THE ROLE OF MAGNESIUM IN INSULIN SECRETION AND INSULIN ACTION

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ABSTRACT

Magnesium (Mg^{2+}) is the fourth most common cation in the body and the second most common intracellular cation. It serves as a co-factor for all enzymatic reactions that require ATP and as a key component in various reactions that require kinases. As a cofactor it is involved in all major cellular processes such as energy metabolism, DNA transcription and protein synthesis. Mg^{2+} plays an essential physiological role in many functions of the body: it is important for bone mineralization, muscle contraction, neuronal activity, control of vascular tone, cardiac excitability, neurotransmitter release, hormone receptor binding and transmembrane ion flux. Plasma Mg^{2+} concentration is tightly regulated by the dynamic balance and interplay between intestinal absorption, exchange from bone and renal reabsorption. Hypomagnesaemia is associated with severe health risks and is involved in the pathogenesis of different chronic diseases such as type 2 diabetes, hypertension, osteoporosis.

The aim of this study is to present the role of magnesium in the insulin secretion by beta cells and insulin action in the peripheral tissues.

***Key words**: magnesium, insulin secretion, insulin action.*

INTRODUCTION

Magnesium (Mg) is the fourth most abundant cation in the body and the second most abundant intracellular cation. Ninety-nine percent of Mg is distributed in the intracellular fluid: 1–5% of Mg is ionized, the remainder is bound to proteins, negatively charged molecules and adenosine triphosphate (ATP) [23]. Intracellular magnesium concentration [Mg] ranges from 5 to 20 mmol/l.

Extracellular Mg represents about 1% of total body magnesium [23]. Approximately 55- 70% of plasma Mg is ionized, free, physiologically active form, 10-15 % is complexed with various anions and 20-30% is protein bound. Of the protein bound fraction, 60–70% is associated with albumin, and the rest is bound to globulins [15]. Magnesium concentration in the plasma of healthy people is carefully regulated within the narrow range of 0.7-1.1 mmol/l [26] . In order to maintain this normal levels, the recommended daily dietary allowance is 6 mg/kg/day which means 400 to 420 mg/day for adult men and 310–320 mg/day for adult women [1].

Magnesium intake depends on the magnesium in drinking water and food composition. Magnesium rich foods are nuts, green leafy vegetables such as spinach and broccoli cereal, grain banana, and legumes. Fruits, meat, fish, and milk based products are in general relatively low in Mg [26].

INSULIN SECRETION

Insulin is produced by the beta-cells of the pancreatic islets. A human pancreas contains 1 to 2 million islets of Langerhans, that are distributed throughout the exocrine parenchyma of the gland and are composed of several types of cells. The beta cells, are about 60 % of all the cells of the islets and lie mainly in the middle of each islet, alpha cells are about 25 % of the total and secrete glucagon, the delta cells secrete somatostatin and are about 10 % of the total. In addition, the PP cell, are present in small numbers in the islets and secrete pancreatic polypeptide [4].

Insulin consists of two polypeptide chains, the A- and B- chains, linked together by disulfide bonds. It is first synthesized as a single polypeptide preproinsulin which is directed to the rough

endoplasmic reticulum, where the signal peptide from preproinsulin is cleaved yielding proinsulin. Proinsulin then undergoes folding and formation of three disulfide bonds. Proinsulin is transported to the trans-Golgi network where are formed immature granules. Proinsulin undergoes maturation into active insulin and the resulting mature insulin is packaged inside mature granules [9,13].

Insulin secretion from pancreatic beta cells is a complex process involving the integration and interaction of multiple external and internal stimuli such as nutrients, hormones and neurotransmitters. The mechanism of glucose-induced insulin secretion is the most extensively studied and glucose appears to be the most potent stimulus. Secretion of insulin in response to the increased plasma glucose concentration is rapid and occurs in a two phases [30]. First-phase insulin release occurs within the first few minutes after exposure to an increased glucose concentration; this is followed by a more permanent second phase of insulin release. Of particular importance is the observation that first-phase insulin secretion is lost in patients with type 2 diabetes [29].

