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MITOCHONDRIA'S ROLE IS CRUCIAL IN GLUCOSE-STIMULATED INSULIN SECRETION

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ABSTRACT

In normal physiological condition, the pancreatic beta cells continuously monitor the blood sugar level and other fuel levels and, in response, secrete insulin to maintain normal fuel homeostasis. During the postpartum period, high plasma glucose level quickly stimulate beta cells to secrete insulin in order to decrease hepatic glucose output and promote glucose uptake in other tissues, particularly muscle and adipose tissue. The mitochondria of the pancreatic beta cells play a major role in this process. In addition to producing energy in the form of ATP to support insulin secretion, they also synthesize metabolites (anapleros) that can act as factors that couple glucose sensing to insulin granule exocytosis. ATP itself, and possibly modulated by these coupling factors, closes ATP-sensitive potassium channels, causing membrane depolarization that increases intracellular calcium to cause insulin secretion. In this review, we have discussed many of the biochemical pathways and the role of ATP-sensitive potassium channels in the regulation of glucose-stimulated insulin secretion (GSIS), which has attracted many scientists in the recent times to work in diabetic research.

KEYWORDS: Glucose, Insulin, Diabetes, Mitochondria, ATP, Potassium channel, Sulfonylurea receptor.

INTRODUCTION

Diabetes is a global health problem. In the early stages, the disease is caused by the inability of the pancreatic β-cells to secrete adequate amounts of insulin. Needless to say, the β-cells of the pancreas are the only source of insulin. β-cells are the specialized type of pancreatic islets of Langerhans that synthesize and secrete insulin, a 51 amino acid-containing protein hormone. The human insulin gene (INS) is a small gene of 1,425 base pairs located on the chromosome 11 (11p15.5) of the human genome and is composed of 3 exons separated by 2 introns.[1] However, the rodent groups and some fish species have two functional insulin genes (INS-1 and INS-2). The presence of glucose in the blood triggers the expression of several transcription factors, such as pancreatic-duodenal homeobox 1 (PDX1), the bHLH transcription factor Neurog3 and MAF bZIP transcription factor A (MafA)[2] and hepatocyte nuclear factor-1-alpha (HNF1α)[3] that bind to the promoter of the INS gene and enhance its transcription. Mutations in the HNF-1a gene showed defective GSIS, which was explained by the decreased ATP generation and increased uncoupling of mitochondrial oxidative phosphorylation.[4] The molecular mechanisms underlying the progressive failure of β-cells to respond to glucose in type-2 diabetes remain largely unresolved. However, most of the scientists agree that β-cell mitochondria play a key role in insulin secretion. Diabetic patients with mutations in the mitochondrial DNA (mtDNA) or mitochondria-associated nuclear DNA has been shown to have impaired insulin secretion primarily by pancreatic β-cells.[5] Apart from the glucose-stimulated insulin secretion (GSIS) some amino acids such as leucine and glutamine also act as stimulants for insulin secretion. However, the circulating glucose is the main and the most potent stimulus for the GSIS. This review discusses cell signaling in insulin secretion, focusing on the role of mitochondria and the molecular targets of ATP, an essential metabolic signal in GSIS.

Structure of Mitochondria and its DNA: Mitochondria are cytoplasmic organelles surrounded by a double-layered membrane, found in most animals, plants and fungi. Cells that require a lot of energy, such as muscle cells, can contain hundreds or thousands of mitochondria. A few types of cells, such as red blood cells, lack mitochondria entirely. As prokaryotic organisms, bacteria and archaea do not have mitochondria. In addition to providing the cellular energy, mitochondria are also involved in other functions, such as signaling, cell division, cell death, as well as regulating insulin secretion in the pancreatic β-

