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Beta-Cell Function and Failure in Type 2 Diabetes

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1. Introduction

Type 2 diabetes mellitus (T2DM) results from a combination of genetic and environmental factors that induces tissue insulin resistance and beta-cell failure.

The purpose of the present chapter is to focus on beta-cell function under physiological conditions and to review the potential beta-cell failure mechanisms, the place in natural history of T2DM and implication for treatment of beta-cell dysfunction.

2. Normal beta-cell function

The main role of beta-cell is to synthesize and secrete insulin in order to maintain circulating glucose levels within physiological range. Although there exist several triggers of insulin secretion like nutrients (amino acids such as leucine, glutamine in combination with leucine, nonesterified fatty acid), hormones, neurotransmitters and drugs (sulfonylurea, glinides), glucose represents the main physiological insulin secretagogue [1].

According to the most widely accepted hypothesis, insulin secretion is a multistep process initiated with glucose transport into beta-cell through specific transporters (GLUT1 and GLUT2 in particular) and phosphorylation by glucokinase, which directs metabolic flux through glycolysis, producing pyruvate as the terminal product of the pathway [2]. Pyruvate then enters the mitochondria and is decarboxylated to acetyl-CoA, which enters the tricarboxylic acid cycle.

The tricarboxylic acid cycle proper begins with a condensation of acetyl-CoA and oxaloacetate, to form citrate, a reaction catalysed by citrate synthase. Aconitase catalyses the convertion of citrate to isocitrate. NAD-linked isocitrate dehydrogenase then oxidatively decarboxylates

isocitrate to form α-ketoglutarate. The α-ketoglutarate is oxidised to succinyl-CoA in a reaction catalysed by α-ketoglutarate dehydrogenase. Succinyl-CoA synthase then catalyses the conversion of succinyl-CoA to succinate, with the concomitant phosphorylation of GDP to GTP. Succinate dehydrogenase catalyses the oxidation of succinate to fumarate. Fumarase catalyses the conversion of fumarate to malate and after that malate dehydrogenase catalyses the final step of the tricarboxylic acid cycle, oxidising malate to oxaloacetate and producing NADH.

Three pathways enable the recycling of the tricarboxylic acid cycle intermediates into and out of mitochondrion, allowing a continuous production of intracellular messengers [3-5]. These three cycles share, as a common terminal step, the conversion of malate to pyruvate concomitant with the production of cytosolic NADPH.

• Pyruvate/malate shuttle,

The oxaloacetate produced by pyruvate carboxylase is converted to malate by mitochondrial malate dehydrogenase. Malate exits the mitochondria to the cytoplasm where it is subsequently oxidised to pyruvate concomitant with the production of NADPH by cytosolic malic enzyme. Pyruvate then re-enters mitochondria for the next round of carboxylation by pyruvate carboxylase [3-5].

• Pyruvate/citrate shuttle,

The oxaloacetate condenses with acetyl-CoA to form citrate, mediated by citrate synthase. Citrate then exits the mitochondrion to the cytoplasm where it is converted back to oxaloacetate and acetyl-CoA by ATP-citrate lyase. Oxaloacetate is converted by cytosolic malate dehydrogenase to malate before being converted to pyruvate by malic enzyme. Acetyl-CoA is subsequently carboxylated by acetyl-CoA carboxylase to form malonyl-CoA for conversion to long-chain acyl-CoA by fatty acid synthase. Malonyl-CoA inhibits carnitine palmitoyl transferase-1, which transports fatty acyl-CoA into mitochondria where it is oxidised, leading to increase in long-chain acyl-CoAs in the cytosol [3-5].

• Pyruvate/isocitrate shuttle

The oxaloacetate condenses with acetyl-CoA to form citrate, mediated by citrate synthase before being converted to isocitrate. Isocitrate then exits the mitochondrion to the cytoplasm via the citrate/isocitrate transporter and is converted to α-ketoglutarate by the cytosolic NADPdependent isocitrate dehydrogenase. α-Ketoglutarate is further converted to oxaloacetate via the malate/aspartate shuttle as mentioned earlier in the NADH shuttle system [3-5].

The sequences of the tricarboxylic acid cycle and of shuttle pathways are followed by synthesis of reducing equivalents (NADH, NADPH, FADH2) in the mitochondria and transfer them to the electron transport chain [6]. The NADPH oxidase complex in the plasma membrane is also activated through protein kinase C, which is activated by fatty acid derived signalling molecules.

