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Research Article

Deficient Activity of FAD-Linked Glycerophosphate Dehydrogenase in the Mitochondria of Insulin-Producing Pancreatic Islets B-Cells: A Possible Cause of the Metabolic Syndrome

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ABSTRACT

A deficient activity of mitochondrial FAD-linked glycerophosphate dehydrogenase in insulin-producing pancreatic islet B-cells was recently identified in selected animal models of non-insulin-dependent diabetes mellitus. The incidence of this enzymatic defect remains however to be unambiguously documented in type-2 diabetic patients. The present review mainly aims at speculating that the altered recognition of nutrients, especially D-glucose, by pancreatic B-cells, as resulting from the above-mentioned enzymatic perturbation could also eventually lead to the development of the metabolic syndrome (MetS).

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Introduction

In a recent study of one hundred young adults (30 to 40 years of age) presenting a metabolic syndrome, attention was drawn to the fact that 26 out of 60 male subjects and 9 out of 40 female subjects could be considered as non-diabetic, displaying a glycemia below 7.0 mM and averaging 6.16 ± 0.26 mM and 5.77 ± 0.21 mM in the male and female patients, respectively, as distinct from an overall mean value of 7.97 ± 0.09 mM in the diabetic MetS patients [1]. The mean insulinemia was almost identical, however, in the non-diabetic MetS subjects (30.1 ± 0.4 μ U/ml) and the diabetic group (32.4 ± 0.5 μ U/ml). These findings could suggest that an impaired insulin secretory response of pancreatic islet B-cells to long-term hyperglycemia represents a far-from-uncommon feature of the MetS. The present review aims at proposing one among several potential candidates to account for the impaired functional response of insulin-producing to the major circulating insulinotropic nutrients, i.e. D-glucose, in non-insulin-dependent diabetes. Such a candidate corresponds to a deficient enzymatic activity of FAD-linked glycerophosphate dehydrogenase in the mitochondria of pancreatic islet B-cells [2].

Experimental Findings

Although the participation of the sweet-taste receptor TIR3 in pancreatic islet insulin-producing B-cells to the stimulation of insulin release by D-glucose was documented over the last decade, as recently reviewed, it remains true that an essential determinant of the insulin secretory response to a rise in extracellular D-glucose concentration consists in the acceleration of D-glucose catabolism in islet B-cells [3-5]. In other words, the so-called receptors and metabolic hypothesis for the recognition of D-glucose by insulin-producing cells are no more considered as conflicting proposals but, instead, as reconciled concepts [6]. The stimulation of D-glucose oxidative metabolism evoked in islet B-cells by a rise in the extracellular concentration of the hexose involves an accelerated circulation of metabolites in the mitochondrial glycerophosphate shuttle. This essential finding was first documented in 1987 [7].

The preferential stimulation of mitochondrial events relative to total glycolytic flux coincides with a preferential stimulation of pyruvate oxidative decarboxylation and, hence, optimizes the yield of ATP

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generated by the catabolism of D-glucose. An accelerated generation of ATP and an increase in its cytosolic concentration are currently considered as a key mechanism coupling the metabolism of nutrients to more distal events in the insulin secretory sequence, especially the closing of ATP-responsive K^+ channels and subsequent gating of voltage-sensitive Ca^{2+} channels. The preferential stimulation by glucose of oxidative glycolysis coincides with and is attributable to activation by Ca^{2+} of mitochondrial flavine adenine dinucleotide-linked glycerophosphate dehydrogenase (m-GDH), which plays a key role in controlling circulation in the glycerol phosphate shuttle for the transfer of reducing equivalents from the cytosol into mitochondria. The specific activity of m-GDH, expressed relative to protein content, is higher in pancreatic islets than in other organs so far examined for such a purpose. In the islets, the enzyme is virtually confined to insulin-producing cells, as distinct from non-B islet cells [7].

The pilot observation of a deficiency in pancreatic islet m-GDH activity was made in adult rats which had been injected with streptozotocin (STZ) during the neonatal period [8-14]. A deficient activity of m-GDH was also observed in pancreatic islet extracts of rats with hereditary non-insulin-dependent diabetes mellitus, i.e. Goto-Kakizaki (GK) rats [15]. An impaired activity in rat pancreatic islet mitochondrial glycerophosphate dehydrogenase was also observed in protein malnutrition [16]. A decreased activity of m-GDH in pancreatic islets was not observed, however, in certain other animal models of diabetes mellitus, e.g. in diabetic Golden spiny mice (*Acomys runates*), in a rat model of B-cell glucotoxicity provoked by the infusion for 48 hours of a hypertonic solution of D-glucose, in obese (*ob/ob*) mice and in diabetes prone BB rats [17-19].

In considering the extension of these investigations to human subjects, it was judged virtually not possible to have access to fresh samples of pancreatic tissue obtained from a large number of diabetic subjects. Nevertheless, between 1993 and 1998, a dozen of studies aimed at gaining information on the possible perturbation of m-GDH activity in human subjects [20-30]. For instance, these investigations dealt with such items as m-GDH activity in lymphocytes of insulin-dependent diabetic subjects, non-insulin-dependent diabetic subjects and relatives, patients with mitochondrial mutation of the tRNA^{Leu(UUR)} gene or women with gestational diabetes, mutation of the calcium-binding domain of the mitochondrial m-GDH gene in a family of diabetic subjects, autoantibodies against mitochondrial m-GDH in patients with either type 1 or type 2 diabetes and the dexamethasone-induced changes of m-GDH mRNA content and activity, as well as insulin release, in human pancreatic islets [21-24, 27-30].

In non-insulin-dependent diabetic subjects (NIDDM), the possible role of a decrease in m-GDH activity in pancreatic islets as a determinant of the impaired secretory response of insulin-producing cells to D-glucose has, up to now, apparently received relatively little attention. One of the major aims of a review published in 2018 was precisely to encourage further investigations on the activity of m-GDH in pancreatic islets of NIDDM subjects [2].

A New Proposal

In the light of the available experimental findings so far summarized in the present review, the following novel hypothetical concept is proposed.

It is postulated that an inherited or acquired deficiency of FAD-linked glycerophosphate dehydrogenase in the mitochondria of pancreatic islet insulin-producing cells may, by impairing the insulin secretory response of B-cells to D-glucose, and possibly other nutrients, eventually result in the development of the metabolic syndrome. Such a proposal thus provides a model in which a primary defect of circulating nutrients recognition as insulinotropic stimuli may lead to the occurrence of the metabolic syndrome. As recently underlined, the further validation of this proposal now requires suitable investigations on the incidence of the incriminated enzymatic defect in human subjects [2].

Author Contributions

W.J.M. and Z.M. contributed to conception, manuscript preparation, and critical revision of the manuscript. They agree with the content of the manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest.

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