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Beta-Cell Function and Failure in Type 1 Diabetes

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1. Introduction

Glucose is an essential energy source for all cells. Therefore, maintaining glucose levels within a normal range is essential for life in vertebrates. Glucose homeostasis in the organism is tightly regulated by insulin, a hormone that acts on the major glucose metabolic tissues such as muscle, liver and adipose tissue. Insulin's main effects include promoting glucose uptake, glycogen synthesis in the liver and muscle, triglyceride formation to be stored in adipocytes, and protein synthesis. Insulin secretion is held by the pancreatic beta-cells, and it is modulated by glucose levels. Insufficient insulin secretion and consequent impairment of insulin's actions lead to Diabetes Mellitus.

Diabetes is a group of metabolic diseases characterized by hyperglycemia, caused by a defect on insulin production, insulin action or both. Type 1 diabetes in particular is due to an autoimmune destruction of the insulin producing pancreatic beta-cell, which usually leads to absolute insulin deficiency (ADA 2009). This type of diabetes accounts for 5-10% of the total cases of diabetes worldwide, and although its onset is commonly during childhood and adolescence, it can occur at any age, even during late adulthood.

As the loss of beta-cells is determinant for the development of overt type 1 diabetes, understanding beta-cell's normal physiology, namely insulin secretion, and how it may be affected during the progression of this disease is essential. Moreover, the development of new therapeutic interventions for type 1 diabetes, such as islet transplantation, beta cell maintenance and replacement, or stem cell therapy, requires a profound knowledge of how the presence of different nutrients and signals may regulate insulin secretion and beta-cell mass.

In this chapter we aim to review the mechanisms involved in normal beta-cell function and beta-cell mass regulation, and how this function may be modulated by glucose, nutrients and signals in the beta-cell milieu. We also review how these mechanisms may be affected by the onset and progression of type 1 diabetes.

2. Normal function of the beta-cell - glucose stimulated insulin secretion

The pancreas is an endocrine and exocrine gland. The exocrine portion corresponds to acinar tissue, responsible for secreting digestive enzymes into the pancreatic juice, while the

endocrine portion comprises the pancreatic islets, which consist of several cell types secreting different hormones: β-cells (insulin), α-cells (glucagon), δ-cells (somatostatin), PP-cells (pancreatic polypeptide) and ε-cells (ghrelin). The endocrine pancreas represents 1% to 5% of the total pancreatic mass (Kim, S.K. & Hebrok, M. 2001). In the islet, beta-cells (β-cells) are approximately 70% to 80% of the total islet cells.

Beta-cells are responsible for secreting insulin in response to rises in blood nutrient levels during the postprandial state. Glucose is the most important nutrient for insulin secretion. The process by which glucose promotes insulin secretion requires its sensing and metabolism by the beta-cell, a process called glucose-stimulated insulin secretion.

2.1 Insulin is secreted in a pulsatile and biphasic fashion

Glucose-stimulated insulin secretion is biphasic and pulsatile (Stagner, J.I. et al. 1980). The secretory pulses of beta-cells are associated with synchronous Ca^{2+} oscillations in response to glucose stimulus (Bergsten, P. et al. 1994), and they have been suggested to be coupled to glycolysis oscillations of the beta cell (Kar, S. & Shankar Ray, D. 2005). Secretory pulses are also regulated and synchronized within the other islet cell types. Insulin and glucagon secretion show asynchronous patterns (Grapengiesser, E. et al. 2006; Stagner, J.I. et al. 1980), whereas somatostatin pulses are synchronized with insulin secretion (Stagner, J.I. et al. 1980).

Glucose-stimulated insulin secretion also shows a biphasic pattern. Shortly after glucose stimulus, a first burst of insulin secretion occurs, followed by a decrease in the rate of secretion. A second sustained phase of insulin secretion can be observed just after this decrease, which can continue for up to several hours until euglycemia is achieved (Curry, D.L. et al. 1968) (Figure 1).

Although the mechanisms involved in the first phase of insulin secretion (termed the triggering pathway) are well understood, mechanisms regulating the sustained second phase (or the amplifying pathway) are yet to be deciphered, and different players that account for it have been proposed (Henquin, J.C. 2009). Notably, most of them are related to glucose metabolism inside the beta-cell.

2.1.1 Mechanisms involved in the first phase of insulin secretion - the triggering pathway

The first phase of glucose-stimulated insulin secretion is a multistep process that requires transport and oxidation of glucose, electrophysiological changes and fusion of insulin-containing secretory granules with the beta-cell plasma membrane (Figure 1). Glucose enters the cell by facilitated diffusion mediated by glucose transporters (GLUT2 in rodents, GLUT1 in humans). Glucose is then phosphorylated to form glucose-6-phosphate by glucokinase. This enzyme plays a critical role in glucose-stimulated insulin secretion and is considered the glucosensor of the pancreatic beta cell. Due to its kinetic characteristics, glucokinase is a determining factor for glucose phosphorylation (Matschinsky, F.M. 1996) and hence for its metabolism through glycolysis and oxidation.

The generation of ATP by glycolysis, the Krebs cycle and the respiratory chain leads to closure of the ATP-sensitive K+ channel (K_{ATP}), a hetero-octamer comprised of four subunits of the sulphonylurea 1 receptor (SUR1) and four subunits of the inwardly rectifying K^+ channel Kir6.2 (Aguilar-Bryan, L. et al. 1998). The closure of K_{ATP} channels, permit the background sodium (Na^+) entry without balance. These two events depolarize the membrane to a range that allows the opening of voltage-dependent T-type calcium (Ca^{2+})

and sodium (Na^+) channels. Na^+ and Ca^{2+} entry further depolarizes the membrane and L-type and maybe other voltage-dependent calcium channels (VDCC) open. Their activation triggers action potentials that increase in intracellular Ca^{2+} ($[Ca^{2+}]i$) (Hiriart, M. & Aguilar-Bryan, L. 2008). Together with calcium mobilized from intracellular stores, this Ca^{2+} increase leads to fusion of insulin-containing secretory granules with the plasma membrane and the release of insulin into the circulation (Rorsman, P. & Renstrom, E. 2003). Following glucose metabolism, the rate-limiting-step for the first phase lies in the rate of signal transduction between sensing the rise in $[Ca^{2+}]i$ and exocytosis of the immediately releasable granules (Straub, S.G. & Sharp, G.W. 2002).

2.1.2 Mechanisms involved in the second phase insulin secretion - the amplifying pathway

The existence of a second phase of insulin secretion was first reported in the 1960s. Curry et. al.(Curry, D.L. et al. 1968) observed that, in total pancreas perfusion with glucose, insulin release showed an early and rapid increase at 2 min after glucose infusion, peaking at 4 min. A second or "slow" phase, characterized by an increasing rate of insulin secretion was sustained during the whole period of glucose infusion. On the other hand, when the pancreas was perfused with tolbutamide, a sulfonylurea that blocks the potassium channels, only the first rapid release peak was observed, suggesting this biphasic insulin secretion is only generated in glucose-stimulated insulin secretion (Curry, D.L. et al. 1968). It was until the 1990s that evidence of mechanisms for glucose-stimulated insulin secretion independent of ionic action (i.e. K_{ATP} potassium channel activation) was found (Aizawa, T. et al. 1998; Gembal, M. et al. 1992). Since then, the concept of a rapid first phase glucose-stimulated insulin secretion, caused by a triggering pathway (or K_{ATP}-dependent mechanism), followed by a sustained second phase due to an amplifying pathway (or K_{ATP}-independent mechanism) has developed (Aizawa, T. et al. 2002; Henquin, J.C. 2000).