cells. A mitochondrion contains outer and inner membranes composed of phospholipid bilayers and proteins with a perimitochondrial space in between, where cytochrome c protein is abundant and the protons (H^+) are stored, creating an electrochemical gradient (see Figure 1). The distance between the two membranes of mitochondria can usually be up to 60 – 80Å (an angstrom is a unit of length that is one-tenth of a nanometer). A variety of voltage-dependent anion channels (VDACs) are anchored in the outer membrane, which transport nucleotides, various ions, and metabolites from the cytoplasm into the perimitochondrial space. In addition, the outer membrane contains several important enzymes, such as monoamine oxidase, rotenone-insensitive NADH-cytochrome c-reductase, kynurenine hydroxylase and fatty acid Co-A ligase. The inner mitochondrial membrane is compartmentalized into numerous folds called cristae, which expand the surface area of the inner mitochondrial membrane, enhancing its ability to produce ATP by the oxidative phosphorylation. The space enclosed by the inner membrane is called matrix, which contains several enzymes and co-enzymes, mitochondrial ribosomes, tRNA, proteins, cholesterol, lipids and several copies of small circular DNAs, which are not protected by "histone" proteins. The major functions of the matrix include oxidation of pyruvate and fatty acids, and the citric acid cycle.

The functional and active mitochondria are crucial in type-2 diabetes mellitus (T2DM) and its vascular complications. In fact, mitochondria are the main regulators of insulin secretion. Therefore, mutations in the mtDNA are associated with the development of type 2 diabetes. The mitochondrial ATP synthase synthesizes adenosine triphosphate (ATP) by oxidative phosphorylation using adenosine diphosphate (ADP) and inorganic phosphate (Pi). The functionality of this enzyme is so critical that a C>G mutation (m.8561) in the ATP synthase (ATP6/8) gene alone is sufficient to cause diabetes and hypergonadotropic hypogonadism.[6] This mutation results in a non-functional ATP synthase with the reduced ATP production. Accumulating evidence indicates that the stimulant glucose regulate insulin secretion by generating ATP as metabolic intermediate that drive the exocytosis of insulin granules, but the molecular mechanisms underlying the progressive failure of β-cells to respond to glucose in type-2 diabetes remain unresolved.

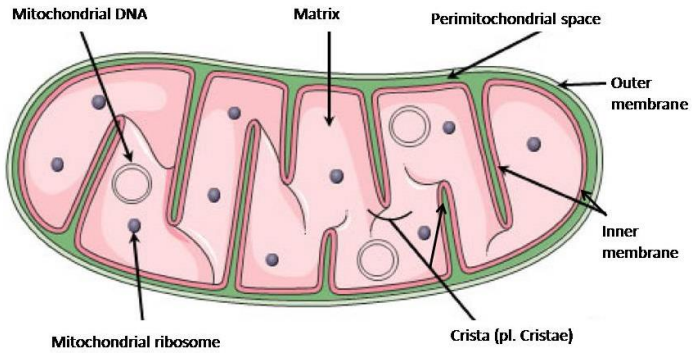

Figure 1. Structure of a mitochondrion. The electron transport and oxidative phosphorylation take place in the inner membranes of the mitochondria.