These events result in an enhanced ratio of ATP to ADP in the cytoplasm, which determines the closure of the ATP-sensitive K^+ channels, depolarization of the plasma membrane, influx

of extracellular Ca^{2+} and activation of exocytosis which takes place in several stages including recruitment, docking, priming, and fusion of insulin granules to the beta-cell plasma membrane [1,6,7].

Two independent studies, using diazoxide for maintaining the ATP-sensitive K^+ channels in the open state or mice in which the ATP-sensitive K^+ channels were disrupted, indicated that glucose –stimulated insulin secretion can also occur independently of ATP-sensitive K^+ channels activity [8].

Under physiological conditions, there is a hyperbolic relation between insulin secretion and insulin sensitivity. Classically, glucose-stimulated insulin secretion is characterized by a first phase, which ends within a few minutes, and prevents or decreases glucose concentration and a more prolonged second phase in which insulin is released proportionally to the plasma glucose [9].

In addition, it has been demonstrated that the release of insulin is oscillatory, with relatively stable rapid pulses occurring at every 8-10 minutes which are superimposed on low-frequency oscillations [10]. In humans the amplitude of insulin oscillations is 100-fold higher in the portal vein than in the systemic circulation implying preferential hepatic extraction of insulin pulses.

Research to further understand the roles of these pathways may provide strategies for future therapies of T2DM.

3. Place of beta-cell dysfunction in natural history of type 2 diabetes

T2DM is a progressive condition caused by genetic and environmental factors that induce tissue insulin resistance and beta-cell dysfunction.

Based on the United Kingdom Prospective Diabetes Study (UKPDS) and on the Belfast Diabetes Study, it is estimated that at diagnosis of T2DM, beta-cell function is already reduced by 50-60% and that this reduction of beta-cell function seems to start with 10-12 years before the appearance of hyperglycemia [11,12].

Several lines of evidence indicated that there is no hyperglycemia without beta-cell dysfunction [13,14].

In most subjects with obesity-induced insulin resistance developing increased insulin secretion, insulin gene expression and beta-cell mass, these compensatory mechanisms can succeed to maintain glucose homeostasis and avoidance of diabetes mellitus [13-15]. Progression from beta-cell compensation to failure in the face of obesity-induced insulin resistance occurs in a subset of genetically predisposed individuals who fail to adequately compensate for the increased insulin demand, leading to glucolipotoxicity.

In this phase insulin secretion (in relation to the degree of insulin resistance), insulin gene expression and beta-cell mass are reduced, causing increased levels of glucose and free fatty acids [13,14].

In T2DM, the typical beta-cell functional alterations are represented by:

- change of threshold for insulin secretion triggering with relatively selective loss of responsivity to glucose compared to other insulin secretagogues like arginin or glibenclamide

- alteration of insulin secretion oscillatory patterns with impairment of both high frequency and ultradian oscillations

- reduced or absent first phase insulin secretion initially to intravenous glucose and then to mixed meal ingestion

- prolongation of second phase of insulin secretion

- gradual, time-dependent irreversible damage to cellular components of insulin production [9,13-18].

Longitudinal studies in humans have clearly demonstrated that beta-cell function deteriorates during the years. In the phase which precedes overt diabetes the decline of beta-cell function is slow but constant (2% per year) [19]. After the development of overt hyperglycemia there appears a significant acceleration (18% per year) in beta-cell failure, and the beta-cell function deteriorates regardless of the therapeutic regimen [11,19,20]. The accelerated beta-cell dysfunction is the consequence of glucolipotoxicity. Consequent deterioration in metabolic equilibrium with increasing levels of glucose and free fatty acids, enhance and accelerate beta-cell dysfunction, lead to beta-cell apoptosis that does not seems to be adequately compensated by regenerative process and subsequent decrease of beta-cell mass.

## 4. Potential mechanism and modulators of beta-cell failure

The main focus of the present chapter is on potential beta-cell failure mechanisms in T2DM.

The initial alterations in beta-cell function are likely to reflect intrinsic defects, whereas the accelerated beta-cell dysfunction which mainly occurs after the development of overt hyperglycemia is the consequence of glucolipotoxicity [21]. This reflects a genetic predisposition for beta-cell defect, whereas the subsequent beta-cell failure may be a consequence of concomitant environmental conditions.

