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REVIEW ARTICLE

Mechanisms of insulin secretion in malnutrition: modulation by amino acids in rodent models

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Abstract Protein restriction at early stages of life reduces β-cell volume, number of insulin-containing granules, insulin content and release by pancreatic islets in response to glucose and other secretagogues, abnormalities similar to those seen in type 2 diabetes. Amino acids are capable to directly modulate insulin secretion and/or contribute to the maintenance of β-cell function, resulting in an improvement of insulin release. Animal models of protein malnutrition have provided important insights into the adaptive mechanisms involved in insulin secretion in malnutrition. In this review, we discuss studies focusing on the modulation of insulin secretion by amino acids, specially leucine and taurine, in rodent models of protein malnutrition. Leucine supplementation increases insulin secretion by pancreatic islets in malnourished mice. This effect is at least in part due to increase in the expression of proteins involved in the secretion process, and the activation of the PI3K/PKB/mTOR pathway seems also to contribute. Mice supplemented with taurine have increased insulin content and secretion as well as increased expression of genes essential for β-cell functionality. The knowledge of the mechanisms through which amino acids act on pancreatic β-cells to stimulate insulin secretion is of interest for clinical medicine. It can reveal new targets for the development of drugs toward the treatment of endocrine diseases, in special type 2 diabetes.

Keywords Malnutrition · Insulin secretion · Amino acids · Leucine · Taurine

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Insulin secretion

The endocrine pancreas is composed of four main types of cells distributed all over the exocrine portion. It is organized into small spherical clusters of cells called islets of Langerhans. The islets have usually an oval shape, and the arrangement of the endocrine cells inside this structure is similar in the majority of the mammalians (Kulkarni 2004). Every islet consists of central agglomerate (nucleus) of β-cells surrounded by α and/or δ cells or by δ and PP cells. It is estimated that an adult human has approximately 2 million islets (2% of the total pancreas weight). In rodents, every islet is constituted of about 2,000–4,000 cells of which 70–80% are insulin-producing β-cells, 5% are somatostatin-producing δ-cells, and 15–20% are composed of the glucagons-containing α-cells or still, PP-type cells which produce pancreatic polypeptide, depending on its localization in pancreas (Orci 1985). Recently, a fifth peptide hormone was discovered. Ghrelin, an orexigenic peptide secreted by enteroendocrine cells of the gastrointestinal tract, is also produced not only by pancreatic α-cells, but also by a new islet cell type, the ε-cell. Ghrelin