The Mitochondrial DNA (mtDNA): The human mitochondrial genome is a circular DNA molecule of 16,569 base pairs, which is only a fraction (1%) of the total DNA in a cell. The mtDNA is double-stranded consisting of a heavy strand rich in purine bases and a light strand rich in pyrimidine bases. In a cell, hundreds, even up to 2000 (liver cells) mitochondria float in the cytoplasm, and each mitochondrion contains several circular DNA molecules. The mtDNA contains 37 genes, all of which are essential for normal mitochondrial function. The genes in the heavy strand encode two ribosomal RNAs (12S rRNA and 16S rRNA), 14 tRNAs and 12 polypeptides, all of which are components of the respiratory chain complexes, as follows: 6 complex I subunits (NADH Dehydrogenase/ND1, ND2, ND3, ND4, ND4, ND4L, ND5), one complex III subunit (Cytochrome b), 3 complex IV subunits (Cytochrome Oxidase/COI, COII, COIII), and 2 complex V subunits (ATPase 6 and ATPase 8). Complex II, with four subunits, is signaled from the nuclear DNA. In addition, 8 tRNAs and one polypeptide (ND6, subunit of complex I) are synthesized from the light strand of the mtDNA. The mtDNA genes have no introns and no intergenic sequences except for the 1118 bp regulatory region. Like the nuclear DNA, the mtDNA is not protected by "histone" proteins, so it is more sensitive to intrinsic or extrinsic mutagenic factors. The antioxidants such as catalases or glutathione neutralize reactive oxygen species (ROS) produced by the respiratory chain. However, when these antioxidant mechanisms are insufficient, damage to the mtDNA must be repaired by enzymes that all come under instructions from the nuclear DNA. Mutations of mitochondrial DNA can lead to a number of diseases, such as: Leigh syndrome, MELAS (lactic acidosis),[7] Leber's hereditary optic neuropathy (LHON),[8] cardiomyopathy,[9] Parkinson's disease,[10] and Type-I and Type-II diabetes.[11] In most multicellular organisms, mtDNA is inherited from the

mother (maternally inherited). The mother passes her mtDNA to all her children, although only the daughters will pass it on to all the members of the next generation. Rarely, the sperm-borne mtDNA is occasionally seen in various animals, including humans.

Oxidative Phosphorylation (OXFOS): There are three main steps of cellular respiration: glycolysis, the citric acid cycle, and OXFOS. Glycolysis takes place in the cytosol, but the citric acid cycle and OXFOS occur in the mitochondrial matrix and the inner mitochondrial membrane, respectively. OXPHOS has two parts: the electron transfer chain (ETC) and chemiosmosis. The oxidation or redox reaction of the ETC involves 4 enzyme complexes: 1) protein complex I (Ubiquinone oxidoreductase); 2) Protein complex II (Succinate-dehydrogenase); 3) Protein complex III (Cytochrome-c reductase) and 4) Protein complex IV (cytochrome-c oxidase). Electrons from the two electron donors or scavengers, NADH (Nicotinamide adenine dinucleotide + hydrogen) and $FADH_2$ (Flavin adenine dinucleotide + hydrogen), generated by the TCA cycle and β-oxidation enter the ETC via complex I and complex II, respectively. From these two complexes, electrons are transferred sequentially to complex III by coenzyme Q (CoQ) and then to complex IV subunits by cytochrome C (see Figure 2). Cytochrome c is oxidized and the electrons are transferred to the oxidant oxygen. During the electron transport, free energy is released through protons (H^+) that accumulate in the perimitochondrial space. Consequently, the proton gradient across the mitochondrial inner membrane is converted into an electrochemical gradient, which acts as the driving force for ATP production and activates an enzyme called protein complex V or ATP synthase, producing ATP. ATP synthase synthesizes one ATP molecule for 4 H^+/proton. Compared to the glycolysis and TCA, each of which generates only 2 ATP molecules, whereas, the ETC-OXFOS generates 34 ATP from one molecule of glucose.[12] Therefore, a total of 38 ATP is produced from one glucose molecule by the abovementioned four processes. Although OXFOS is an important part of metabolism, the mitochondrial ROS, such as superoxide anion radical (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radical (OH^-), damage mtDNA, membranes, proteins and lipids, and they also contribute to various diseases including diabetes. The mitochondrial dysfunction with 40% less OXFOS is responsible for insulin resistance.[13]

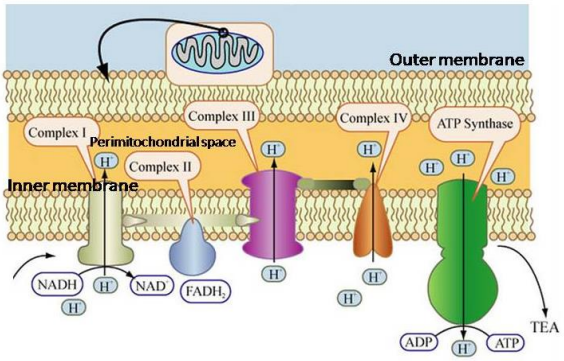

Figure 2. The components of the electron transport chain and oxidative phosphorylation. Through the process of ETC and OXFOS 34 ATP molecules are synthesized from one molecule of glucose.