Schematic representation of the role of cellular dysfunction in the natural history of T2DM is included in Figure 1.

5. Genetic factors

Several genes associated with increased risk of developing T2DM have been identified in genome-wide association studies [22]. There were detected several genetic variants of genes that confer risk of diabetes by interfering with next three mechanisms:
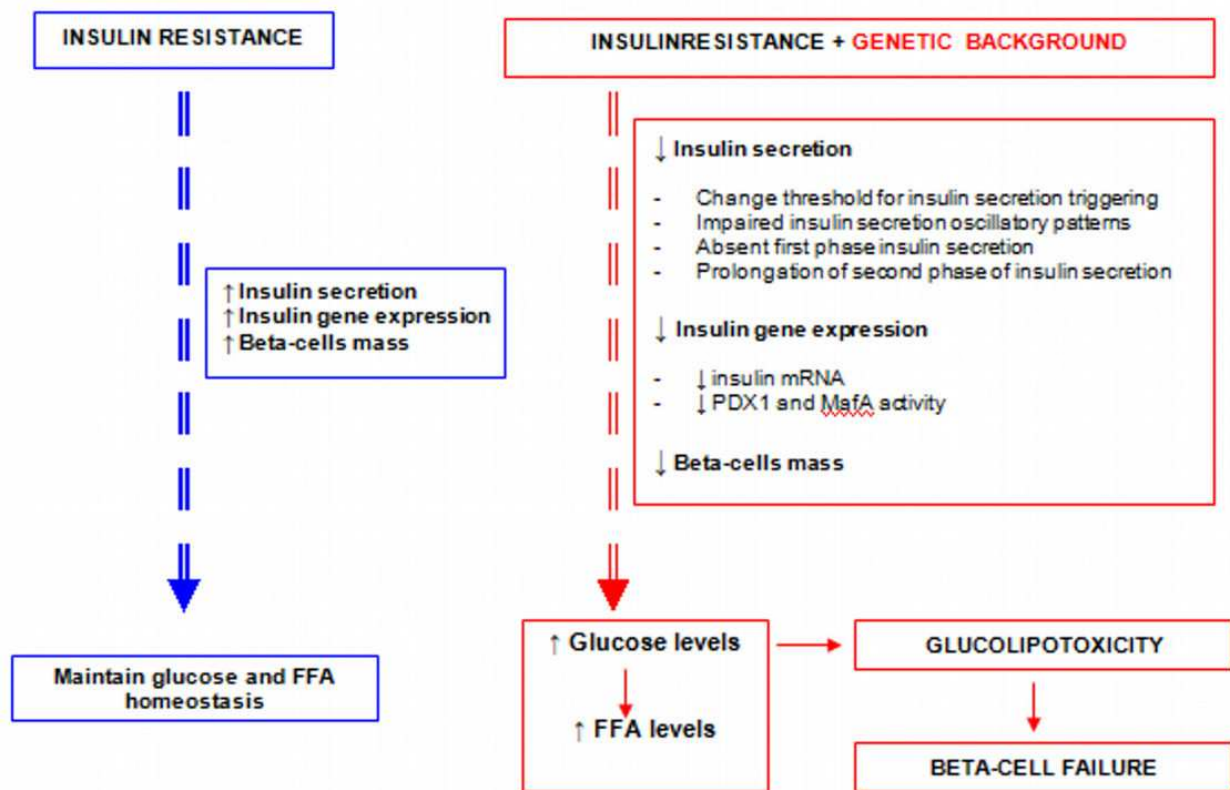
Figure 1. Place of beta-cell dysfunction in natural history of type 2 diabetes

- **reduction of insulin secretion**: KCNJ11 [23], HHEX [24-26], SLC30A8 [25,27], CAPN10 [28], CDKAL1 [29,30], IGF2BP2 [30,31], CDKN2A/B [24], MTNR1B [32-36], CDC123/CAMK1D [35,37], JAZF1 [37] and TSPAN8/LGR5 [37]

- **impairment in incretin release**: TCF7L2 [38], WFS1 [39], KCNQ1 [40,41]

- **impaired proinsulin-to-insulin conversion**: CAPN10 [28], TCF7L2 [42-45], SLC30A8 [42], and CDKAL1 [42]

The most important so far type 2 diabetes risk gene, *TCF7L2*, interferes with all three mechanisms.