Biphasic insulin secretion has been explained by the existence of different pools of insulin-containing granules inside the beta cell (Aizawa, T. & Komatsu, M. 2005; Straub, S.G. & Sharp, G.W. 2004). There is a reserve pool of granules located in the cytoplasm which accounts for approximately 94% of the total granules, and a releasable pool of granules which are docked to the plasma membrane. It has been suggested that the docked granules have different ability to be released and therefore constitute two subsets, the readily releasable pool, and the immediately releasable pool. The granules from the immediately releasable pool are the first to be secreted in response to intracellular Ca^{2+} increase during the triggering pathway, leading to the first phase of insulin secretion. At the lowest point of secretion in between the two phases, the granules from the readily releasable pool are converted to the immediately releasable pool, an ATP-dependent process termed "priming". This priming has been suggested to be the rate-limiting step for exocytosis, and the target process for signals involved in the amplifying pathway that leads to the sustained second phase of insulin secretion (Straub, S.G. & Sharp, G.W. 2004) (Figure 1). Given the glucose-stimulated nature of biphasic insulin secretion and the ATP-dependence of priming, most of these signals are proposed to be derived from glucose metabolism. Some of these signals are reviewed in the next section.

2.2 Transcription factors regulating beta cell function

Transcription factors in the beta-cell act in a cooperative manner, forming transcriptional networks, to induce not only insulin expression, but also the expression of other genes

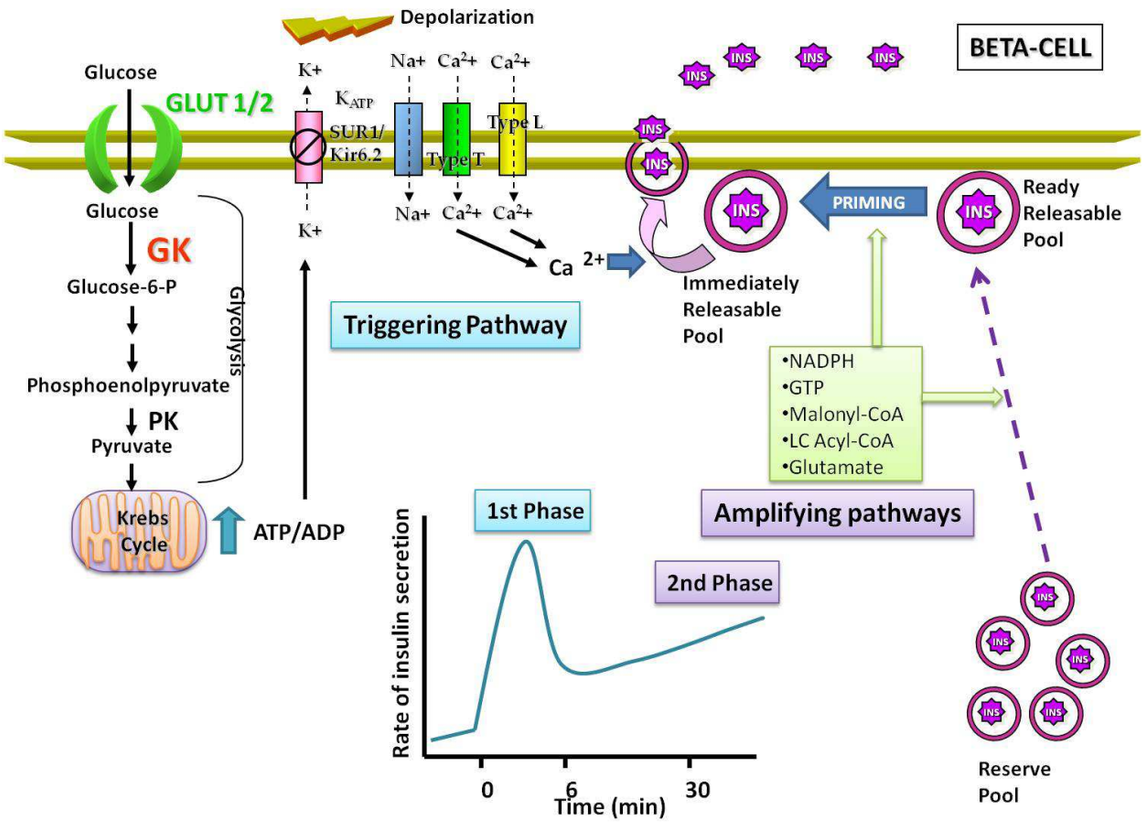

Fig. 1. Mechanism of biphasic glucose-stimulated insulin secretion.
Glucose enters the cell by glucose transporters (GLUT2 in rodents, GLUT1 in humans) and is then phosphorylated for its metabolism through glycolysis and oxidation. The generation of ATP by glycolysis, the Krebs cycle and the respiratory chain closes the ATP-sensitive K+ channel (KATP), allowing sodium (Na^+) entry without balance. These two events depolarize the membrane and open voltage-dependent T-type calcium (Ca^{2+}) and sodium (Na^+) channels. Na^+ and Ca^{2+} entry further depolarizes the membrane and L-type and maybe other voltage-dependent calcium channels (VDCC) open. This activation increases intracellular Ca^{2+} ($[Ca^{2+}]i$), which leads to fusion of insulin-containing secretory granules with the plasma membrane and the first phase insulin secretion. A sustained second phase of insulin secretion is held when the granules from the readily releasable pool are converted to the immediately releasable pool, an ATP-dependent process termed "priming". Most of the signals involved in this process also come from glucose mitochondrial metabolism, comprising the amplifying pathways.

involved in insulin gene regulation and insulin secretion, thus establishing and maintaining beta-cell's phenotype and function (Lazo-de-la-Vega-Monroy, M.L. & Fernandez-Mejia, C. 2009). Some of these factors include PDX-1, HNF4α, MAFA, FOXA2 and NeuroD1 (Lazo-de-la-Vega-Monroy, M.L. & Fernandez-Mejia, C. 2009).
PDX-1 is one of the most important transcription factors regulating the insulin gene transcription. This factor is determinant for pancreatic function. β-cell-specific knockout studies show that when *pdx1* is ablated, β-cell function is impaired and mice present diabetic phenotypes (Ahlgren, U. et al. 1998). Many of the target genes for *pdx1* are crucial for

glucose-induced insulin secretion, such as glucose transporter *glut2* (Ahlgren, U. et al. 1998), the insulin gene (Chakrabarti, S.K. et al. 2002), and other transcription factors (Ahlgren, U. et al. 1998; Chakrabarti, S.K. et al. 2002; Raum, J.C. et al. 2006; Thomas, H. et al. 2001). PDX1 plays a role in the maintenance and proliferation of beta-cells as well (Holland, A.M. et al. 2005). Its overexpression in diabetic mice (*Irs2* knockouts) participates in beta-cell mass recovery and helps ameliorate glucose tolerance (Kushner, J.A. et al. 2002), whereas *pdx1* haploinsufficiency causes β-cell apoptosis (Kulkarni, R.N. et al. 2004).
PDX1 decrease has also been associated with apoptosis and reduced expression of the anti-apoptotic genes Bcl_{XL} and Bcl-2 (Johnson, J.D. et al. 2006), defects in post-translational processing of insulin, inhibition of GLP-1 receptor expression (Wang, H. et al. 2005), glucotoxicity (Olson, L.K. et al. 1993) and lipotoxicity (Gremlich, S. et al. 1997; Hagman, D.K. et al. 2005).

