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PATHOGENESIS OF TYPE 2 DIABETES AND INSULIN RESISTANCE (RM WATANABE, SECTION EDITOR)

The Forgotten Role of Glucose Effectiveness in the Regulation of Glucose Tolerance

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Abstract Glucose effectiveness (S_G) is the ability of glucose per se to stimulate its own uptake and to suppress its own production under basal/constant insulin concentrations. In an individual, glucose tolerance is a function of insulin secretion, insulin action and S_G. Under conditions of declining insulin secretion and action (e.g. type 2 diabetes), the degree of S_G assumes increasing significance in determining the level of glucose tolerance both in fasted and postprandial states. Although the importance of S_G has been recognized for years, mechanisms that contribute to S_G are poorly understood. Research data on modulation of S_G and its impact in glucose intolerance is limited. In this review, we will focus on the role of S_G in the regulation of glucose tolerance, its evaluation, and potential advantages of therapies that can enhance glucose-induced stimulation of glucose uptake and suppression of its own production in conditions of impaired insulin secretion and action.

Keywords Glucose effectiveness · Glucose tolerance · Diabetes

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Introduction

Glucose tolerance in humans is dependent on a composite interaction of insulin secretion, insulin action and glucose effectiveness (S_G). In glucose intolerance states, impairment in one of the components is compensated for, at least in part, by greater contribution of another component to maintain normoglycemia [1]. When combined defects in insulin action, secretion or S_G upsurge and compensatory mechanisms fail, hyperglycemia occurs. Hyperglycemia in type 2 diabetes (T2DM) results due to either inappropriately increased rates of glucose production or inappropriately decreased glucose disposal or both, in reference to prevailing glucose and insulin concentrations [2–10]. The concept that glucose, per se, increases glucose utilization and decreases glucose production is well established [5, 11–19], but its role in the regulation of glucose tolerance is forgotten.

S_G which is defined as the effect of acute increase in glucose concentrations to facilitate its own metabolism (i.e. to stimulate glucose uptake and suppress hepatic glucose release) at fasting insulin plays a pivotal compensatory mechanism to maintain normal glucose tolerance during insulin resistance states in humans. Acute hyperglycemia contributes towards restoration of normal blood glucose by mechanisms that are both dependent and independent of accompanying dynamic insulin response [20, 21].

Various mechanisms have been proposed which act synergistically during acute hyperglycemia to normalize plasma glucose concentrations independent of dynamic changes in insulin concentrations. Defects in these mechanisms can lead to impairment in S_G, thus contributing to fasting and postprandial hyperglycemia in the evolution of T2DM.

1. Insulin-independent mechanisms of glucose restoration involve the mass action effect of glucose on its disposal

and suppression of endogenous glucose production (EGP) [11, 19, 22]. This mechanism was reported to be impaired in T2DM [23].

2. Apart from mass action effect, acute hyperglycemia enhances glycogen stores in the liver via stimulation of glucokinase (rate limiting) and glycogen synthase enzyme activity and reduces glycogen phosphorylase enzyme activity which prevents glycogenolysis and hence suppresses hepatic glucose release [8, 24].
3. Acute increase in plasma glucose decreases EGP by diminished fluxes of substrates for gluconeogenesis. Increase in glucose concentrations suppresses lipolysis causing lowering in plasma FFA, thus decreasing the supply of substrate to liver for gluconeogenesis [12, 25, 26]. This effect of glucose to decrease plasma FFA was found to be impaired in patients with T2DM irrespective of plasma insulin concentration [23].
4. In vitro and vivo experiments have suggested that glucose enhances abundance of GLUT 4 glucose transporters on the cell surface of skeletal muscle independent of insulin concentrations [27] and hyperglycemia-induced glucose transport is probably mediated via a Ca^{2+}-dependent signaling system which is insulin independent and different from the mass action effect of glucose [28].

Methods to Assess Glucose Effectiveness

The S_G can be measured/quantified by using either glucose clamp/prandial glucose infusion technique or by minimal model (MM) analysis.

Glucose Clamp Approach

One approach to quantitation of glucose's role independent of dynamic changes in insulin concentrations is the glucose clamp method, considered by many to be the gold standard for in vivo assessment of glucose metabolism. By the use of somatostatin pancreatic clamp to inhibit islet hormone secretion, it has been possible to examine glucose uptake under steady-state conditions at different insulin and glucose concentrations [26, 29•].

Under somatostatin suppression and replacement insulin (and glucagon) infusions, near-basal fasting insulin concentrations can be maintained and glucose uptake can be estimated at different glucose concentrations. Glucose uptake represents the effect of glucose itself to enhance glucose disposal at basal insulin and is therefore a measure of the component of S_G related to glucose disposal. This value is known as $S_{GD(CLAMP)}$, where S_G stands for glucose effectiveness, the letter D refers to disposal and CLAMP specifies that the value was obtained through a clamp study [26]. However, whole-body S_G ($S_{G(CLAMP)}$) is the sum of glucose disposal and the decrease in EGP. This can be expressed as

$$S_{G(CLAMP)} = S_{GD(CLAMP)} + S_{GA(CLAMP)}$$

where $S_{GA(CLAMP)}$ is the endogenous glucose appearance [26].