TCF7L2 encodes for the transcription factor TCF7L2, which induces the expression of a number of genes including the insulin gene [46], the gene coding for intestinal proglucagon [47], genes coding for proprotein convertases 1 and 2 [43] and for proteins important in insulin exocytosis and genes critical for beta-cell proliferation [48].

The *KCNJ11* encodes the Kir6.2 subunit of the ATP-sensitive K channel of beta-cells. Genetic variation in this gene obviously affects the beta-cell excitability and insulin secretion [23].

HHEX encodes a transcription factor necessary for the organogenesis of the ventral pancreas [49] and two SNPs (rs1111875, rs7923837) in *HHEX* were found to be associated with reduced insulin secretion [24-26].

SLC30A8 encodes the protein zinc transporter 8, which provide zinc for maturation, storage and exocytosis of the insulin granules [50]. Variants in this gene show to be associated with reduced glucose-stimulated insulin secretion [25,27] and alterations in proinsulin to insulin conversion [42].

A number of SNPs, and particularly the rs10830963 C>G SNP in *MTNR1B* enhances the melatonin-induced inhibition of insulin secretion, leading to higher fasting blood glucose and an increased T2DM risk [32-36].

The molecular mechanisms by which loci or SNPs in the other genes affect glucose-stimulated insulin secretion, proinsulin to insulin conversion and incretin-induced insulin secretion are currently poorly understood.

These observations suggest that a genetic predisposition is associated with an initially beta-cell intrinsic defect which, in case of increased demand as it is in obesity and insulin resistance, leads to beta-cell failure.

6. Glucolipotoxicity

Growing evidence indicated that long-term elevated plasma levels of glucose and fatty acids contribute to beta-cell function decline, a phenomenon known as glucolipotoxicity. Glucolipotoxicity differs from beta-cell exhaustion, which is a reversible phenomenon characterized by depletion of insulin granules due to prolonged exposure to secretagogues. Unlike glucolipotoxicity, beta-cell exhaustion is associated with normal production of insulin [51].

A multitude of clinical and preclinical studies have shown deleterious effects of beta-cells chronic exposure to elevated glucose levels.

Given the existence of insulin resistance and a predisposing genetic background, there occurs the elevation of glucose levels, which lead to progressively decreases of insulin secretion, insulin gene expression and insulin promoter activity (PDX-1 and MAFA) [52,53].

Chronic exposure of beta-cells to hyperglycemia can also induce beta-cells apoptosis by increasing proapoptotic genes expression (Bad, Bid, Bik) while antiapoptotic gene expression Bcl-2 remains unaffected [54].

There is a strong relationship between glucotoxicity and lipotoxicity. Thus, hyperglycemia increases malonyl-CoA levels, leading to the inhibition of carnitine palmitoyl transferase-1 and subsequently to decreased oxidation of fatty acids and lipotoxicity [52].

Increased fatty acids in the pancreas leads to intrapancreatic accumulation of triglycerides [55]. Lim E et al showed that the intrapancreatic fat is associated with beta-cell dysfunction and that sustained negative energy balance induces restoration of beta-cellular function [56].

Elevated levels of glucose and saturated fatty acids in beta cells, stimulates AMP-activated protein kinase, which contributes to increased expression of sterolregulatory-element-

binding-protein-1c (SREBP1c), leading to increased lipogenesis [57]. Glucose also increases the expression of liver X receptor which then contributes to enhancing SREBP1c expression [58].

Several studies provide evidence that prolonged exposure of beta cells to elevated levels of free fatty acids can have many deleterious effects, such as:

- **Decreased glucose-stimulated insulin secretion** [52,59]. Activation of the isoform of protein kinase C (PKCε) by free fatty acids which has been suggested as a possible candidate signaling molecule underlying the decrease in insulin secretion [60].

- **Impaired insulin gene exexpression** by down-regulation of PDX-1 and MafA insulin gene promoter activity [61]. PDX-1 is affected in its ability to translocate to the nucleus, whereas MafA is affected at the level of its expression [61]. Free fatty acid impairs insulin gene expression only in the presence of hyperglycemia [62]. Palmitate affects both insulin gene expression and insulin secretion, unlike oleate which affects only insulin secretion [63]. Extracellular-regulated kinase (ERK) 1/2 phosphorylation, JNK activation, PKB phosphorylation, and Per- Arnt-Sim kinase (PASK) signalling pathways mediate the palmitate-induced inhibition of insulin gene expression [64,65].

