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NOVEL ASPECTS OF INSULIN SECRETION: FOCUS ON GLICLAZIDE

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KEYWORDS :

Introduction

Type 2 diabetes mellitus, a heterogeneous disease is characterised by decrease in both insulin secretion and insulin sensitivity.[1] In non-diabetic persons, insulin secretion in response to glucose shows a rapid peak within a few minutes (first phase), followed by a gradual rise ± the second phase.[2] In type 2 diabetics, the first phase is strongly diminished, absent or even paradoxically decreased, whereas second phase insulin release is markedly reduced.[3,4] Sulfonyl urea derivatives (SU), extensively used in the treatment of type 2 diabetes, stimulate insulin secretion by closing the pancreatic β-cell ATP-sensitive K^+ channels.[5,6,7]

Glucose-induced insulin secretion (GIIS) is the principal mechanism of insulin secretion (Fig. 1a). Early studies proposed two models of beta cell glucoreceptor signalling in GIIS: the regulatory-site model and the substrate-site model, although most studies supported the latter model. Following the discovery of the ATP-sensitive K^+ (K_{ATP}) channel in cardiomyocytes by electrophysiology, the KATP channel and the glucose-regulated K^+ channel were also found in pancreatic beta cells. As the KATP channel couples glucose metabolism to electrical activity of the beta cell, the discovery of the channel supported the notion that glucose metabolism is essential for GIIS.[8]

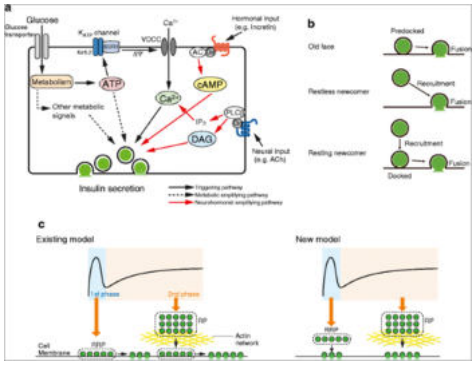

Figure 1 : a Glucose-induced insulin secretion and its potentiation. Glucose is transported thorough the glucose transporter into the pancreatic beta cell. Metabolism of glucose increases ATP production (ATP/ADP ratio), closing the KATP channels, depolarising beta cell membrane (ΔΨ), opening the voltage-dependent Ca2+ channels (VDCCs) and allowing Ca2+ influx, thereby triggering insulin secretion (formerly called the KATP channel-dependent pathway, presently called the triggering pathway). In addition to the triggering pathway, metabolic signals generated by glucose metabolism amplify insulin secretion (formerly called the KATP channel-independent pathway, presently called the metabolic amplifying pathway). Insulin secretion is also amplified by hormones and neurotransmitters that generate intracellular signals such as cAMP, DAG, and IP3 (neurohormonal amplifying pathways). PLCβ, phospholipase C-β; AC, adenylyl cyclase; ACh, acetylcholine. b Modes of insulin granule exocytosis. There are three modes of insulin granule exocytosis based on the dynamics of the granules. 'Old face': predocked granules that are fused to the plasma membrane by stimulation. 'Restless newcomer': granules that are newly recruited by stimulation and immediately fused to the plasma membrane. 'Resting newcomer': granules that are newly recruited by stimulation, docked and fused to the plasma membrane by stimulation. c Models of glucose-induced insulin secretion. In the existing model of GIIS, the first phase of insulin secretion results from an RRP comprising predocked insulin granules (old face); the second phase secretion results from an RP comprising granules located farther away (resting newcomer), granules that are newly recruited upon stimulation, docked, and fused to the plasma membrane. In the new model, both phases are caused by restless newcomer granules that are recruited upon stimulation and immediately fused to the plasma membrane without docking.