Thus, $S_{G(CLAMP)}$ can be defined as the relationship between glycemia and the rate of glucose infusion required to maintain the clamped glycemia and can be calculated by the arithmetic sum of $S_{GD(CLAMP)}$ and $S_{GA(CLAMP)}$ divided by the difference between the clamped glucose concentration and the baseline glucose concentration [26].

At higher insulin infusions, the slope of glucose uptake versus glucose concentration relationship increases substantially, increasing up to four times that of $S_{GD(CLAMP)}$ [26].

Minimal Model Approach

The MM is a simplistic mathematical construct that accounts for glucose dynamics. It considers S_G in its modelling. This enhances the importance of this concept in the determination of glucose disposal [26].

The MM, derived from the standard intravenous glucose tolerance test (IVGTT), analyses glucose dynamics after a single glucose bolus injection into two individual components, one dependent on glucose per se, at basal insulin concentrations, i.e. S_G, and the other one dependent on the β cell insulin response (insulin sensitivity). Hence, the MM includes measurement of whole-body S_G (Fig. 1) [26, 30].

According to this model, when the dynamic insulin response is suppressed and basal insulin maintained, the response to glucose injection is expected to be (approximately) exponential, with a time constant equal to S_G [26].

An insulin-modified IVGTT has also been used to evaluate glucose kinetics to generate a richer dynamic for model identification [30]. In this protocol, a weight-based insulin bolus is administered 20 min after the single glucose injection. Insulin-modified IVGTT data can be analysed with the MM [30, 31].

By means of tracer dilution technique (radioactive or a stable isotope), the labelled or hot MM allows an enhanced sophisticated assessment of S_G (S_G*), separating whole-body S_G into its peripheral and hepatic components. This approach indicates that, at basal insulin, about two thirds of the effect of glucose to enhance net glucose uptake is due to the disposal effect, with the remainder accounted for by EGP suppression [15, 26].

Since S_G is a hybrid parameter that describes at the same time the effects of glucose per se on glucose disposal and production and the exchange kinetics between the two glucose compartments, discrepancies are to be expected between the different models [30]. In fact, one limitation of the MM is that

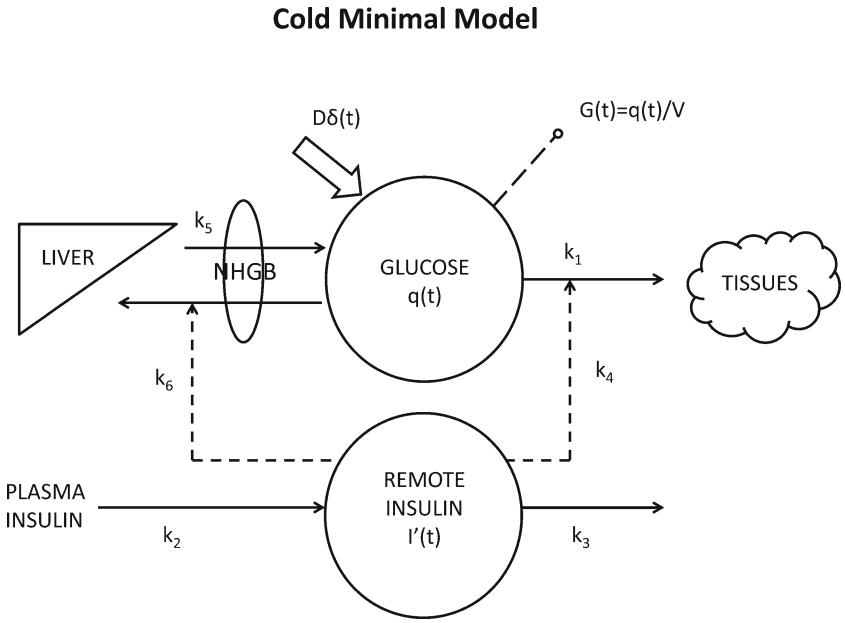

Fig. 1 The cold minimal model of glucose disposal [30]. *NHGB* net hepatic glucose balance, *q* glucose mass, *V* glucose volume, *G(t)* glucose concentration in plasma, *I(t)* insulin concentration in plasma, *D* glucose dose. *k* parameters are rate constants characterizing either material fluxes (*solid lines*) or control actions (*dashed lines*). *Flux from k1 and k5* denotes S_G (i.e. glucose effectiveness) (adapted with permission from [30])

it overestimates S_G, probably because it assumes a single compartmental distribution of glucose [30, 32, 33]. To evaluate the impact of the single compartment assumption on the metabolic indexes of MM and hot MM, Vicini et al. proposed a glucose-insulin reference model (RM) which is a more physiological model that consists of two different glucose disposal compartments: an insulin-independent one and a slower insulin-dependent compartment [30]. The RM allows to generate noisy synthetic plasma concentrations of glucose, tracer glucose and insulin during cold and the hot standard and insulin-modified IVGTT, which are then analysed with MM and hot MM. When comparing S_G of the MM and S_G obtained from the RM, the authors demonstrated that S_G from the single compartmental MM correlates weakly with the index from the RM and that S_G of MM is most affected by the single compartment approximation and S_G of hot MM is more robust than the one of MM [30].