- **Increased synthesis of ceramides** from palmitic acid only, which impairs insulin gene expression, induces cell death by inhibition of anti-apoptotic protein Bcl2, without affecting insulin secretion [62,66,67].

- **Up regulation of UCP2**, leading to reduction of glucose-stimulated ATP generation [68].

- **Activation** of the **oxidative stress** [69].

- **Activation** of the **unfolded protein response** [70].

- **Increased beta-cells inflammation** by stimulations of NF-kB, Il-1β and IFN-γ production [71].

- **Beta-cell apoptosis** mediated by several mechanism including increased ceramides, caspases activation, decreased Bcl2 expression, inflammation response, ROS production, unfolded protein response [66,72-74]. Saturated fatty acids are involved in beta-cell apoptosis, whereas unsaturated fatty acids are usually protective [75,76].

- **Increased islet amyloid polypeptide** [77].

Recent studies suggest that deleterious effect of free fatty acids are expressed mostly in the presence of hyperglycemia which inhibits fatty acid oxidation and lead to accumulation of cytosolic long-chain acyl-CoA esters, generation of ceramide and lipid partitioning.

Increased intracellular cholesterol content may also lead to glucolipotoxicity. ATP-binding cassette transporter subfamily A member 1 (ABCA1) appears to mediate intracellular cholesterol accumulation and impaired insulin secretion, probably at the level of insulin exocytosis [78].

Several mechanisms have been proposed for glucolipotoxicity induced beta-cell dysfunction and death, such as: endoplasmic reticulum stress, mitochondrial dysfunction and reactive oxygen species production, islet inflammation and islet amyloid polypeptide increasing.

There is a significant relationship between the mechanisms triggered by glucolipotoxicy, creating thus a vicious cycle that eventually leads to beta-cell failure (Figure 2.).
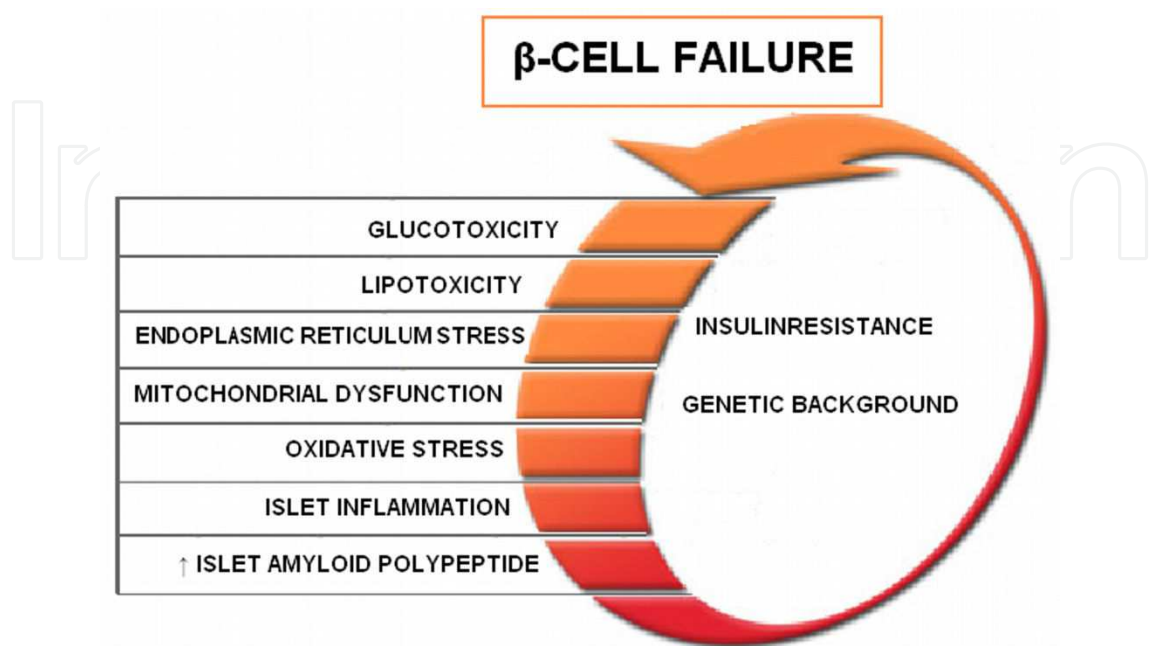
Figure 2. Potential mechanism of beta-cell failure