Physiological Basis of Sulfonylurea Action and Clinical Implications

The sulfonylureas stimulate insulin secretion by binding to specific receptors on the pancreatic b-cells, resulting in closure of K_{ATP}channels in the b-cell plasma membrane and opening of voltage-gated calcium channels. K_{ATP} channels are a complex of two proteins: a pore forming subunit (Kir6.2) and a drug-binding subunit (SUR); the latter functioning as the receptor for sulfonylureas (Figure 2). Two genes for sulfonylurea receptors have been identified encoding the proteins SUR1 and SUR2. The predominant type of SUR varies between tissues: SUR1 is predominantly found in pancreatic b-cells, SUR2A in cardiac muscle, and SUR2B in smooth muscle (Figure 2).[9]

The opening of cardiac K_{ATP} channels is believed to protect the heart during periods of ischemia. Sulfonylureas with affinity for cardiac KATP channels may inhibit the opening of K_{ATP} channels in the cardiovascular system, while those that act selectively on the pancreatic b-cell SUR receptors may pose less of a cardiovascular risk and are preferred especially in individuals at high risk for myocardial ischemia.[9]

While ß-cell oxidative stress is linked to chronic hyperglycemia, it has been suggested that certain sulfonylureas may directly increase generation of reactive oxygen species and cause oxidative stress related b-cell apoptosis. Gliclazide is known to be a general free radical scavenger, mediated by the azabicyclooctyl ring on its sulfonylurea core, and several experimental and clinical studies suggest that gliclazide may protect pancreatic b-cells from apoptosis induced by oxidative stress.[9]

Gliclazide Mainly Affects Insulin Secretion in Second Phase of Type 2 Diabetes Mellitus

The study group intended to examine the effect of the acute administration of gliclazide at 160 mg on insulin release during hyperglycaemic clamps in 12 type 2 diabetes patients, age 50 ± 9.0

years, diabetes duration 5.5 ± 4.8 years, fasting blood glucose 9.6 ± 2.1 mmol/L (means ± SD).[10]

Inclusion criteria were: age between 30 and 65 years, Body Mass Index (BMI) 20±28 kg/m2, duration of type 2 diabetes more than 2 years, SU therapy more than 1 year, glycated haemoglobin (HbA1C) < 8.5% (normal value < 6.1%) at least twice in the previous 4 months, fasting blood glucose during SU therapy < 8 mmol/L, no insulin treatment, no treatment with biguanides, normal laboratory values for kidney and liver function and a normal blood pressure.[10]

The subjects were examined in the fasting state on two occasions separated by 7 days in a randomised, double-blind study design. The SU medication of the patients had been stopped 3 days prior to each study day. In one arm, a cannula was used for infusion of insulin and glucose (20%); arterialised venous blood (558 C) was obtained from the other arm. Starting at t=± 270 min, a 210-minute hyperinsulinaemic, euglycaemic clamp was performed with an insulin infusion of 50 mU/kg/hr aiming at a blood glucose level of 4.5 mmol/L. Glucose (20%) was infused where necessary; to each 500 mL glucose solution, 10 mmol of potassium chloride was added. After 210 minutes (t=± 60 min), the insulin infusion was stopped and gliclazide (160 mg) or placebo was given by mouth.[10]

Plasma C-peptide levels increased significantly after the administration of gliclazide (increment 0.17 ± 0.15 vs. 0.04 ± 0.07 nmol/L, p = 0.024) before the clamp. After initiating the hyperglycaemic clamp, the areas under the curve (AUC) for insulin and C-peptide did not differ from 0±10 min (first phase) with gliclazide. But, second-phase insulin release (30±240 min) was markedly enhanced by gliclazide. AUC plasma insulin (30 to 240 min) was statistically significantly higher after gliclazide (12.3 □ 13.9 vs. ±0.56 ± 9.4 nmol/L x 210 min, p = 0.022); similarly, AUC plasma C-peptide (30 to 240 min) was also higher: 128 ± 62 vs. 63 ± 50 nmol/L x 210 min, p = 0.002). In conclusion, in long-standing type 2 diabetes the acute administration of gliclazide significantly increases second phase insulin release at a moderately elevated blood glucose level. In contrast to earlier findings in mildly diabetic subjects, these 12 type 2 diabetes patients who had an inconsiderable first phase insulin release on the placebo day, only showed an insignificant increase in first phase with gliclazide.[10]