2.3 Metabolic coupling factors and glucose-stimulated insulin secretion

As noted earlier, an ATP/ADP ratio increase caused by glucose metabolism in the beta-cells is the mechanism by which the first phase of glucose-stimulated insulin secretion is triggered. However, glucose metabolism can also render a series of signals, or metabolic coupling factors, that may initiate and sustain the second phase of insulin secretion, presumably by favoring mobilization of the insulin granules form the reserve pool and the replenishment of the immediately releasable pool of insulin granules. Some of these metabolic coupling factors participate in mitochondrial shuttles, involving NADPH, pyruvate, malate, citrate, isocitrate, acyl-CoAs, and glutamate (Jitrapakdee, S. et.al. 2010). There are also various signaling pathways that, when activated, may contribute to maintaining or increasing glucose-stimulated insulin secretion, including the CaMKII (Calcium-Calmodulin-Dependent Protein Kinase II) , PKA (Protein Kinase A), PKC (Protein Kinase C) and PKG (Protein kinase G) pathways. Notably, most of other insulin secretagogues, namely nutrients, hormones and neurotransmitters, also modulate insulin secretion by these pathways.

2.3.1 Mitochondrial signalling

The role of mitochondria in the second phase of glucose-induced insulin secretion has been established by several studies in cell lines and humans (Jitrapakdee, S. et.al. 2010; Maechler, P. & Wollheim, C.B. 2001). There is even evidence of an uncommon subform of diabetes, mitochondrial diabetes, where mutations in mitochondrial DNA cause pancreatic beta-cell dysfunction (Maechler, P. & Wollheim, C.B. 2001).
Besides rendering the initial increase of ATP/ADP ratio, mitochondrial metabolism and anaplerotic metabolites are also involved in sustaining second phase insulin secretion. Pyruvate, the end product of glycolysis, plays an important role in this process, as it participates in several cycles whose final products constitute amplifying signals for insulin secretion. Particularly, NADPH, GTP, Malonyl-CoA, long-chain acyl-CoA, and glutamate have been suggested to sustain insulin secretion, although the exact mechanisms by which they have their effects remain to be elucidated (Jitrapakdee, S. et.al. 2010).
Once entering the mitochondria, pyruvate may be either converted to Acetyl-CoA by pyruvate dehydrogenase, or carboxylated to oxalacetate by pyruvate carboxylase, and therefore enter the Krebs cycle (Figure 2). Notably, there is a high expression of pyruvate carboxylase in the pancreatic islets comparable to that in gluconeogenic tissues, but islets

lack phosphoenolpyruvate carboxykinase (PEPCK), the first enzyme in the glyconeogenic pathway (MacDonald, M.J. 1995). Moreover, several studies have correlated pyruvate carboxylation with insulin secretion (Han, J. & Liu, Y.Q.; Hasan, N.M. et al. 2008; Lu, D. et al. 2002; Xu, J. et al. 2008).

Oxalacetate from pyruvate carboxylation may be converted to malate, exit the mitochondria, and re-converted to pyruvate, producing NADPH (Pyruvate/malate cycle). Oxalacetate may also condense with acetyl-CoA to form citrate, which either continues in the TCA cycle, or exits the mitochondria, and converts again to oxalacetate and acetyl-CoA by the ATP-citrate lyase (pyruvate/citrate cycle). Oxalacetate may re-enter the pyruvate/malate cycle which will produce NADPH, while acetyl-CoA is carboxylated by Acetyl-CoA carboxylase and form malonyl-CoA, the initial step of fatty acid synthesis (Jitrapakdee, S. et.al. 2010). As the pancreatic islet is not a lipogenic tissue, the fact that acetyl-CoA activity is high in this tissue may indicate that malonyl-CoA can also act as a metabolic coupling factor for insulin secretion (Prentki, M. et al. 1992).

Metabolites from the Krebs cycle can also exit the mitochondria and enter other cycles. Isocitrate, for example, is converted to α-ketoglutarate by the NADP-dependent isocitrate dehydrogenase, rendering NADPH. α-ketoglutarate may re-enter the mitochondria to continue in the TCA cycle, or can be converted to glutamate by the glutamate dehydrogenase (GDH). Glutamate has been suggested to be another metabolic coupling factor for insulin secretion, possibly by entering insulin secretory granules and promoting exocytosis (Maechler, P. & Wollheim, C.B. 1999).

Finally, GTP may be produced by an isoform of the succinyl-CoA synthetase, which catalyzes the conversion of succinyl-CoA to succinate in the TCA cycle. It has been suggested that GTP participates in insulin secretion. In beta-cells, suppression of GTP production by this pathway reduced glucose-induced insulin secretion, independently of changes in NADPH or the ATP/ADP ratio (Kibbey, R.G. et al. 2007).

2.3.2 Calcium signaling and calcium-calmodulin-dependent protein kinase II (CaMKII)

As noted earlier, glucose-stimulated insulin secretion is a Ca^{2+}-mediated process. The increase of cytosolic calcium inside the beta-cell must be sensed and transduced in order to exert a secretory response. One of the candidate proteins involved in this transducing system is CaMK II. CaMK II activation has been correlated with glucose-stimulated insulin secretion. Besides being localized at the insulin secretory granules, CaMKII phosphorylates proteins involved in the secretory machinery, including synapsin I (Matsumoto, K. et al. 1995), MAP-2 (microtubule-associated protein 2) (Krueger, K.A. et al. 1997), VAMP/synaptobrevin (Nielander, H.B. et al. 1995) and others. Insulin release is then suggested to be modulated by CaMK II by mobilizing the secretory granules toward the cell membrane by MAP-2 phosphorylation and by potentially regulating the docking or priming mechanisms via VAMP and synapsin I protein phosphorylation. Since CaM kinase II remains active after glucose stimulation, it is suggested as a mechanism of readily releasable pool replenishment. (Easom, R.A. 1999).

2.3.3 The G-protein coupled signaling pathways: PKA and PKC

The guanyl-nucleotide-binding (GTP) protein system or G-protein coupled system plays an important role on insulin secretion. In the beta-cells, two G-protein regulated pathways, the Adenylate cyclase (AC)/PKA, and the phospholipase C (PLC)/PKC pathways, modulate