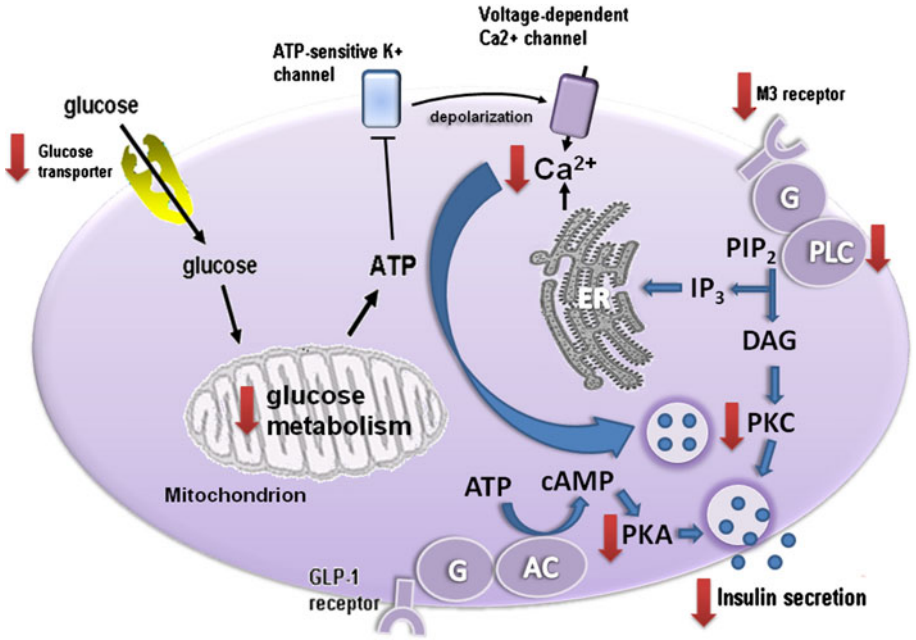

Fig. 1 Simplified schematic view of the mechanisms of insulin secretion by pancreatic *β*-cell. The *red arrows* indicate proteins downregulated in malnourished animals, as discussed in the text. *AC* adenylate cyclase, *PIP2* phosphatidyl-inositol-biphosphate, *PLC* phospholipase C, *IP_3* inositol-1,4,5-trisphosphate, *DAG* diacyl glycerol, *PI* phosphoinositides, *PKC* protein kinase C, *G* G-proteins, *PKA* protein kinase A, *cAMP* cyclic adenosine monophosphate, *ER* endoplasmic reticulum, *M3 receptor* type 3 muscarinic receptor, *GLP-1 receptor* glucagon-like peptide 1 receptor

function in the pancreas is not known (Wierup et al. 2002; Collombat et al. 2006).

Figure 1 shows a simplified view of the mechanisms of glucose-stimulated insulin secretion (GSIS). Glucose is the main stimulator of insulin secretion, and its metabolism induces periodic rises of cytoplasmic ATP in the *β*-cell, due to oscillatory glycolysis (Hellman 2009). According to the consensus model, increase of ATP, or the ATP/ADP ratio, causes the closure of the ATP/ADP-sensitive K^+ channels (K_{ATP}). The resulting decrease in K^+ conductance depolarizes the membrane, which opens the voltage-activated Ca^{2+} channels, with subsequent Ca^{2+} influx and an increase in intracellular calcium concentration ($[Ca^{2+}]_i$), triggering insulin exocytosis (Koster et al. 2005). Additional mechanisms seem to participate in GSIS, such as the volume-sensitive anion channel. An increase in sugar metabolism with consequent accumulation of its metabolites would lead to *β*-cell swelling via osmotic entry of water and chloride efflux through the opening of an anion channel, further depolarizing the *β*-cell plasma membrane (Best 2005; Best and Brown 2009).

Increased $[Ca^{2+}]_i$ also activates enzymes such as some isoforms of adenylyl cyclase, via calmodulin, generating cyclic AMP (cAMP) (Valverde et al. 1979; Cooper 2003; Delmeire et al. 2003), and phospholipase C (PLC), producing diacylglycerol (DAG) and inositol-1,4,5-triphosphate (IP_3) (Berridge 1987; Zawalich et al. 1988). These messengers amplify the Ca^{2+} signal through Ca^{2+} release from intracellular stores and by promoting the phosphorylation of proteins that sensitize the secretory process (Flatt 1996; Niwa et al. 1998; Yu et al. 2000; Tengholm and Gylfe 2009). ATP also has the effect of sensitizing the secretory machinery to Ca^{2+} signal and, as a component of the secretory granule, its concomitant release with insulin activates, in an autocrine fashion, the purinergic P_2 receptors, leading to the activation of phospholipase A_2, with generation of arachidonic acid, a substance known to inhibit the K_{ATP} channels (Larsson-Nyrén et al. 2007; Hellman 2009).

The rise in $[Ca^{2+}]_i$ in response to nutrient secretagogues follows an oscillatory kinetic which is coupled to pulsatile insulin release. Interestingly, pulsed intravenously administered insulin has been shown to induce greater hypoglycemic effect than continuous delivery in healthy and diabetic subjects (Matthews et al. 1983; Bratusch-Marrain et al. 1986) and the disappearance of this oscillatory pattern of insulin secretion has been considered as an early indicator of diabetes in man (Henquin et al. 1998; Soria and Martin 1998; Tengholm and Gylfe 2009).