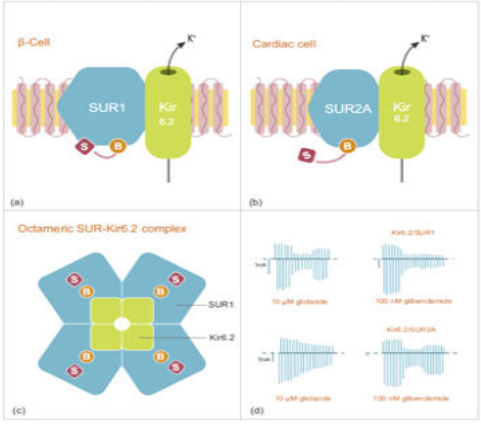

Figure 2 : (a) The transmembrane complex of the SUR1 sulfonylurea receptor and the ATP- sensitive Kir6.2 potassium efflux channel on the pancreatic b-cells. Each SUR1 has a cytosolic sulfonylurea (S) binding site and a benzamido (B) binding site. (b) SUR2A on cardiac muscle cells (and SUR2B on vascular smooth muscle cells) does not have a sulfonylurea binding site. While all sulfonylureas have the same general mechanism of action, they exhibit differences in tissue specificity, interacting to varying degrees with the different types of SUR. Using recombinant channels expressed in vitro and endogenous KATP channels in native tissues it has been shown that glimepiride and glibenclamide inhibit cardiac and smooth muscle KATP channels in addition to those in b-cells with similar affinity and are only slowly reversible. In contrast, tolbutamide and gliclazide are more selective, blocking b-cell KATP channels with high affinity, but not the cardiac or smooth muscle types of KATP channel, and are reversible. (c) The SUR1–Kir6.2 complex is a non-covalently bonded octamer comprising 4* SUR1 and 4*Kir6.2, illustrated fromthe cytosolic surface to show the sulfonylurea and benzamido binding sites. (d) Inhibition of cloned b-cell (Kir6.2/SUR1) and cardiac (Kir6.2/SUR2a) KATP channels illustrating specificity and reversibility of gliclazide for SUR1. Glibenclamide inhibited both b-cell and cardiac KATP channels and exhibited non-reversible SUR1 inhibition .

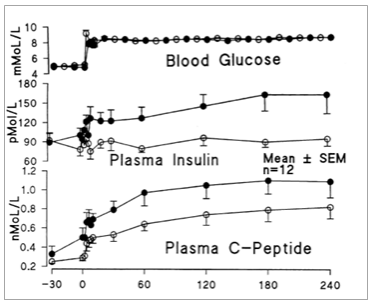

Figure 3 : Mean (□ SEM) blood glucose levels (upper panel) plasma insulin (middle panel), and plasma C-peptide levels (lower panel) during the 240 min hyperglycaemic clamp in 12 type 2 diabetes patients; closed symbols are with, and open symbols are without gliclazide.

Hence, the acute administration of gliclazide significantly enhances second phase insulin release at a moderately elevated blood glucose level in long-standing type 2 diabetes, while its effect on first-phase insulin secretion appears to be clinically insignificant. 10

Summary

SU derivatives are widely used in the treatment of type 2 diabetes that stimulate insulin secretion by closing the pancreatic β-cell ATP-sensitive K+ channels. The SU gliclazide has been shown to increase first- and second-phase insulin release during hyperglycaemic clamps in non-diabetic subjects. It has been found an improvement of (first-phase) insulin release after 3 weeks of gliclazide treatment in very mildly diabetic subjects.

However, Ligtenberg et al reported that the acute administration of gliclazide significantly enhances second phase insulin release at a moderately elevated blood glucose level in long-standing type 2 diabetes, while its effect on first-phase insulin secretion appears to be clinically insignificant.

Further, Gliclazide is a well known free radical scavenger, mediated by the azabicyclooctyl ring on its sulfonylurea core, and several experimental and clinical studies suggest that gliclazide may protect pancreatic b-cells from apoptosis induced by oxidative stress.

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