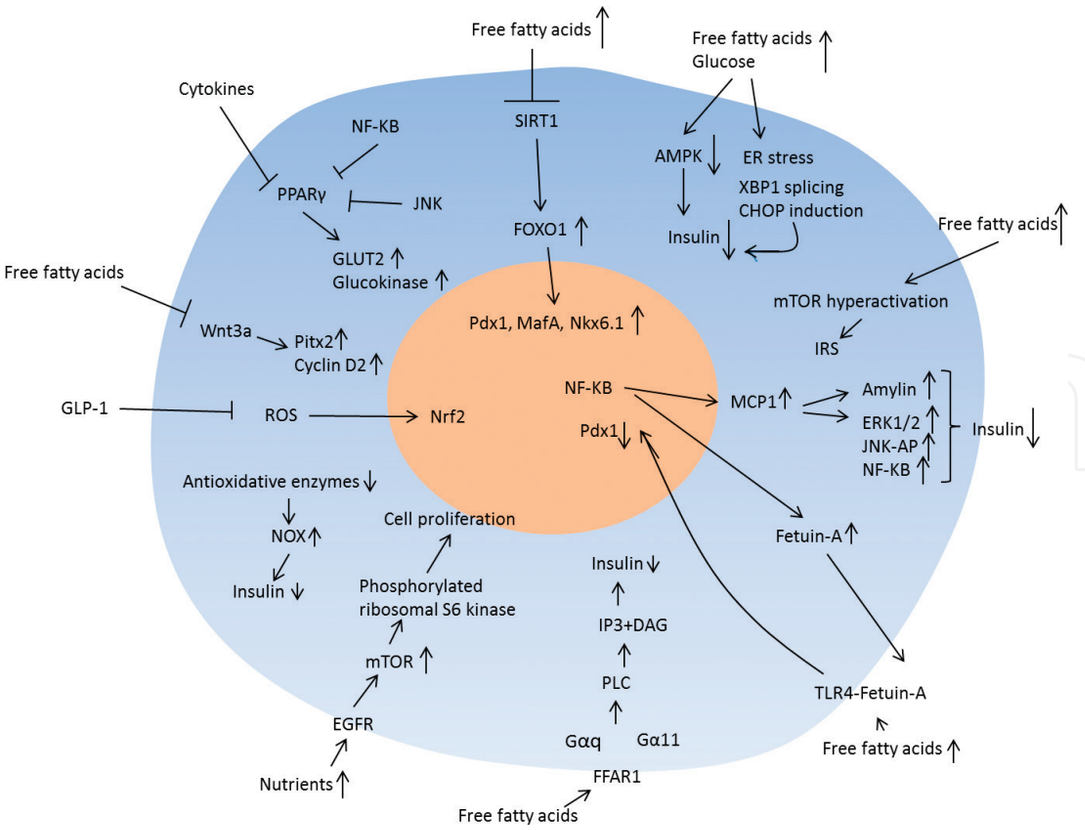

Figure 3.
Various signaling pathways regulating insulin secretion signaling [90, 91, 98, 99, 106, 107, 120, 129, 132, 134, 135, 137, 139–142, 153–157].

membrane phospholipids leading to the formation of IP_3 and DAG [155, 156]. Glucose tolerance and insulin secretion is impaired in mice due to β-cell-specific inactivation of the genes encoding the G protein α-subunits $G\alpha_q$ and $G\alpha_{11}$. Thus, G_q/G_{11}-mediated signaling pathway mediates insulin secretion by glucose stimulation [157] (**Figure 3**).

5. Conclusion

In conclusion, insulin secretion is stimulated by glucose, free fatty acids and amino acids after their breakdown in gut following ingestion. Glucose potentiates K_{ATP} channel-dependent insulin secretion. Free fatty acids result in insulin secretion from β-cells through free fatty acid receptor (FFAR)-1. Under incretin stimulation the amino acids trigger insulin secretion by binding to their cell surface receptors. Hormones like GLP-1 and estrogen stimulate insulin secretion, melatonin has both stimulatory and inhibitory effect and leptin and growth hormone have only inhibitory effects upon insulin secretion. Discussing about the various signaling pathways, mainly Wnt, G-proteins, EGFR, mTOR, SIRT1, PPARγ mediate increased insulin secretion, β-cell proliferation and improved GSIS in presence of nutrients, while in case of excessive nutrient load TLR4, MCP1, inflammasomes and Nrf2 impairs insulin secretion and conduces β-cell death. These excess of nutrients are the key players behind glucotoxicity and lipotoxicity, which ultimately lead to compensatory insulin secretion, β-cell mass expansion initially and β-cell death under chronic nutrients overload. Our major concern should be leading a healthy lifestyle, active routine, regular exercise, balanced diet and constant awareness about the incidence of type 2 diabetes, for eradication and curing of the disease to some extent.

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Conflict of interest

The authors declare no conflict of interest.

Notes/thanks/other declarations

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