Besides its peripheral action, insulin is also endowed with paracrine and autocrine function. We first demonstrated that elements involved in the insulin-signaling pathway of traditional target tissues are also present in pancreatic islets and are potentially involved in auto- and paracrine-signaling in this organ (Velloso et al. 1995). In malnourished rats, we found that reducing the expression of insulin cell signaling through members of the IRS family of proteins in isolated rat pancreatic islets improves glucose-induced insulin secretion, reinforcing the role of insulin paracrine and autocrine signaling in the control of its own secretion (Araujo et al. 2004).

Several nutrients, neurotransmitters and peptide hormones may also modulate insulin secretion. Free fatty acids (FFAs), keto acids and amino acids are among the nutrients that influence insulin release (Eizirik et al. 1993; Gao et al.

2003; Li et al. 2004; Um et al. 2004). The mechanisms by which amino acids enhance insulin secretion are varied. Leucine and alanine are expected to exhibit an elevated anaplerotic activity, promoting a markedly increase in the content of tricarboxylic acid (TCA) cycle intermediates, which results in increased intracellular ATP content, further stimulating insulin secretion by reducing the K^+ permeability in β-cells (Newsholme et al. 2006). The positively charged amino acid arginine does so by direct depolarization of the plasma membrane (Herchuelz et al. 1984; Sener et al. 2000). Amino acids co-transported with Na^+ can also depolarize the cell membrane as a consequence of Na^+ transport and thus induce insulin secretion by activating voltage-dependent calcium channel (McClenaghan et al. 1998; Sener and Malaisse 2002).

Amino acids, besides affecting insulin secretion, may influence gene and protein expression in pancreatic islets. The reduction in amino acid availability by a low protein diet after weaning induced several alterations in gene expression pattern in rats (Delguingaro-Augusto et al. 2004). Conversely, amino acid supplementation with either taurine or leucine increases insulin secretion in control and malnourished mice, which is associated with increased expression of genes and proteins essential for the secretory process (Carneiro et al. 2009; Ribeiro et al. 2009; Filiputti et al. 2010; Amaral et al. 2010).

Malnutrition and insulin secretion

The effects of protein malnutrition have been modeled in rodents fed protein-restricted diets. These animal models have provided important insights into the adaptive mechanisms involved in insulin secretion in malnutrition, since there are obvious limitations in investigations with human subjects. During the last 25 years, our research group developed a model of protein malnutrition using rodents, mainly rats and mice, fed a low protein diet containing 6% protein versus the 17% protein content in the control diet (de Mello and Cury 1988, 1989). The normal protein diet contains amounts of carbohydrate (39.7% cornstarch, 13.2% dextrin, and 10% sugar), fat (7.0% soy oil), fibers (5.0% cellulose micro fiber), salt (3.5%), and vitamin mix (1.0%), in accordance with the 1993 recommendations of the American Institute of Nutrition (AIN-G93) (Reeves et al. 1993). The low protein diet contains more carbohydrate (44.4% cornstarch, 17.8% dextrin, and 14.9% sugar) but the same amounts of fat, fibers, salt, and vitamin mix as the balanced standard protein diets (Latorraca et al. 1998b).

Epidemiological studies have shown a strong relationship between low birth weight and the plurymetabolic syndrome at adult age (Hales and Barker 1992). We have investigated the role of fetal and infant protein malnutrition in the development of the plurymetabolic syndrome in this rodent model during intra-uterine, lactation and/or after weaning period, evaluating its effects on the mechanisms of insulin secretion and action at adulthood (Carneiro et al. 1995; Reis et al. 1997; Latorraca et al. 1998a, b; Ferreira et al. 2003, 2004). Several of the abnormalities observed in pancreatic islets from malnourished animals are similar to those seen in type 2 diabetes and result in hampered insulin secretion (Swenne et al. 1992; Carneiro et al. 1995; Latorraca et al. 1998a, b; Arantes et al. 2002; Ferreira et al. 2003, 2004; Delguingaro-Augusto et al. 2004).