7. Endoplasmic reticulum stress

The endoplasmic reticulum is responsible for the protein synthesis, being involved in protein translation, folding and assessing quality before protein secretion. Chronic hyperglycemia, elevated levels of saturated free fatty acid in beta-cell lead to sustained increased demand for insulin biosynthesis via increasing both insulin transcription and translation, and to increased proinsulin biosynthesis, which generates a heavy load of unfolded/misfolded proteins in the endoplasmic reticulum lumen. Accumulation of unfolded and misfolded protein in the endoplasmic reticulum lumen may impose endoplasmic reticulum stress [79,80]. Inflammatory cytokines such as IL-1β and IFN-γ, can also cause endoplasmic reticulum stress [72].

Endoplasmic reticulum stress induced beta-cell activation of an adaptive system named unfolded protein response by which it attenuates protein translation, increases protein folding and promotes misfolded protein degradation [81,82].

The unfolded protein response is mediated by activation of three transmembrane endoplasmic reticulum proteins:

- protein-kinase-RNA-(PKR-) like ER kinase/ eukaryotic translation initiation factor 2 alpha (PERK/eIF2α)

- inositol-requiring 1/X-box- bindingprotein-1 (IRE1/XBP-1)

- activating transcription factor 6 (ATF6) [83,84].

The unfolded protein response alleviates endoplasmic reticulum stress by inducing a number of downstream responses:

- decrease new proteins arrival into the endoplasmic reticulum by attenuation of further translation of mRNAs via PERK/eIF2α activation. Thus, it prevents additional protein misfolding and further accumulation of unfolded protein;

- increase the folding capacity of the endoplasmic reticulum to deal with misfolded proteins via the induction of endoplasmic reticulum chaperones. This response is mediated by IRE1/XBP-1 and ATF6;

- increase in the extrusion of misfolded proteins from the endoplasmic reticulum and subsequently endoplasmic reticulum-associated protein degradation (ERAD);

- triggering apoptosis by the activation of CCAAT/enhancendoplasmic reticulum-binding homologous protein (CHOP) [81-85].

Among the three different signaling pathways of the endoplasmic reticulum stress response (ATF6, IRE1/XBP-1, and PERK/eIF2α), only ATF6 down-regulated PDX-1 and MafA insulin gene promote activity [86].

Extensive studies have indicated that IRE1/XBP-1 activation leads to increases of proinsulin biosynthesis under transient high glucose conditions like postprandial hyperglycemia and, by contrast, causes suppression of insulin mRNA expression and increases insulin mRNA degradation under chronic high glucose exposure [87,88].

Given these data it can be asserted that the appearance of endoplasmic reticulum stress, due to glucolipotoxicity and inflammatory cytokines, can lead to beta-cell dysfunction and death.

8. Mitochondrial dysfunction and ROS production

Beta cell mitochondria play a key role in the insulin secretion process, not only by providing energy in the form of ATP to support insulin secretion, but also by synthesising metabolites that can act as factors that couple glucose sensing to insulin granule exocytosis [3].

Mitochondrial dysfunction and abnormal morphology occur before the onset of hyperglycemia and play an important role in beta-cell failure [89]. In diabetic state, the proteins from the mitochondrial inner membrane are decreased, and also may exist transcriptional changes of the mitochondrial proteins [89].

Mitochondrial dysfunction, induced by glucolipotoxicity, plays a pivotal role in beta-cell failure and leads to increased ROS production as a result of metabolic stress.

Under conditions of normoglycemia production of ROS - superoxide anion (O2 • -) and hydrogen peroxide (H2O2) - is performed during mitochondrial electron transport or through several oxidoreductases and metal-catalyzed oxidation of metabolites [90].

In the presence of hyperglycemia, hexosamine, sorbitol, PCK activations and Shiff reaction pathways, may represent sources of oxidative stress along with oxidative phosphorylation and auto-oxidation of glucose in mitochondria [91].

ROS effects can be reduced by activation of antioxidant enzymes including: superoxide dismutase, which converts $O_2 \bullet -$ to H_2O_2 and also catalase, glutathione peroxide and peroxiredoxin that convert H_2O_2 into oxygen and water. Levels of antioxidant enzymes in beta cells are very low (catalase and glutathione peroxide levels were much lower than those of superoxide dismutase), making beta cells be vulnerable to oxidative stress [92].