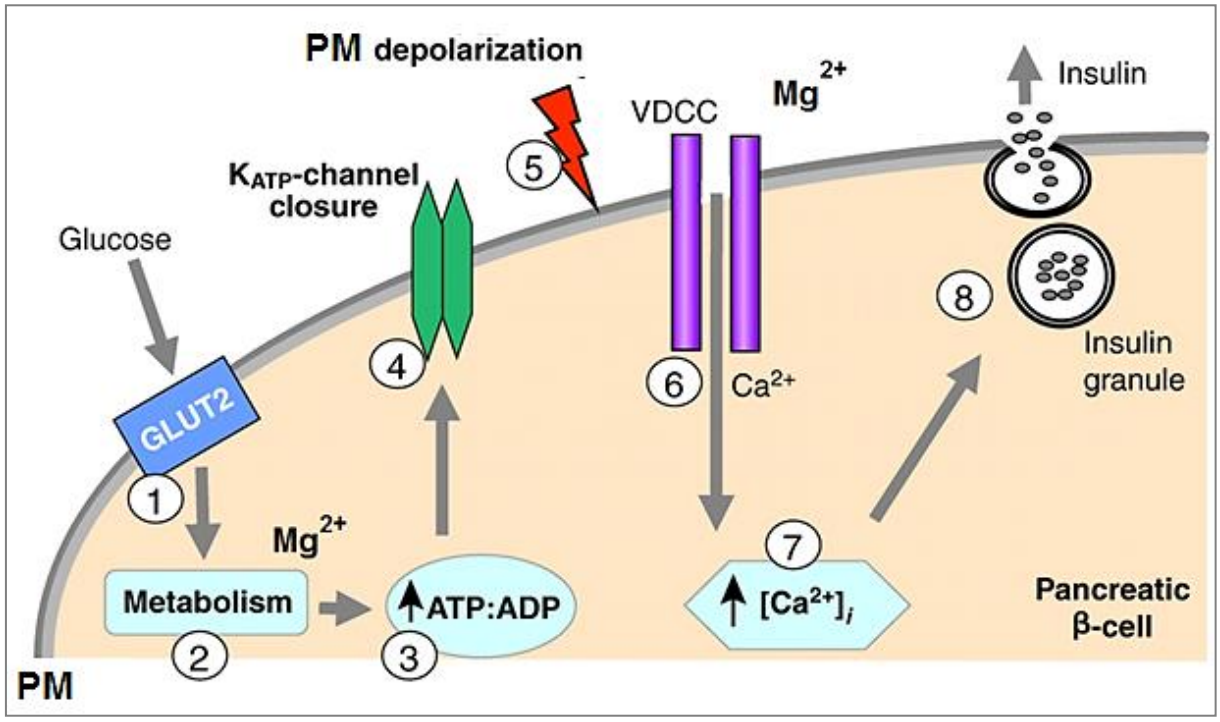

Figure 1. The mechanism of glucose-induced insulin secretion.

The insulin producing beta-cells are electrically excitable and use changes in membrane potential to couple variations in blood glucose to changes in insulin secretion. The mechanisms by which glucose and other secretagogues stimulate electrical activity and insulin secretion have been the subject of numerous reviews [9, 29]. The beta-cells contain different ion channel proteins but two types are especially important for the initiation of insulin secretion. The K^+ATP-channels are active at low glucose concentrations, probably because channel activity is stimulated by high intracellular ADP concentration. Increased concentration of ATP causes closure of the K^+ATP-channels leading to membrane depolarization. Pancreatic beta-cells contain at least three pharmacologically separable types of Ca^{2+}- channels. L-type Ca^{2+}-channels are particularly important for exocytosis of the insulin-containing granules because they mediate the Ca^{2+}- influx required for fast release of insulin [27, 29]. Glucose induced insulin release take place in several steps (fig. 1):

- Glucose enters the beta -cells through the glucose transporters, GLUT2
- Glucose is metabolized via the glycolytic pathway, the tricarboxylic acid cycle and

oxidative phosphorylation to ATP. Numerous enzymes in these metabolic pathways are dependent on Mg^{2+}

- An increased intracellular ATP: ADP ratio closes the ATP-sensitive K^+ channel. This prevents potassium ions (K^+) from leaving the cell, leading to the depolarization of the cell membrane
- Upon depolarization, voltage-gated Ca^{2+} channels open, which allows Ca^{2+} to move into the cells
- Significantly increased amounts of Ca^{2+} in the cells causes the release of previously synthesized insulin, which has been stored in secretory vesicles [29].

Extracellular Mg^{2+} acts as Ca^{2+} antagonist and inhibits Ca^{2+} influx, required for insulin secretion. Thus a decreased concentration of extracellular free Mg^{2+} results in an increased Ca^{2+} influx and increased concentration of intracellular free Ca^{2+}. The increased intracellular Ca^{2+} stimulates insulin secretion by beta -cells, as was demonstrated in experiments with an insulinoma cell line [10]. The effect of extracellular Mg^{2+} on insulin secretion was found in healthy human subjects. In subjects with 0.79 mM plasma Mg^{2+}, fasting plasma insulin was 23 μU/mL, while in those with plasma Mg^{2+} 0.87 or 1.00 mM, fasting plasma insulin amounted to 11 μU/mL [22]. The effects of magnesium deficiency on glucose-stimulated insulin secretion and insulin action on skeletal muscle were also studied in rats. Mg^{2+} depletion affects glucose metabolism and impairs insulin secretion [33]. There are inconsistent results concerning the effect of extracellular Mg^{2+} concentration on the insulin plasma concentration in experiments with Mg-deficient rats. Chaudhary at al. have found an increased plasma insulin concentration in Mg-deficient rats, but in other experiments with Mg deficient rats the plasma insulin concentration was not significantly changed [5,10].