Rats fed a low protein diet after weaning exhibit a reduced insulin secretion together with reduced glucose sensitivity by pancreatic islets (Carneiro et al. 1995; Reis et al. 1997; Latorraca et al. 1999). Such poor secretory capacity may be related to a defect in the ability of glucose to increase Ca^{2+} uptake and/or to reduce Ca^{2+} efflux from β-cells (Carneiro et al. 1995; Latorraca et al. 1999; de Mello et al. 2003). Leucine-induced insulin secretion was also reduced in low protein fed rats (Filiputti et al. 2008).

We also found lower serum insulin concentration and severely reduced insulin secretion by pancreatic islets in response to glucose in pups of rat dams fed a low protein diet during pregnancy and lactation (Latorraca et al. 1998a, b; Arantes et al. 2002). At weaning, the islet area and the protein expression of the pancreatic duodenal homeobox-1 (PDX-1) were also reduced (Arantes et al. 2002). PDX-1 is a transcription factor important in the development of pancreas both in experimental animals and humans. It regulates a number of genes including insulin, GLUT2 and glucokinase, and its mutation is related with abnormalities in β-cell function and development of diabetes in humans and mice (Macfarlane et al. 1999; Hansen et al. 2000; León and Stanley 2007; Kaneto et al. 2008). Accordingly, we observed reduced mRNA content of both insulin and GLUT2 in these rats at adult age (de Barros Reis et al. 2008). A well-established feature of protein restriction/malnutrition is the elevated level of serum FFAs, and it is known that FFA reduces PDX-1 gene expression in pancreatic islet (Gremlich et al. 1997). High levels of FFA, together with a reduced content of malonyl-CoA, could be responsible for the increased carnitine palmitoyltransferase-1 (CPT-1) activity, increasing FFA oxidation and reducing GSIS (de Barros Reis et al. 2008).

Protein-energy restriction may also affect the autonomic nervous system. Cholinergic agents modulate β-cell function by acting synergistically with glucose to stimulate insulin secretion (Leon-Quinto et al. 1998). The binding of the cholinergic agonist to muscarinic (M3) receptors in the β-cell plasma membrane leads to hydrolysis of phosphoinositides (PI) via PLC activation, through a G-protein-coupled mechanism (Verspohl and Herrmann 1996). PI hydrolysis results in the formation of IP_3 and DAG. IP_3

releases calcium from intracellular stores and DAG activates protein kinase C (PKC), both stimulating insulin release (Niwa et al. 1998; Ahrén 2000). We have showed that pancreatic islets from rats fed a low protein diet after weaning present a reduced insulin secretory response to carbamylcholine (a M3 agonist) and phorbol 12-myristate 13-acetate (a PKC activator), probably due to the reduced PLC and PKC protein expression (Ferreira et al. 2003).

PKA (cAMP-dependent protein kinase) is another important kinase in the process of insulin exocytosis, mediating most of the cAMP actions (Cooper 2003). Its activation in β-cell is important for the signaling required for insulin secretion (Ämmälä et al. 1993; Liu et al. 1996; Takahashi et al. 1997). Forskolin, an adenylyl cyclase activator, potentialized insulin secretion in a much more pronounced way in control than in low protein fed rats, an effect mediated, at least in part, by the reduced protein and gene expression of the catalytic subunit of PKA in pancreatic islets (Ferreira et al. 2004). PKA expression was also reduced in islets from pregnant rats fed a low protein diet (Milanski et al. 2005).

In addition, patch-clamp measurements showed a resting membrane potential more hyperpolarized in β-cells from low protein fed mice. Depolarization and generation of action potentials in response to glucose were also impaired and all these alterations were attributed to the higher K_{ATP} channel activity in resting conditions and the lower efficiency and time delay of glucose to induce the closure of these channels. Since β-cell Ca^{2+} signals depend on electrical activity, Ca^{2+} fluctuations were also affected. Finally, islets from low protein fed mice exhibited a decreased level of cell-to-cell synchronization of Ca^{2+} signals, which was probably due to the low expression levels of connexin 36 (Soriano et al. 2010).