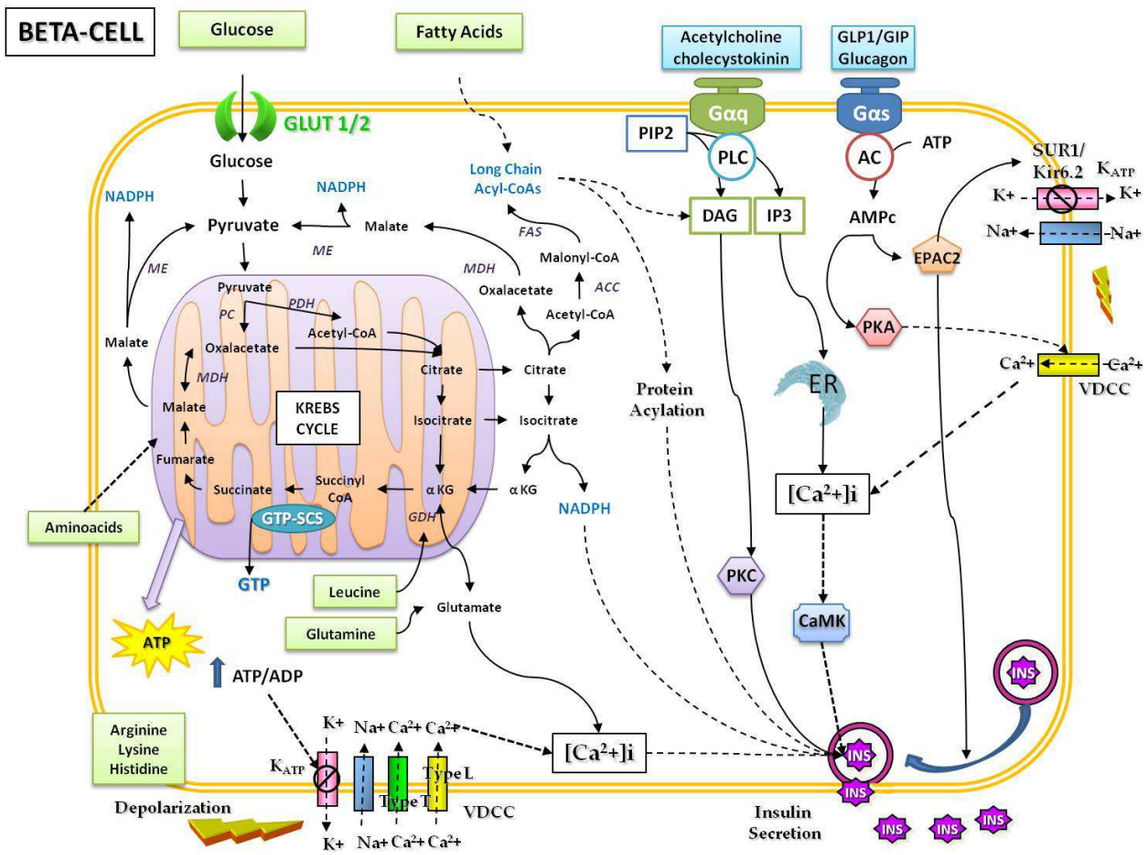

Fig. 2. Regulation of glucose-stimulated insulin secretion by nutrients, hormones and neurotransmitters.

Glucose-stimulated insulin secretion may be modulated by several mechanisms. Glucose metabolism increase ATP/ADP ratio and closes ATP-sensitive pottasium channels (K_{ATP}), depolarizing the membrane, opening voltage-dependent calcium channels (VDCC), and thus increasing intracellular calcium ([Ca2+]i). Glucose metabolism by the Krebs Cycle also renders a series of metabolic coupling factors that may initiate and sustain insulin secretion. These metabolic coupling factors participate in mitochondrial shuttles, involving NADPH, pyruvate, malate, citrate, isocitrate, acyl-CoAs, and glutamate. Signaling pathways that contribute to maintaining or increasing glucose-stimulated insulin secretion include PKA and PKC. Glucagon, glucagon-Like peptide 1 (GLP-1), and glucose-dependent insulinotropic peptide (GIP) act through PKA pathway, while acetylcholine and cholecystokinine act through the PKC pathway. Fatty acids may contribute to insulin secretion through the PKC pathway through formation of diacylglycerol (DAG) or through protein acylation. Aminoacids may stimulate insulin release by increasing ATP production from the Krebs Cycle, by membrane depolarization, or by participating in intracellular calcium increase. (αKG: alpha-ketoglutarate, ACC: Acetyl CoA Carboxylase, FAS: Fatty Acid Synthase, GDH: Glutamate Dehydrogenase, GTP-SCS: GTP-Succinyl CoA Synthetase, ER: endoplasmic Reticulum, ME: Malic enzyme, MDH: Malate Dehydrogenase, PC: Pyruvate Carboxylase, PHD: Pyruvate Dehydrogenase, PIP2: Phosphatidyl Inositol Biphosphante, IP3: inositol 1,4,5-trisphosphate).

insulin secretion in response to nutrients and other peripheral signals (Doyle, M.E. & Egan, J.M. 2003). Depending on the type of Gα subunit present, these signals will activate or inhibit Adenylate Cyclase ($G\alpha_s$ and $G\alpha_i$ subunits respectively). $G\alpha_q$ subunits are associated with the phosphatidyl inositol system (Gomperts, B.D. et al. 2003).

When the Adenylate Cyclase is activated in the beta-cell, it converts ATP in cyclic AMP (cAMP), which in turn can activate the cAMP-dependent protein kinase (PKA) and the Rap guanine nucleotide exchange factor (GEF) 4 or Epac2. PKA will phosphorylate several proteins, including L-type voltage-dependent calcium channels and proteins from the exocytotic machinery, increasing sustained insulin secretion (Ammala, C. et al. 1993) . Epac2 has been shown to favor insulin secretion by increasing the size of the reserve pool and facilitating the recruitment of the granules to the plasma membrane (Shibasaki, T. et al. 2007), mediating pulsatility of insulin secretion (Idevall-Hagren, O. et al. 2010), and binding to the SUR1 subunit of the K_{ATP} channels (Zhang, C.L. et al. 2009). The insulin gene itself has cAMP response elements in its promoter that modulate insulin transcription in response to this nucleotide (Melloul, D. et al. 2002).

Therefore, ligands that increase the activity of adenylate cyclase and cAMP have a positive effect on insulin synthesis and secretion (Sharp, G.W. 1979), while ligands that decrease adenylate cyclase activity affect insulin secretion in a negative way (Jones, P.M. & Persaud, S.J. 1998). Hormones and neurotransmitters mostly act on insulin secretion by this pathway (see below).

Phospholipase C (PLC) is the other effector protein regulated by G-protein coupled receptors in the beta-cell. PLC activation cleaves phosphoinositides into two second messengers, inositol 1,4,5-trisphosphate (IP_3), involved in Ca^{2+} release from the endoplasmic reticulum, and diacylglycerol (DAG). DAG is involved in the activation of the Protein kinase C (PKC). PKC phosphorylates the K_{ATP} channels and the voltage-dependent Ca^{2+} channels and mobilize the secretory vesicles (Doyle, M.E. & Egan, J.M. 2003), therefore promoting insulin secretion. Both nutrients and neurotransmitters may act through PKC activation, albeit by different mechanisms. It has been proposed that nutrients may activate atypical isoforms of PKC (-ζ, -ι, and –μ) by a non-identified mechanism independent of DAG, while the typical isoforms (-α, -β, -δ, and -ϵ) of PKC (Protein Kinase C) are activated by DAG (Jones, P.M. & Persaud, S.J. 1998).

2.3.4 The cGMP/PKG pathway

The cyclic GMP (cGMP) pathway is regulated basically by two factors: calcium and protein kinase G (PKG). Calcium increases the activity of calcium-dependent nitric oxide synthases, a key step in the synthesis of cGMP by soluble guanylyl cyclase (cGC). Calcium may also decrease cGMP synthesis by activating a calcium-dependent phosphodiesterase (PDE1). On the other hand, protein kinase G (PKG), an enzyme activated by cGMP, may phoshporylate different targets and modulate intracellular calcium concentration, primarily closing K_{ATP} channels (Soria, B. et al. 2004).

Although several studies have pointed to a role of sGC and cGMP on insulin secretion (Laychock, S.G. et al. 1991; Russell, M.A. & Morgan, N. 2010), a precise mechanism of action has not been yet elucidated for this pathway. As phosphorylation of PKG has been identified in rat islets (Jones, P.M. & Persaud, S.J. 1998), this is likely the enzyme mediating cGMP actions on insulin secretion. It has also been shown that PKG activity is necessary to increase ATP content in response to cGMP (Vilches-Flores, A. et al. 2009), and that glucose produces small increases in islet cGMP content (Laychock, S.G. et al. 1991; Schmidt, H.H. et al. 1992).

3. Nutrient modulation of insulin secretion

Beta-cells may be considered fuel sensors, as they are continually monitoring and responding to nutrient concentration in the circulation in order to secrete insulin and therefore, regulate glucose homeostasis. Given that meals are composed by multiple nutrients, it is important to examine the interplay between glucose-sensing in the beta-cell and other dietary nutrients, such as amino acids, fatty acids and vitamins. Cumulatively, the mixed nutrient sensing generates the metabolic coupling factors working as signals for insulin exocytosis.