INSULIN ACTION

Insulin action begins with the binding of insulin to a insulin receptor (IR) on the cell membrane of the target cells.

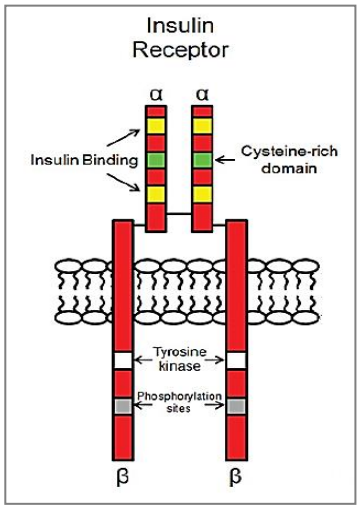

Figure 2. Insulin receptor structure.

The IR is a transmembrane glycoprotein with tyrosine kinase activity (fig. 2). It is a homodimer with each subunit consisting of an extracellular α subunit and a transmembrane spanning β subunit [32]. The ligand binding region is located in the extracellular α subunits and the tyrosine kinase domain is located in the cytoplasmic region of the β subunits. β subunits have three compartmental domains: extracellular, transmembrane and cytosolic domains. Binding of insulin to the receptor results in conformational change that activates the kinase domain residing on the intracellular portion of the β subunits [16]. The activation of protein kinase receptor is an important step in transmembrane signaling for insulin action. The activated kinase autophosphorylates tyrosine residues of the receptor. Insulin receptor complex is internalized and phosphorylates IRS 1-6 (insulin receptor substrate 1-6) and other kinases in the insulin signaling cascade [14]. When the intrinsic tyrosine kinase activity of the receptor is triggered by insulin binding, two major signalling pathways have been activated (fig. 3):

- Ras-mitogen-activated protein kinase (MAPK) pathway, which controls cell growth and differentiation.
- Phosphoinositide 3-kinase/Akt (PI3K/Akt). Binding of IRSs to the regulatory subunit of

phosphoinositide 3-kinase (PI3K) results in activation of PI3K, which phosphorylates membrane phospholipids and phosphatidylinositol 4, 5-bisphosphate (PIP2). This complex activates the 3 phosphoinositidedependent protein kinases (PDK-1 and PDK-2) resulting in activation of Akt/protein kinase B and atypical protein kinase [8, 24]. Activated Akt phosphorylates its 160 kDa substrate, which stimulates the translocation of insulin-mediated GLUT4 from intracellular vesicles to the plasma membrane [25].