The protein and gene expression of s6k, a downstream target of mTOR involved in the protein translation process (Thomas and Hall 1997), was also reduced in pancreatic islets of malnourished rats (Filiputti et al. 2008), being a plausible mechanism to explain a general reduction in protein expression.

Thus, protein restriction at early stages of life causes several alterations in pancreatic islets resulting in impaired insulin release in response to different stimulus. Defects in the stimulus secretion coupling and reduced expression of proteins and genes essential for the perfect functioning of the mechanisms of insulin secretion seem to play a critical role in the diminished insulin secretion in malnutrition state.

The role of amino acids on β-cell function

Type 2 diabetic patients have altered levels of several amino acids in serum, what could contribute to the disturbances in insulin secretion (Menge et al. 2010). In view of the potential role of amino acids in modulating insulin secretion as well as maintenance of β-cell function, the knowledge of the mechanisms of amino acids action can reveal new targets for the development of drugs aiming the treatment of endocrine diseases, in special type 2 diabetes. In this sense, our group has focused on investigating two amino acids, leucine, a strong regulator of protein synthesis, and taurine, which seems to modulate the intracellular Ca^{2+} concentration and stimulate insulin secretion, and their effects in pancreatic islets from normal and malnourished rodents.

Leucine

Leucine is an essential, branched-chain amino acid (BCAA). It is necessary for protein and neurotransmitter synthesis and is also an important source of nitrogen for synthesis of nonessential amino acids. There is increasing evidence of the pivotal role of BCAAs in regulating the anabolic process involving both protein synthesis and degradation. They also have therapeutic potential due to the reported effects on sparing lean body mass during weight loss, wound healing promotion and muscle protein anabolism in muscle wasting with aging or cancer cachexia (Tom and Nair 2006; Ventrucci et al. 2007).

Leucine increases insulin secretion both in vivo and in vitro. The proposed mechanism by which L-leucine stimulates insulin release from pancreatic β-cells includes ATP production, via leucin metabolism through its transamination to α-ketoisocaproate (KIC) and subsequent entrance into the TCA cycle via acetyl-CoA, followed by K_{ATP} channel-dependent membrane depolarization. In addition, leucine allosterically activates glutamate dehydrogenase (GDH), the enzyme that converts glutamate to α-ketoglutarate, an important anaplerotic substrate for the second span of TCA (Gylfe 1976; Sener and Malaisse 1980; Newsholme et al. 2006). GDH expression is reduced in islets of malnourished rats. However, leucine supplementation restored GDH expression as well as glucose-, leucine- and KIC-stimulated insulin secretion in low protein fed rats (da Silva et al. 2010).

In addition to its effects on insulin secretion, leucine is the most effective amino acid in activating the mTOR complex (Xu et al. 2001). The mTOR pathway is a key regulator of cell growth and proliferation (Dickson and Rhodes 2004; Fatrai et al. 2006), and its activation is of particularly importance in conditions of elevated demand for insulin, such as obesity and insulin resistance. Accordingly, leucine supplementation restores partially or completely insulin secretion by pancreatic islets in protein-restricted mice and rats (Filiputti et al. 2010; Amaral et al. 2010). It augmented the PI3K and mTOR protein

expression in low protein fed rats, and this pathway could be involved in the improved insulin secretion in these rats (Filiputti et al. 2010). In malnourished mice, leucine supplementation increases or even normalizes the expression of key proteins involved in the mechanism of insulin secretion, such as the muscarinic receptor M3, PKC, PKA and the β2 subunit of the L-type calcium channel, an effect that may also be mediated by the PI3K pathway, since the expression of AKT and p-AKT is increased in these mice (Amaral et al. 2010).