Potassium channel: Potassium (K^+) channels are the most ubiquitously distributed ion channels and are found virtually in all types of cells, including the pancreatic β-cells. Potassium channels are the potassium-selective pores that span the cell membranes of the β-cells and they are very crucial for insulin secretion. Generally, potassium channels have a tetrameric structure in which four identical protein subunits associate to form a central ion conducting pore through which potassium ions pass. More than 80 genes encoding the K^+ channels were identified and they represent the largest group of ion channels regulating the electrical activity of cells in different tissues.[14] Generally, there are four major classes of potassium channels: 1) calcium-activated potassium channels (in which the potassium channel is activated in the presence of calcium); 2) inwardly rectifying potassium channels (they pass positively charged current more easily in the inward direction into the cell); 3) tandem pore domain potassium channels; and 4) voltage-gated potassium channels (they open or close in response to changes in the transmembrane voltage). However, some types of potassium channels are activated by muscarinic receptors and these are called muscarinic potassium channels. They are available in the heart and activated by parasympathetic signals through M2 muscarinic receptors. Potassium channels normally transport potassium ions (K^+) across the cell membrane depending on their concentration gradient; they tend to move from the higher to the lower concentration.

The ATP-sensitive K^+ (K_{ATP}) channels are members of the Kir superfamily. The K_{ATP} channel, a unique ABC transporter protein, is an octameric complex of four pore-forming Kir6.2 subunits and four regulatory SUR1 subunits, and it links cell metabolism to the electrical activity in many cell types, including the β-cells.[15] The SUR1 subunit is encoded by the ABCC8 gene, which is located on chromosome 11p15.1 and is mainly found in

the pancreatic beta cells.[16] A K_{ATP} in the β-cells regulate insulin secretion based on the intracellular ATP concentration, so mutations in SUR1 can cause insulin secretion disorders that can lead to diabetes. Anti-diabetic drugs such as sulfonylureas (e.g. glipizide, glimepiride) work in exactly this way by blocking the SUR1 receptor and increasing insulin secretion from the β-cells.

Role of the TCA Cycle in Insulin Secretion: The tricarboxylic acid (TCA) cycle, also named Kreb's cycle, is a mitochondrial metabolic hub that coordinates the metabolism of carbohydrates, proteins, and fats into carbon dioxide and ATP. The β-cells are a special type of endocrine cell that act as glucose sensors, adjusting insulin output to the prevailing blood glucose level in order to maintain a normal blood glucose homeostasis. After glucose enters the β-cell, it gets phosphorylated to glucose-6-phospate by the enzyme glucokinase, which constitutes the flux determining step for glycolysis.[17] In fact, glucokinase is the "glucose sensor" that senses the rise of the glucose level in the blood. The stimulation of insulin secretion is followed with a decrease in glucose output from the liver and the stimulation of glucose metabolism in other tissues, mainly muscle and adipose tissue. Many present studies argue that the glucose transporter 1 and 3 (GLUT1 and GLUT3) are the main glucose transporters in human β-cells.[18] Also, GLUT2 seems to contribute to glucose uptake in human β-cells, but does not cover a dominant role as this is the case in rodents. However, GLUT4 is the main glucose transporter in human adipose and muscle cells.[19]