Pacini et al. compared the standard versus the insulin-modified IVGTT in a cohort of healthy individuals. The insulin sensitivity index for both techniques was the same, but S_G was highest for the insulin-modified IVGTT, probably because of the effects of the circulating insulin [31]. Lack of correlation of S_G and S_G* has been described between the cold and the hot MM [34].

Comparison Between the Glucose Clamp Approach and the MM Approach

$S_{G(CLAMP)}$ and S_G have the same theoretical definition as whole-body S_G and are considered analogous in spite of the fact that they are calculated from different techniques: the former from glucose clamp studies and the latter from the MM. Elegant studies have compared clamp-derived and model-derived and have found them similar and consistent [31].

However, even though clamp studies are considered the gold standard for glucose kinetic assessment, they are elaborated, and usually cumbersome, studies that require a trained research team. The MM analysis from IVGTT studies provides a simpler approach for calculation of glucose metabolism indices with reliable and comparable data.

Glucose Effectiveness in the Pathogenesis of Type 2 Diabetes

Studies have suggested that S_G plays an important role in the development of glucose intolerance and is an important determinant of future progression to T2DM [35, 36]. Several studies have explored S_G in first-degree relatives (FDR)/offsprings of T2DM using MM analysis [37–39] or dynamic glucose infusion [40, 41] and reported unaltered [40, 41], increased [37] or decreased [38, 39] S_G in FDR of T2DM.

We [42–45] and numerous investigators [46–49] have used various methods to quantify S_G in patients with T2DM; however, the results from these studies have not been consistent. Most of these studies [46–48] reported decrease in S_G in people with T2DM assessed by MM analysis. We [44, 45], using model-independent methods applying prandial glucose infusion/glucose clamp technique, and others [49], using MM analysis, have observed normal glucose-stimulated suppression of hepatic glucose release but impaired glucose-stimulated glucose disposal in individuals with T2DM. The differences observed in these studies can be attributed to the differences in experiment designs and limitations of the

studies. Moreover, MM analysis is based on certain assumptions which may overestimate the S_G. S_G measurement using traditional intravenous glucose tolerance test and cold MM results in overestimation due to rapidly changing glucose and insulin concentrations [50], and the magnitude of the overestimate depends on the prevailing insulin concentration [51]. The errors observed may be in part caused by use of a single compartment technique in cold MM to depict glucose kinetics [34, 52, 53].

Evidences suggest that several neuronal areas of the brain play a role in glucose homeostasis [53–59]. There is an assumption that apart from enhancing insulin secretion, GLP-1 increases S_G via centrally mediated action in brain hypothalamus [29•, 60, 61].

Pharmacological Intervention and Glucose Effectiveness

Studies have suggested that in glucose-intolerant individuals, metformin decreases ATP and energy stores in liver and skeletal muscles and enhances glucose-mediated glucose disposal and inhibits hepatic gluconeogenesis and EGP [62–64]. Recently, a study in women with polycystic ovary syndrome has reported improvement in S_G following 12 weeks of treatment with metformin [65••]. This further supports that adjuvant interventions that improve S_G will help to maintain glucose homeostasis in glucose-intolerant people.

Exercise and Glucose Effectiveness

The short- and long-term beneficial effects of exercise on glucose homeostasis have been demonstrated in individuals with normal [66, 67] and impaired glucose intolerance [68, 69]. Most of the exercise-induced alterations are attributed as insulin sensitizing with improvement in insulin actions in insulin-resistant individuals [32, 70]. However, studies have shown that exercise also enhances S_G [26, 66, 71–77]. Although the exact mechanism for this enhancement was not described in these studies, it is believed that exercise induces GLUT 4 translocation to the plasma membrane [78] and increases AMP-activated protein kinase (AMPK) [70, 79] which leads to an insulin-independent increase in glucose transport following exercise. Bordenave et al. did not observe any significant change in S_G following acute bout of exercise in T2DM and concluded that exercise-induced enhancement in S_G is markedly blunted in T2DM compared to non-diabetic individuals [32].

Conclusion

The ability of glucose to regulate its own metabolism in the presence of basal insulin concentrations is markedly decreased in individuals with glucose intolerance, and this decrement in S_G likely contributes significantly to fasting and postprandial hyperglycemia in people with T2DM with compromised insulin secretion and/or action. Therefore, therapeutic strategies targeting to correct impairment in S_G will likely restore normal glucose tolerance in glucose-intolerant individuals.

Compliance with Ethics Guidelines

Conflict of Interest Simmi Dube, Isabel Errazuriz-Cruzat, Ananda Basu and Rita Basu declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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