Taurine

Taurine is a conditionally essential amino acid for human and non-human primates (Schuller-Levis and Park 2003). It is found in meat, fish and milk, but may also be biosynthesized from methionine and cysteine. Taurine is involved in many important biological functions including retina and nervous system development, Ca^{2+} modulation, membrane stabilization, reproduction, immunity and osmoregulation (Aerts and Van Assche 2002).

In pancreas, taurine is found at high concentrations inside glucagon and somatostatin-containing cells in the pancreatic islets, suggesting that its release is necessary for an efficient modulation of insulin secretion (Bustamante et al. 2001). Taurine increases insulin secretion (Kaplan et al. 2004; Cherif et al. 1996; Cherif et al. 1998; Kalbe et al. 2005) and sensitivity (Nakaya et al. 2000; Tsuboyama-Kasaoka et al. 2006) as well as glucose tolerance (Kaplan et al. 2004; Carneiro et al. 2009) in different experimental conditions. However, the exact mechanism of taurine action on glucose homeostasis as well as on endocrine pancreas is not well established.

Taurine reduces the rate of apoptosis (Merezak et al. 2001) and acts on DNA synthesis, preventing abnormal development of the endocrine pancreas (Boujendar et al. 2003). It also increases glucose sensitivity of UCP2-overexpressing β-cells by enhancing mitochondrial metabolism (Han et al. 2004) by acting on the mechanism for Ca^{2+} sequestration into the mitochondrial matrix (Lee et al. 2004). Finally, taurine inhibits K_{ATP} channel activity in adult rat β-cells (Park et al. 2004). In addition, there is evidence that the hypoglycemic action of taurine is due to the potentiation of the effects of insulin (Lapson et al. 1983) and its interaction with the insulin receptor (Maturo and Kulakowski 1988).

We have recently found increases in insulin secretion in response to stimulatory glucose or leucine (Ribeiro et al. 2009), in insulin content and glucose sensitivity (Carneiro et al. 2009) in pancreatic islets of mice supplemented with 2% taurine in the drinking water for 30 days. Leucine oxidation was 28% higher in taurine-supplemented mice. However, no alterations in ATP, ATP/ADP ratio or glucose oxidation were observed. Still, calcium uptake in the presence of 22 mM glucose was increased. Protein expression of the β_2 subunit of the calcium channel (Ribeiro et al. 2009) and the transcription factor PDX-1 (Carneiro et al. 2009) was higher. We also observed improved glucose tolerance in these animals, which appear to be due to the increased phosphorylation of both basal- and insulin-stimulated tyrosine phosphorylation of the insulin receptor in skeletal muscle and liver (Ribeiro et al. 2009; Carneiro et al. 2009).

We are now investigating the effects of taurine supplementation on the mechanisms of insulin secretion in rats fed a low protein diet after weaning. Our preliminary results have shown an improvement on insulin secretion at stimulatory glucose concentrations (Batista et al. 2008, unpublished results). In an animal model of fetal protein malnutrition, taurine supplementation normalized islet cell proliferation and insulin secretion in response to different secretagogues (Kalbe et al. 2005; Cherif et al. 1998). However, taurine failed in restoring insulin secretion in vitro, indicating its importance during development for a normal fetal β-cell function (Kalbe et al. 2005; Cherif et al. 1998).

Conclusion

Protein restriction during the early stages of life causes several alterations in pancreatic islets resulting in impaired insulin secretion. Amino acids can directly stimulate insulin secretion as well as acting on protein synthesis and gene transcription. Leucine supplementation restores partially or completely insulin secretion in undernourished mice. Taurine has been shown to increase insulin content and secretion, and both leucine and taurine increase the expression of genes and proteins essential for β-cell functionality. The knowledge of the mechanisms through which amino acids act on pancreatic β-cells to stimulate insulin secretion is of interest for clinical medicine. It can reveal new targets for the development of drugs aiming the treatment of endocrine diseases, in special diabetes.

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