3.1 Insulin secretion in response to fatty acids

While it would appear that free fatty acids do not stimulate insulin secretion in the absence of glucose, there is a substantial body of evidence that they are essential for glucose-stimulated insulin secretion (Salehi, A. et al. 2005). It has been proposed that, in the presence of glucose, fatty acid oxidation is inhibited, due to formation of malonyl-CoA by acetyl-CoA carboxylase. This permits the accumulation of long-chain acyl-CoA in the cytosol that then stimulate insulin secretion directly or through the formation of other lipid compounds such as diacylglycerol and various phospholipids (Nolan, C.J. et al. 2006). The mechanisms which could be involved in this process are (Yaney, G.C. & Corkey, B.E. 2003): a) activation of protein kinase-C enzymes; b) enhanced fusion of insulin-secretory vesicles with plasma membrane and insulin release; c) modulation of K_{ATP} channel activity directly or via complex lipid formation; d) Stimulation of Ca2+-ATPases; e) Protein acylation of GTP-binding proteins; f) Inhibition of lipase activity.

The effects of fatty acids on glucose-stimulated insulin secretion are directly correlated with chain length and the degree of unsaturation, where long-chain fatty acids (such as palmitate or linoleate) acutely improve insulin release, however, chronic increase of long-chain fatty acids reduce insulin release in response to glucose stimulation (Newsholme, P. et al. 2007b).

3.2 Insulin secretion in response to amino acids.

In addition to fatty acid involvement in glucose-stimulated insulin secretion, amino acids derived from dietary proteins and those released from intestinal epithelial cells, in combination with glucose; stimulate insulin secretion, *in vivo*. Amino acids individually are poor insulin secretagogues and a relatively small number of amino acids promote or synergistically enhance glucose stimulated insulin release from pancreatic beta-cells (Newsholme, P. et al. 2010). Leucine, glutamine, alanine, arginine, lysine, and histidine induce insulin secretion. The mechanisms by which these amino acids elicit insulin release may vary.

Glutamine and alanine are quantitatively the most abundant amino acids in blood and extracellular fluids and therefore might be the most relevant to insulin secretion (Newsholme, P. et al. 2010). Alanine increase ATP production in islet beta-cells, an event that has potential to promote the K+ATP channel triggering pathway. Alanine is also one of the electrogenic amino acids, being co-transported with Na+ so that its import depolarizes the plasma membrane and promotes Ca2+ influx, events that trigger insulin secretion (McClenaghan, N.H. et al. 1998). Although glutamine is rapidly transported and metabolized by islets, it does not promote insulin secretion by itself or enhance glucose-stimulated insulin secretion, but can elicit insulin release in the presence of leucine (Newsholme, P. et al. 2007a). It is believed that this is because leucine activates glutamic

dehydrogenase, which then increases the capacity of glutamine to contribute to anaplerosis via alpha-ketoglutarate (Newsholme, P. et al. 2007a).
Similarly as glucose-stimulated insulin release, leucine acts by generating ATP thought its metabolism, thus causing closure of ATP-sensitive potassium channels, membrane depolarization via opening of the L-voltage-dependent calcium channels, leading to calcium influx and increased cytoplasmic calcium concentrations. Furthermore, leucine acutely stimulates insulin secretion by serving as both metabolic fuel and allosteric activator of glutamate dehydrogenase, resulting in conversion of glutamate to 2-ketoglutarate, a compound that has been proposed to be a common mediator of glucose, amino acid, and organic acid insulin secretion (Odegaard, M.L. et al. 2010). Additionally, transamination of leucine to α-ketoisocaproate and entry into TCA cycle via acetyl-CoA can contribute to ATP generation by increasing the oxidation rate of the amino acid and thus stimulation of insulin secretion.
Other amino acids also stimulate insulin secretion by elevating cytosolic calcium concentration, although their mechanisms are achieved independently of ATP generation. Positive charged amino acids such as arginine, lysine and histidine, elicit insulin secretion by beta-cell inward transport of positive charge, triggering depolarization of cytoplasm membrane, and influx of extracellular calcium (Newsholme, P. et al. 2010).

3.3 Insulin secretion in response to vitamins

3.3.1 Vitamin A

Vitamin A is found in the organism either as retinol, retinal or retinoic acid forms. Retinoic acid is the active form, and the majority of its effects involve the activation of ligand-dependent transcription factors from the superfamily of hormonal nuclear receptors. Two of these receptors are known: the retinoic acid receptors (RARs) and the rexinoid receptors (RXRs). These can bind as heterodimers to specific DNA sequences named Retinoic Acid Response Elements, (RAREs) in the promoters of their target genes, or interact with other receptors such as Vitamin D receptors (VDRs), thyroid hormone receptors and PPARs (Peroxisome Proliferation Activating Receptors).
Retinol is essential for insulin secretion (Chertow, B.S. et al. 1987) and retinoic acid increases insulin secretion in cultured islets (Cabrera-Valladares, G. et al. 1999), presumably by its stimulatory effect on pancreatic glucokinase expression and activity (Cabrera-Valladares, G. et al. 1999). Retinoic acid is also capable of increasing insulin (Cabrera-Valladares, G. et al. 1999) and GLUT2 mRNA (Blumentrath, J. et al. 2001).

3.3.2 Vitamin D

Vitamin D is syntethized under the skin thanks to exposure to UVB radiation. It can also be obtained from food in the form of ergocalcipherol (vitamin D2) or cholechalcipherol (vitamin D3). When UVB radiation is absorbed through the skin, 7-dehydrocholesterol reserves form the pre-vitamin D3, which is transformed into vitamin D3 ($1,25(OH_2)D_3$) in a further process, by the action of the $25(OH_2)D_3$ hydroxylase (Holick, M.F. 2003). Vitamin D acts on Vitamin D receptors (VDRs), which are either in the nucleus or in the membrane, rendering two different mechanisms of action, genomic, and non-genomic (rapid response) (Norman, A.W. et al. 2001)
Both VDRs (Johnson, J.A. et al. 1994) and $25(OH_2)D_3$ hydroxylase are expressed in the pancreatic beta-cells (Bland, R. et al. 2004), suggesting there may be vitamin D synthesis and

effects in these cells. In vitro, 1,25(OH_2)D induces the biosynthesis of insulin in rat beta-cells (Bourlon, P.M. et al. 1999). It has been suggested that increases in cytosolic Ca^{2+}, a non-genomic effect of vitamin D, can increase insulin secretion (Norman, A.W. 2006). This increase may be modulated by activation of the PKC (Billaudel, B.J. et al. 1995) and PKA (Bourlon, P.M. et al. 1997) signaling pathways (d'Emden, M.C. et al. 1989).

3.3.3 Biotin

Biotin is a water-soluble vitamin that acts as a prosthetic group of carboxylases. Unrelated to this classic role, pharmacological concentrations of biotin regulate gene expression at both the transcriptional and the translational level (Rodriguez-Melendez, R. & Zempleni, J. 2003; Zempleni, J. 2005), and have a wide repertoire of effects on systemic processes such as development (Watanabe, T. 1996), reproduction (Baez-Saldana, A. et al. 2009; Paul, P.K. & Duttagupta, P.N. 1976; Simmins, P.H. & Brooks, P.H. 1983), and metabolism (Dakshinamurti, K. 2005; Fernandez-Mejia, C. 2005).