Low concentrations of ROS contribute to increased glucose-stimulated insulin secretion, but only in the presence of glucose-induced elevations in ATP [93].

Li N. et al indicated that transient oxidative stress can cause impaired glucose-induced ATP generation, decreased glucose-stimulated insulin secretion, down-regulation of the respiratory chain and increased mitochondrial ROS production [94]. All these effects are reversible in time after transient increase ROS.

Chronic and significant elevation of ROS, resulted from an imbalance between ROS production and scavenging by endogenous antioxidants, may lead to beta-cell failure [95,96].

Persistent oxidative stress mediates beta-cell failure through several different mechanisms, including:

- **Decreased insulin secretion**. Oxidative stress inhibits the respiratory chain, allowing the transfer of electrons to molecular oxygen to form superoxide, and also inhibits the enzymes involved in glucose metabolism (glyceraldehyde-3-phosphate-dehydrogenase from glycolytic pathway and aconitase from Krebs cycle), leading to reduced ATP / ADP ratio and to impaired insulin release [97-100].

- **Decreased insulin gene expression** via activation of JNK pathway, also by posttranscriptional loss of PDX-1 and posttranslational loss of MafA [21,52,101].

- **Islet inflammation** due to activation of NF-kB pathway [102].

- **Mitochondrial dysfunction** by promoting DNA fragmentation, the peroxidation of membrane phospholipids such as cardiolipin [16,103].

- **Increased islet amyloid polypeptide and endoplasmic reticulum stress** [104-106].

- **Beta-cells apoptosis** by activating uncoupling protein-2 which results in proton leak leading to reduced ATP synthesis [107].

- **Beta-cells lipid accumulation** via SREBP1c [108].

The antioxidant effect varies depending on the type of exposure of beta cells to ROS. Thus, under beta-cells exposure to low concentrations of ROS, antioxidants lower the insulin secretion [109,110]. Instead, under the glucolipotoxicity, antioxidants increase the insulin secretion and reduce beta cell apoptosis [108].

9. Islet inflammation

Several studies indicated that prolonged exposure of pancreatic islet to chronic hyperglyce‐mia, increased levels of saturated fatty acids and increased ROS may trigger the production of inflammatory cytokines such as nuclear transcription factor kB (NF-κB), interleukin-1β (IL-1β) and γ-interferon (IFN-γ), TNF-α, leading to beta-cells dysfunction and apoptosis [71]. Additionally, beta-cells dysfunction and apoptosis may also be triggered by pro-in‐flammatory signals from other organs, such as adipose tissue [111,112].

Transient activation of **NF-κB** may be beneficial to insulin secretion [113], but persistent ac‐tivation of NF-kB may induce cell dysfunction, due to the reduction of beta-cell protein ex‐pression including insulin, GLUT-2, and PDX-1 concomitant with an increase in iNOS expression [113].

There is good evidence that NF-kB mediates direct or through Il-1β, the activation of induci‐ble nitric oxide synthase (iNOS) in pancreatic beta-cells which, in turn, induces the expres‐sion of proinflammatory genes, interferes with electron transfer and inhibits ATP synthesis in mitochondria, leading to decreased insulin secretion and beta-cell dysfunction [114].

Chronic exposure of beta-cell to inflammatory cytokines, like **Il-1β, IFN-γ or TNF-α**, can cause endoplasmic reticulum stress and the unfolded protein response activation in beta-cells, and also beta-cells apoptosis [72,115]. Because, as indicated by Donath *et al*, the apop‐totic beta-cells can provoke, in turn, an immune response, a vicious cycle may develop [115].

Another cytokine involved in beta-cells dysfunction is the PANcreatic DERived factor (PANDER). PANDER is a novel cytokine that is highly expressed in pancreatic islets [116]. Because PANDER protein is cosecreted with insulin from pancreatic beta-cells [117] it is reasonable to speculate that PANDER may regulate the insulin secretion process [117, 118].

The adipocytokines released by adipocytes, including adiponectin, leptin, resistin, visfatin, TNF-α and IL-6, may also modulate the beta-cell function and survival.

Adiponectin receptors were found in human and rat pancreatic beta-cells and their expres‐sion can be upregulated by unsaturated fatty acid but not by saturated fatty acid [116].