ATP-dependent insulin secretion: Glucose is converted to pyruvate through a process called glycolysis. Pyruvate then enters the mitochondria and is decarboxylated to acetyl-CoA, which enters the TCA cycle, resulting in the production of NADH and $FADH_2$. The last two reducing equivalents are subsequently oxidized in the ETC and OXFOS across the mitochondrial inner membrane to enable ATP production. It is worth mentioning that both pyruvate dehydrogenase (PDH) and pyruvate carboxylase (PC) are abundant in the human β-cells. The conversion of glycolysis-derived pyruvate to acetyl-CoA via oxidation links the process of glycolysis to the TCA cycle. The role of PC in GSIS is crucial. Evidence for this has been found in the laboratory where the molecular suppression of PC also decreases insulin secretion.[20] In addition, oxaloacetate (OAA), an intermediate product in the TCA cycle, stimulates the insulin signaling pathway by increasing Akt Ser473 phosphorylation, mTOR Ser2448 phosphorylation, and P70S6K Thr389 phosphorylation.

In fact, the mitochondria of pancreatic β-cells play a key role in insulin secretion. Pancreatic β-cells synthesize insulin and its secretion is mainly modulated by glucose levels. Excess blood glucose stimulates the rate of OXFOS in β-cells, increasing the ATP/ADP ratio.[21] Two key biochemical processes involve glycolysis to produce ATP/ADP via the TCA-cycle, which inactivates K_{ATP}[22,23] in turn activating the voltage-gated calcium channels. As a result, the intracellular calcium (Ca^{2+}) increases, resulting in a state of depolarization of the cell, i.e., the cell's membrane potential becomes more positive than the steady state, which stimulates the release of insulin into the bloodstream to maintain blood glucose homeostasis (see Figure 3). Furthermore, the cytosolic NADPH stimulates centrin/SUMO-specific protease-1 (SENP1) which also activates the insulin secretion pathway (exocytosis), as the knockout of SENP1 in mouse β-cells abrogates the exocytotic response to glucose or NADPH.[24] Therefore, the insulin secretion is dependent on the bioenergetic state of the mitochondria. However, glucose deficiency or defects in electron transport or/and OXFOS have been shown to cause insulin resistance.[13] ATP released out of the β-cell also activates the purine 2 (P2) receptor located on the plasma membrane of the β-cell as a signaling molecule, resulting in increased Ca^{2+} and enhances insulin secretion.[25] Moreover, recent evidence shows that the K_{ATP} channels are also regulated by the membrane-associated pyruvate kinase (PK) and phosphoenolpyruvate (PEP) cycle that provides ATP, in addition to the mitochondrially-derived ATP.[26, 27]

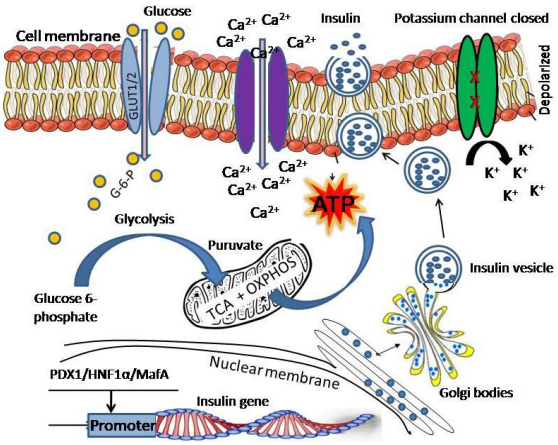

Figure 3: ATP-dependent insulin secretion in pancreatic beta cells. Courtesy: R. Haque.