Biotin exerts beneficial effects on endocrine pancreas physiology. We have found that biotin stimulates insulin and pancreatic glucokinase expression(Romero-Navarro, G. et al. 1999), an enzyme that plays an important role in glucose homeostasis regulating insulin secretion in response to changes in blood glucose concentrations. Our group found that biotin concentrations of 10 to 1000 nM augmented glucokinase activity and mRNA abundance in cultured rat pancreatic islets (Romero-Navarro, G. et al. 1999). A similar stimulatory effect on pancreatic glucokinase was observed in the insulinoma RIN 1046-38 cell line (Borboni, P. et al. 1996). A positive effect of biotin on insulin secretion has been reported (Romero-Navarro, G. et al. 1999; Sone, H. et al. 2000; Sone, H. et al. 1999; Vilches-Flores, A. et al. 2009). Studies by our group (Romero-Navarro, G. et al. 1999; Vilches-Flores, A. et al. 2009) and others (Sone, H. et al. 2000; Sone, H. et al. 1999) have revealed that glucose-stimulated insulin secretion increases in response to acute exposure to pharmacological doses of biotin in either primary cultured islets (Romero-Navarro, G. et al. 1999), perifused pancreas (Sone, H. et al. 1999) or perifused islets (Sone, H. et al. 2000). This effect of biotin on insulin secretion also appears to be dose-dependent (Sone, H. et al. 1999). In isolated pancreatic islets, using blockers and inhibitors of different signaling pathways, we have discovered that the induction of glucokinase mRNA and the increase on insulin secretion by biotin involves guanylate cyclase and PKG activation, which triggers ATP production (Vilches-Flores, A. et al. 2009). The increase of ATP induces insulin secretion via ATP-sensitive potassium channels. Insulin, in an autocrine manner, activates PI3K/Akt signaling, which increases pancreatic glucokinase mRNA expression (Vilches-Flores, A. et al. 2009).

Although the acute effect of biotin on *in* vitro insulin secretion has been well documented, further studies addressing the effect of this vitamin on *in vivo* models, resembling the actual doses and periods of treatment currently recommended for diabetes treatment, need to be done.

4. Other modulatory signals of insulin secretion - hormones and neurotransmitters

Insulin secretion in response to the plasmatic concentration of glucose can be increased or decreased by several hormones (including insulin itself) and neurotransmitters via activation of their membrane receptors on the beta-cells (Flat, P.R. 1996). The G protein receptors and adenylate cyclase pathway are responsible for mediating most of these effects.

The adenylate cyclase pathway may be activated by some neurotransmitters, like acetylcholine, and hormones like GLP-1. GLP-1 is also an important factor for insulin synthesis and secretion, having a trophic effect on the beta-cells as well (Baggio, L.L. & Drucker, D.J. 2007). Other modulating pathways are activated in the beta-cells in response to oxidative stress caused by high glucose levels, like the JNK pathway, which ablates insulin synthesis and interferes with its action (Kaneto, H. et al. 2006).

4.1 Insulin and the beta-cell autocrine signaling

Various studies have shown an autocrine role of insulin on beta-cell function and survival (Aikin, R. et al. 2006; Navarro-Tableros, V. et al. 2004; Xu, G.G. & Rothenberg, P.L. 1998). In this process, insulin binding to tyrosine-kinase receptors located in the beta-cell promotes the receptor's autophosphorylation, catalyzing subsequent tyrosine phosphorylation of other proteins like IRS (IRS1 and IRS2). Once phosphorylated, these proteins interact with signaling molecules, which results in a phosphorylation cascade where PI3K, PDK and Akt are sequentially activated. Akt is a serine/threonine kinase which regulates cell survival, proliferation, growth and nutrient metabolism, through phosphorylation of different proteins like GSK3, FOXO and CREB (Song, G. et al. 2005). The activated receptor may act on the Ras signaling pathway, which in turn activates MAP kinases ERK1/2, in this way regulating growth, cellular differentiation and protein synthesis (Kahn, S.E. et al. 2006). In human islets, insulin has a positive effect on insulin production at the transcriptional level, as well as on beta-cell proliferation (Persaud, S.J. et al. 2008) .

4.2 Insulin secretion in response to glucagon

Glucagon is considered the contrarregulatory hormone of insulin, as its systemic actions are contrary to the ones exerted by insulin. Glucagon stimulates glucose production, glycogen degradation, and lipolysis. Paradoxically, it has been shown that glucagon stimulates insulin secretion both in rats (Kawai, K. et al. 1995) and humans (Ahren, B. et al. 1987). Glucagon induces a transient increase in plasma insulin up to 1 mg glucagon concentrations, and this increase is seen before glucose levels rise (Ahren, B. et al. 1987). There is evidence that the positive effect of glucagon on insulin secretion is mediated by activation of glucagon receptors in the beta-cells (Kawai, K. et al. 1995), and this activation may increase cAMP levels, leading to the PKA pathway.

4.3 Effects of incretins on insulin secretion

Incretins are hormones secreted in the postprandial state by the enteroendocrine cells in the gut. Their main physiological role is to modulate insulin secretion. Two incretins have been described GIP (glucose-dependent insulinotropic peptide) and GLP-1 (glucagon-like peptide-1) (Brubaker, P.L. 2010).

GLP-1 is released rapidly into the circulation after oral nutrient ingestion, and its secretion occurs in a biphasic pattern starting with an early (within10–15 min) phase that is followed by a longer (30 –60 min) second phase (Herrmann, C. et al. 1995). Incretin-receptor activation leads to activation of adenylate cyclase and elevation of cAMP. Its actions include stimulation of glucose-dependent insulin secretion, induction of beta-cell proliferation, and enhanced resistance to islet cells apoptosis (Brubaker, P.L. 2010). GLP-1 stimulates insulin secretion via mechanisms that include the following: 1) direct inhibition of K_{ATP} channels, which leads to beta-cell membrane depolarization; 2) increases in intracellular calcium levels

resulting from GLP-1–dependent influx of extracellular calcium through voltage-dependent calcium, channels, activation of nonselective cation channels, and mobilization of intracellular calcium stores; 3) increases in mitochondrial ATP synthesis, which lead to further membrane depolarization; 4) closure of voltage-dependent potassium (Kv) channels and consequent reductions in Kv currents, thereby preventing beta-cell repolarization; and 5) direct effects on beta-cell insulin storage granule exocytosis that occur distal to increases in ATP and intracellular calcium (Baggio, L.L. & Drucker, D.J. 2007).

Both GIP and GLP-1 are cleaved and inactivated by the enzyme dipeptidyl peptidase 4 (DPP4). The rapid degradation of GLP-1 by DPP4 has led to the development of degradation-resistant GLP-1–receptor agonists and dipeptidyl peptidase-4 inhibitors, in order to increase the incretin effects. These drugs are currently used for diabetes treatment (Brubaker, P.L. 2010).

4.4 Neurotransmitters in the regulation of insulin secretion

Besides nutrients, neurohormonal signals such as autonomic innervation can markedly modulate glucose-stimulated insulin secretion. Islets are thoroughly innervated by autonomic nerves, which contain an extensive variety of neuropeptide transmitters. Increased sympathetic activity affects insulin secretion in situations of stress, exercise and trauma. Activation of parasympathetic nerves before and during feeding by the smell, taste and digestive tract, along with incretin hormones derived from the gut are responsible for enhancing insulin response to meals.

Parasympathetic neurotransmitters that stimulate insulin secretion include acetylcholine, vasoactive intestinal polypeptide and gastrin-releasing polypeptide. Sympathetic neurotransmitters inhibit insulin release; these include norepinephrine, galanin and neuropeptide Y. The enteroinsular axis, mediated by incretin hormones, explains why the insulin response to an ingested nutrient load is greater than when the same load is given parenterally. Gastrointestinal hormones such as gastric inhibitory peptide, glucagon-like peptide-1 (7-36) and cholecystokinin exert physiological relevant insulinotrophic effects (Flatt, P.R. 2003). In particular glucagon-like peptide-1 (7-36) has attracted attention by its potential role in the treatment of diabetes (see above).