In beta-cells, adiponectin may induce phosphorylation of acetyl coenzyme A carboxylase, leading to inhibition of fatty acids synthesis and preventing of lipid accumulation in beta-cells [112]. There have not been revealed significant effects of adiponectin on basal or glu‐cose-stimulated insulin secretion [112].

Leptin is another adipocytokine that may interfere with beta-cell function and survival. In studies on animal model, leptin has been shown to inhibit insulin secretion via activation of ATP-regulated potassium channels and reduction in cellular cAMP level [116], inhibit insulin biosynthesis by activating suppressor of cytokine signalling 3 (SOCS3) [119], sup‐press acetylcholine-induced insulin secretion [116] and induce the expression of inflam‐matory genes [120].

Studies performed on human islets indicated that chronic exposure to leptin stimulates the release of IL-1β and inhibits UCP2 expression, leading to beta-cell dysfunction and apoptosis [111].

Other adipocytokines including TNF-α, IL-6, resistin, visfatin may also modulate beta-cell function and survival, although it is unclear whether the amount released into the circulation is sufficient to affect beta-cells [111].

10. Islet amyloid polypeptide

Human islet amyloid polypeptide (amylin) is expressed almost exclusively in beta-cells and is costored and coreleased with insulin in response to beta-cells secretagogues. Glucolipotoxicity causes increased insulin requirement and those lead to increased production of both insulin and amylin. High concentrations of amyloid are toxic to beta-cells and have been implicated in beta-cell dysfunction and apoptosis [121,122].

The effect of Islet amyloid polypeptide on beta-cell function is not fully elucidated.

Studies *in vivo* have shown that the islet amyloid polypeptide inhibits the first and second phase of glucose-stimulated insulin secretion, but this occurs only at concentrations of islet amyloid polypeptide above physiological range [77].

In vitro studies, however, have yielded contradictory results. Several studies have indicated an inhibitory effect of islet amyloid polypeptide physiological concentration on insulin secretion [123], but other studies have reported no inhibitory effect of islet amyloid polypeptide on insulin release [77].

One possible explanation for these inconsistent results may be that there was not taken into consideration the islet amyloid polypeptide increased tendency to aggregate in amyloid-like fibrils and thus the effects of early islet amyloid polypeptide preparations may be questioned [77].

Studies performed on islet amyloid polypeptide knock-out or transgenic mice, using pure and fully active islet amyloid polypeptide, suggest that islet amyloid polypeptide limits glucose-induced insulin secretion [124].

11. Beta-cell failure — Implication for treatment

Understanding the causes for beta-cell failure is of capital importance to develop new and more effective therapeutic strategies.

Taking into consideration the existence of early beta-cell dysfunction and the significant reduction of beta-cell mass in the natural history of T2DM as well as the progressive character of these pathophysiological modifications, **insulin therapy** could be an important option for obtaining and maintaining an optimal glycemic control.

Li Y. et al indicated that short term intensive insulin therapy of newly diagnosed T2DM may improve cell function, by restoring the first-phase insulin secretion and by decreased proinsulin/insulin ratio [125].

Increasing insulin levels by exogenous insulin administration for the control of hyperglycemia may appear initially contraindicated in patients with evidence of insulin resistance, so it is imperative to simultaneously address insulin resistance with metformin.

Several lines of evidence indicated that **metformin** could improve beta-cell function and survival. Incubation of T2DM islets with metformin was associated with increased insulin content, insulin mRNA expression and glucose responsiveness, and also with reduced cell apoptosis by normalization of caspase 3 and caspase 8 activities [103].

It has been shown that metformin, and also the **PPAR gamma agonists** can protect beta-cell from deleterious effects of glucolipotoxicity [126,127].

Other therapeutic options for beta-cell protection, such as **incretins** are actually under debate. Recent studies have shown that effects of incretins vary depending on the time of exposure of beta-cells to GLP-1 or GLP-1R agonists.

Thus, acute exposure of cells to the incretins, determine stimulation of glucose-dependent insulin secretion, the subacute exposure leads to increased insulin biosynthesis and insulin gene transcription, whereas the chronic exposure induces beta-cell mass increase by stimulation of cell proliferation, neogenesis and inhibition of cell apoptosis [21].

Changing profile of cytokines secretion from pancreatic beta-cells and also of adipocytokines may be promising therapeutic options for beta-cellular dysfunction [116].

Future advances in the area of beta-cell failure mechanism and modulators may lead to the identification of possible novel therapeutic strategies.

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