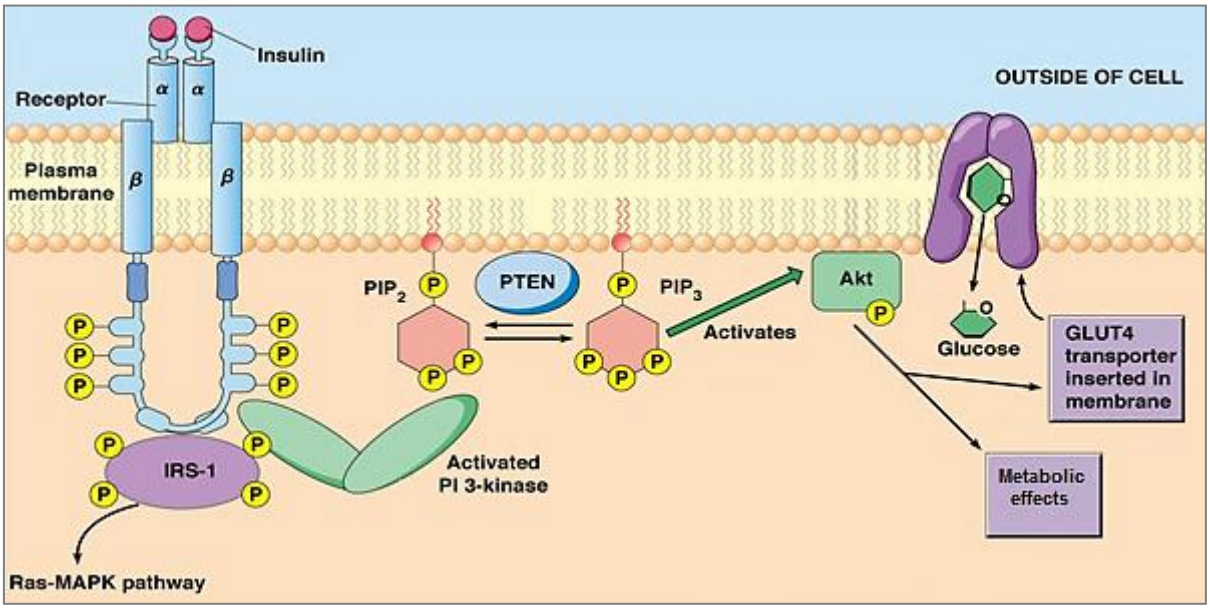

Figure 2. The insulin receptor signalling pathways.

The PI3K/Akt pathway is a key component of the insulin signaling cascade, which is necessary for the metabolic effects of insulin and GLUT4 translocation [28]. Since Mg is a necessary cofactor in all ATP transfer reactions $[Mg^{2+}]_i$ is critical in the phosphorylation of the insulin receptor and other kinases [3]. In all these reactions Mg^{2+} operates together with ATP as a kinase substrate. Additionally Mg^{2+} is bound to a regulatory site of the insulin receptor tyrosine kinase (IRTK). The apparent affinity of the IRTK for Mg ATP increased as the concentration of free Mg^{2+} increased, and the apparent affinity of the IRTK for free Mg^{2+} increased as the concentration of Mg ATP increased [10]. There are evidences that show a link between decreased magnesium concentration and reduction of tyrosine-kinase activity at the insulin receptor level, which results in the impairment of insulin action and development of insulin resistance [18]. Studies in multiple insulin resistant cell models have demonstrated that an impaired response of the tyrosine kinase to insulin stimulation is one potential mechanism causing insulin resistant-state in type 2 diabetes T2DM [12]. Nadler *et al*. have reported that insulin sensitivity decreases even in nondiabetic individuals after induction of magnesium deficiency [20].

Diabetes mellitus is a metabolic disease of multiple etiology, characterized by hyperglycemia resulting from defects in the insulin secretion and/or the insulin action [2]. Both insulin secretion and insulin action are impaired in T2DM. In the absence of a defect in beta-cell function, individuals can compensate indefinitely for insulin resistance with appropriate hyperinsulinemia [29]. Diabetes is frequently associated with both extracellular and intracellular Mg depletion. Epidemiologic studies have found a high prevalence of hypomagnesaemia in subjects with T2DM, especially in those with poorly controlled glycemic control. Cross sectional studies on diabetic patients showed lower serum Mg concentrations in comparison with non-diabetic patients, but some other have reported normal and even high magnesium levels [7,11].

Inadequate dietary intake of Mg is independent risk factor for the development of T2DM . Lopez-Ridaura et al., evaluating 37309 participants free of cardiovascular disease, cancers, and type 2 diabetes, have found a significant inverse association between magnesium intake and diabetes risk [17]. Van Dam et al. reported a similar relationship. Their findings indicated that a diet high in magnesium - rich foods, particularly whole grains, is associated with a substantially lower risk of T2DM [31]. Hruby et al. found that a higher Mg intake was associated with lower fasting glucose and insulin [6]. Benefits of Mg supplementation in diabetic subjects have been found in some clinical studies. Martha RM et al. reported that Mg supplementation improves insulin sensitivity as well as insulin secretion in patients with type 2 diabetes [18]. Rodriguez -Moran et al. found improved insulin sensitivity and metabolic control in type 2 diabetic patients after oral supplementation with $MgCl_2$ solution [21]. Mooren et al. have shown beneficial effect of oral Mg supplementation on insulin sensitivity in overweight, non-diabetic subjects [19].

CONCLUSION

Magnesium could influence both insulin secretion and insulin action. Magnesium plays an important role in the activities of various enzymes which are involved in glucose oxidation, and it plays a role in the release of insulin. As a calcium antagonist Mg regulates calcium entrance in pancreatic beta cells, regulating insulin secretion. Intracellular free magnesium concentration is critical in the phosphorylation of the tyrosine-kinase of the insulin receptor, other protein kinases, and all ATP and phosphate transfer-associated enzymes. Magnesium deficiency results in a defective tyrosine-kinase activity, post-receptor impairment in insulin action, altered cellular glucose transport and decreased cellular glucose utilization, which promotes peripheral insulin resistance with a postreceptor mechanism. Magnesium is crucial for optimum insulin activity and proper functioning of many co-enzymes and kinases vital for glucose metabolism. Hypomagnesemia may lead to insulin resistance and may play a role in the pathogenesis of the diabetes.

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