There are at least three potential sites were insulin can be modulated by hormones, peptides and neurotransmitters. Firstly, these may affect the ion channels that regulate membrane potential and calcium influx. Secondly, they may influence the mobilization of intracellular calcium stores, mainly the endoplasmic reticulum, and therefore cytosolic calcium concentration. Thirdly, they may modify the calcium sensibility of the contractile protein interactions that lead to the release of the insulin secretory granules (Flatt, P.R. 2003). The two better known targets of hormones, peptides and neurotransmitters within the beta-cell are related to adenylate cyclase and phospholipase C.

Activation of adenylate cyclase produces cyclic adenosine monophosphate (cAMP), which inhibits calcium sequestration within intracellular stores. Activation of cAMP-dependent protein kinase (PKA) results in phosphorylation of intracellular proteins that enhance calcium sensitization. PKA also promotes phosphorylation of voltage-dependent calcium channels thereby increasing calcium influx (Flatt, P.R. 2003).

Phospholipase C activation cleaves phosphatidylinosistol in the membrane producing inositol-1,4,5 triphosphate wich in turn inhibits calcium sequestration into the endoplasmic reticulum, while the adjacent cleavage product, diacylglycerol activates protein kinase C. Similarly to the effects of adenylate cyclase signaling pathway, activation of phospholipase

C alters insulin secretion by mechanisms related to calcium sensitivity and protein phosphorylation (Flatt, P.R. 2003).

5. Beta-cell mass

Besides a correct beta-cell function, the organism's beta-cell mass is also important for maintaining adequate insulin production and secretion. Beta-cell mass is determined by cell number as well as cell size, and it increases progressively during fetal, neonatal and growth periods in the life of an organism, reaching a plateau during adulthood and decaying gradually with age (Ackermann, A.M. & Gannon, M. 2007).

Diverse processes participate in increasing and maintaining the beta cell mass, such as neogenesis (newly forming of cells from precursors), proliferation (cell replication), beta-cell size increase (hypertrophy), and apoptosis (cell death) (Ackermann, A.M. & Gannon, M. 2007). Although beta-cell progenitors have been identified in the pancreas (Bonner-Weir, S. et al. 2008; Xu, X. et al. 2008), the participation of neogenesis during post-natal and adult beta cell mass is limited (Dor, Y. et al. 2004), being proliferation (Meier, J.J. et al. 2008) and hypertrophy (Montanya, E. et al. 2000) the mainly responsible mechanisms for post-natal beta cell expansion (Ackermann, A.M. & Gannon, M. 2007). The organism is also capable of modifying beta-cell mass depending on its insulin requirements. In insulin resistance states, such as pregnancy and obesity, beta-cell mass is increased (Rhodes, C.J. 2005) a process driven by proliferation (Ackermann, A.M. & Gannon, M. 2007).

The mechanisms by which adult beta-cell proliferation is driven remain unknown. Nevertheless, some of the factors regulating this process have been identified, such as growth factors (growth hormone, lactogens, insulin, insulin-like growth factors), incretins, cell cycle proteins, and transcription factors (PDX-1) (Ackermann, A.M. & Gannon, M. 2007). Although many of the molecular regulators of postnatal beta-cell mass and beta-cell turnover have been identified in rodent models, it has been observed that human beta-cells' ability to proliferate under the same signals is very restricted compared to rodent ones (Parnaud, G. et al. 2008). Moreover, in humans, beta-cell proliferation has suggested to occur only until early adulthood, as proliferation studies in humans have shown that there is no beta-cell replication after the first 30 years of life (Perl, S. et al. 2010).

6. Beta-cell failure and death in type 1 DM

Overt hyperglycemia and therefore, the onset of type 1 diabetes occurs when 70-80% of the beta-cell mass is gone. But the progressive loss of beta-cells is suggested to occur slowly over several years (Cnop, M. et al. 2005). This progressive damage may also account for a reduction of the first-phase insulin secretion seen in patients positive to islet cell antibodies but who had not developed hyperglycemia yet (Srikanta, S. et al. 1983). Nevertheless, the rate of beta-cell destruction in type 1 diabetes patients is variable and so can be the first manifestations of the disease. While some patients, mainly children and teenagers, may present ketoacidosis as first sign of diabetes, others (usually adults) could show modest fasting hyperglycemia, which may not evolve to severe hyperglycemia nor ketoacidosis for several years due to remaining function of the beta-cell (ADA 2009).

Regardless this variable nature, type 1 diabetes progression after the initiation of the autoimmune response may be divided in two different phases: insulitis and overt diabetes (Mathis, D. et al. 2001) (Figure 3). Apoptosis of the beta-cell is present even in the initiation

and, evidently, both in insulitis and diabetes. These observations suggest that the beta-cell has a more important role in the pathophysiology of the disease than previously thought (Eizirik, D.L. et al. 2009; Mathis, D. et al. 2001).

It has been proposed that beta-cell death possibly participates in the initiation of the autoimmune response, particularly in autoantigen presentation (Filippi, C.M. & von Herrath, M.G. 2007; Kaminitz, A. et al. 2007; Mathis, D. et al. 2001). It is known that beta-cells, both in rodents (Finegood, D.T. et al. 1995) and humans (Kassem, S.A. et al. 2000), may undergo physiological periods of apoptosis, particularly during the perinatal period. Moreover, viral infections or inflammatory cytokines may induce accumulation of misfolded proteins, causing ER stress, which can also lead to beta-cell apoptosis (Eizirik, D.L. et al. 2009). Immunological

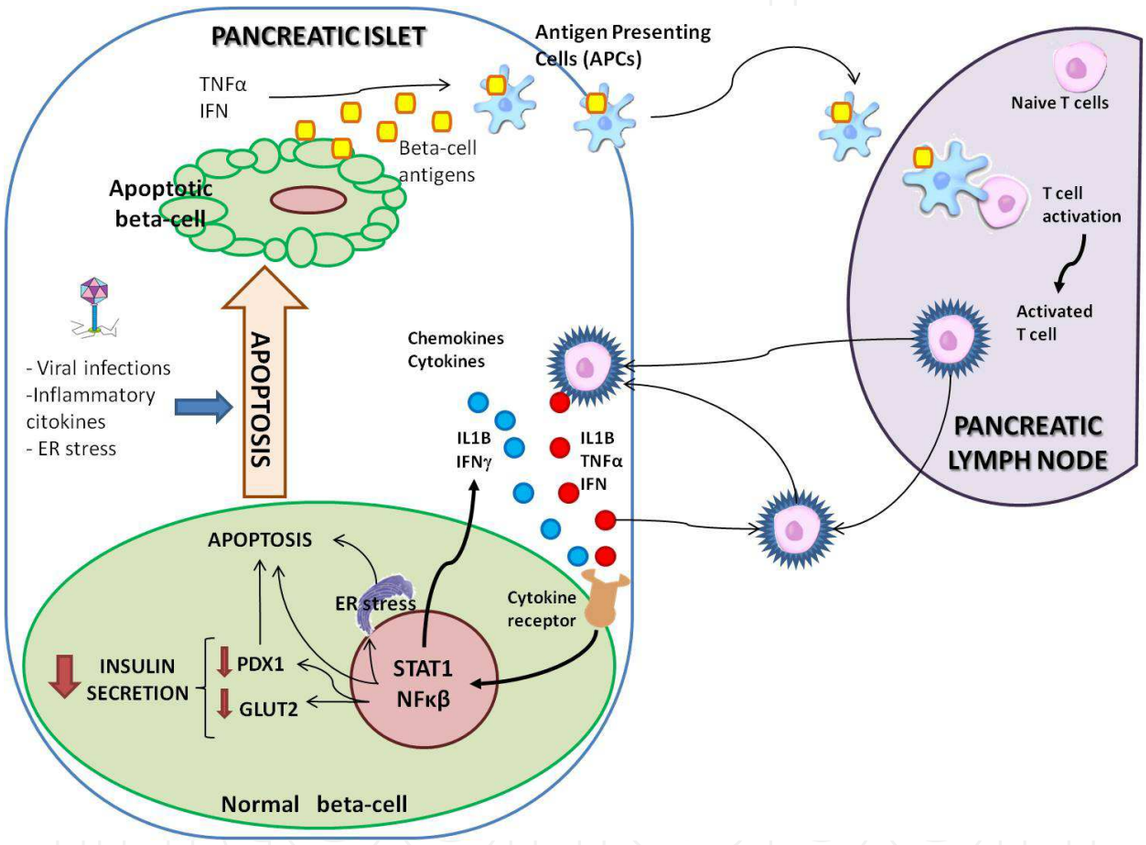

Fig. 3. Induction and progression of insulitis.