ATP-independent insulin secretion: In addition to ATP-dependent pathway of insulin secretion, the potassium channels can independently enhance GSIS secretion in an ATP-independent manner. Therefore, the maximal insulin secretion is ensured by both K_{ATP}-dependent and K_{ATP}-independent activity in response to glucose. In addition to ATP production, mitochondria also synthesize anapleurotic metabolites, which aid in insulin secretion. Therefore, regulating the concentration of TCA cycle metabolites in mitochondria is crucial for cells. Pyruvate carboxylase is an anaplerotic enzyme that plays an essential role in various cellular metabolisms, including the gluconeogenesis, fatty acid synthesis, amino acid synthesis, and GSIS. The PC enzyme that converts pyruvate to oxaloacetate (OAA) is an intermediate product in several metabolic pathways, including the TCA cycle, gluconeogenesis, and glyceroneogenesis. OAA-converted malate from the TCA cycle is released into the cytoplasm where it reverts to pyruvate. The movement of these two metabolites produces NADPH, the oxidized form of $NADP^+$ which acts as a source of protons.

In an alternative pathway, OAA is converted to citrate, which is released into the cytoplasm via the citrate/isocitrate transporter protein (CTP). This pathway involves the direct conversion of cytoplasmic isocitrate to α-ketoglutarate, also named as 2-oxoglutarate (2OG), via the NADP-dependent isocitrate dehydrogenase (IDH) enzyme. The TCA cycle flows through isocitrate dehydrogenase-2 (IDH2) is critical for the glucose- and glutamine-stimulated insulin secretion. This pathway serves as a source of citrate and isocitrate to drive cytoplasmic NADPH production by IDH1, thereby activating the insulin secretion pathway (exocytosis). It has been shown that the molecularly suppressing CTP expression decreases the cytoplasmic citrate, thereby reducing GSIS. Similarly, the suppression of IDH enzyme expression also greatly reduced the rate of insulin secretion.

An increase in the NADPH/$NADP^+$ ratio as a consequence of glucose metabolism occurs shortly after the increase in glucose concentration in the β-cells that stimulates insulin secretion. In addition, NAD^+ is converted to $NADP^+$ by catalysis or phosphorylation by NAD kinase (NADK) and thus regulates the NADPH:$NADP^+$ ratio in β-cells and regulates the insulin secretion. GSIS was inhibited significantly by NADK knockdown in both INS-1 832/13 cells and mouse islets[28] demonstrating that NADK is an integral part of the β-cell oxidative and metabolic network.

CONCLUSIONS

Studies over the past two decades have provided ample evidence that the mitochondrial function is closely related to metabolic disorders, such as pancreatic β-cell dysfunction, insulin resistance, obesity, and the diabetes-related circulatory complications. Mitochondria are highly dynamic cellular organelles that play an important role in β-cell insulin secretion through β-oxidation and ATP production. However, short- and long-term metabolic problems in the mitochondria lead to impaired insulin secretion. Several studies have shown that the dysfunctional mitochondria develop insulin resistance, which is a hallmark of T2DM. Excess fat intake also causes mitochondria to become dysfunctional. Mutations in the mtDNA are prominent among the genetic causes of mitochondrial dysfunction. More than fifty mutations in mtDNA, including mutations in the leucine tRNA gene, have been identified that are directly associated with T2DM. In addition, mutations in the transcription factors involved in insulin gene expression and insulin secretion also inhibit the glucose-stimulated insulin secretion. For example, mutations in the TFAM (mitochondrial transcription factor A) and HNF-1a genes inhibit mitochondrial ATP production. In addition, mutations in the SUR1 subunit gene (ABCC8) of the K_{ATP} channel also cause abnormalities in insulin secretion. Nutritional quality of food, such as omega-3 fatty acids, low-fat diet, bioactive components in food - i.e. polyphenols (sources: nuts, olives, tea-coffee, berries), carotenoids (colorful fruits and vegetables), terpenoids (orange and citrus fruits), saponins (soybeans, chickpeas, beans, burdock and other legumes) glucosinolate-rich vegetables (such as broccoli, cauliflower, radishes), antioxidants, vitamins and are known to increase the insulin-sensitivity and prevent all mitochondria-associated metabolic problems.

Conflicts of Interest: The authors declare no conflict of interest.

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