Viral infections or inflammatory processes may lead to beta-cell apoptosis. Apoptotic beta-cells undergoing secondary necrosis may release beta-cell antigens, which would activate the antigen presenting cells. These cells could activate naive T cells in the pancreatic lymph nodes. When T cells reencounter the islet-antigens, they are retained in the islet, releasing inflammatory factors and inducing insulitis. Inflammatory cytokines activate transcription factors NFκβ and STAT-1, which decrease PDX1 and GLUT1 expression, leading to insufficient insulin production and secretion. Activation of NFκβ and STAT-1 also trigger ER stress, apoptotic processes and beta-cell release of citokines, leading to a vicious cycle of inflammation/beta-cell destruction that maintains and eventually amplifies the autoimmune attack.

recognition of antigens released by apoptotic beta-cells undergoing secondary necrosis, particularly in the presence of inflammatory factors such as TNF or interferons, could be an important signal to activate antigen presenting cells, which may then reach the pancreatic lymph nodes and be recognized by T cells (Filippi, C.M. & von Herrath, M.G. 2007). When these T cells reencounter the islet-antigens, they are retained in the islet, triggering the inflammatory process or insulitis (Mathis, D. et al. 2001).

Beta-cells also participate in the progression of insulitis (Eizirik, D.L. et al. 2009; Kaminitz, A. et al. 2007). Beta-cells themselves are capable of producing chemokines and cytokines in response to inflammatory factors such as IL-1β and IFNγ (Cardozo, A.K. et al. 2003), a process mediated by activation of the transcription factors NFκβ and STAT-1 (Cardozo, A.K. et al. 2001; Cnop, M. et al. 2005). This cytokines, besides promoting beta-cell death, can contribute to the recruitment and activation immune cells (Eizirik, D.L. et al. 2009). A localized inflammatory process starts within the islet beta-cell milieu, in which immune cells produce more inflammatory cytokines (IL-1β, TNF and interferons) that would activate NFκβ and STAT-1, leading to a vicious cycle of inflammation/beta-cell destruction that maintains and eventually amplifies the autoimmune attack (Eizirik, D.L. et al. 2009; Kaminitz, A. et al. 2007).

Once insulitis is established, selective destruction of the beta-cells occur mainly by two proposed mechanisms: a recognition-linked mechanism and activation-linked mechanism. The former involves direct recognition of the beta-cell antigens by cytotoxic T-cells, while the latter is caused by exposure of soluble mediators secreted by T-cells that induce beta-cell death (Cnop, M. et al. 2005; Mathis, D. et al. 2001) such as cytokines, perforin or Fas/Fas ligand interactions, nitric oxide and reactive oxygen species (Cnop, M. et al. 2005; Mathis, D. et al. 2001).

Insulitis can be maintained in certain patients without evolving to overt diabetes. Studies in NOD mice have suggested that before the appearance of hyperglycemia, and after insulitis has been triggered, beta-cell function impairment precedes beta-cell apoptosis in response to the autoimmune attack (Strandell, E. et al. 1990). Surprisingly, beta-cell function may be recovered if the islets of these animals are either removed from their inflammatory milieu and cultured *in vitro* or if the inflammation is stopped with antibodies against the effector T cells (Strandell, E. et al. 1990), suggesting beta-cell damage in this stage is reversible. In addition, there is evidence that NFκβ activation in response to inflammatory factors also reduces PDX1 and GLUT2 expression (Cardozo, A.K. et al. 2003), two proteins which are crucial for insulin production and secretion.

Together with an initial loss of beta-cell function, the inflammatory process found in type 1 diabetes appears to stimulate beta-cell proliferation during the first stage of the disease. An increase in beta-cell mass may maintain metabolic demands for the period before the development of hyperglycemia, but it may also expose more and new epitopes, favoring and increasing the autoimmune destruction (Akirav, E. et al. 2008).

Given the important role of the beta-cell during the initiating and progression stages of insulitis that may lead to type 1 diabetes, current research is being directed toward maintenance and improvement of beta-cell function and mass before and during the inflammatory process, establishing important therapeutic targets. New therapeutic approaches suggest that using combinatory treatments comprising a first immune intervention, followed by stimulation of beta-cell proliferation and function (perhaps with GLP-1-receptor agonists), and maintenance of normal glucose levels, together with the already used immunomodulatory therapy, may help not only to stop the progression of the

disease, but even to recover the remaining beta-cell mass and function (Akirav, E. et al. 2008; Weir, G.C. & Bonner-Weir, S. 2010).

7. Conclusions

Type 1 diabetes is one of the most serious chronic diseases of childhood. In spite of all the efforts in finding efficient therapeutic approaches for this disease, insulin keeps being the only effective treatment, as islet transplantation and beta-cell generation from stem cells have shown difficulties in getting donors or generating effective glucose-coupled insulin secreting cells.

As the loss of beta-cells is determinant for the development of overt type 1 diabetes, understanding beta-cell normal physiology, namely insulin secretion, and how it may be affected during the progression of this disease is essential. Moreover, the development of new therapeutic interventions for type 1 diabetes, such as islet transplantation, beta cell maintenance and replacement, or stem cell therapy, require a profound knowledge of how the presence of different nutrients and signals may regulate insulin secretion and beta-cell mass.

Recent studies on the different stages of type 1 diabetes have shed light on an important role of beta-cell in the progression of the inflammatory process, and even evidence of reversal of the beta-cell damage present in the disease. These findings may provide tools to propose new integral and combinatorial therapeutic interventions that may aid in fighting this disease.

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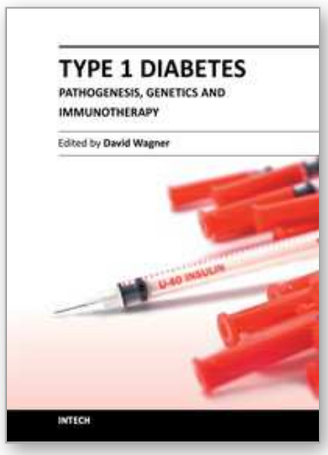

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This book is a compilation of reviews about the pathogenesis of Type 1 Diabetes. T1D is a classic autoimmune disease. Genetic factors are clearly determinant but cannot explain the rapid, even overwhelming expanse of this disease. Understanding etiology and pathogenesis of this disease is essential. A number of experts in the field have covered a range of topics for consideration that are applicable to researcher and clinician alike. This book provides apt descriptions of cutting edge technologies and applications in the ever going search for treatments and cure for diabetes. Areas including T cell development, innate immune responses, imaging of pancreata, potential viral initiators, etc. are considered.

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