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Minkowski Award, 1972, Madrid

Willy J. Malaisse was born in 1936 in Antwerp, Belgium. He obtained an M. D. in 1960 and Ph. D. in 1969 from Brussels Free University, where he has been for more than 20 years Director of the Laboratory of Experimental Medicine and Professor of Chemical Pathology. He was awarded the Berson Lecture of the International Society of Endocrinology in 1984 and the Morgagni Medal under the auspices of the University of Padua in 1989. He is a corresponding member of the Belgian Royal Academy of Medicine. In his extensive work on pancreatic islet function, six major steps may be identified. They concern (i) the multifactorial regulation of insulin release by nutrients, hormones and neurotransmitters, (ii) the sequence of cytophysiological events involved in stimulus-secretion coupling, (iii) the definition and validation of the fuel concept for nutrient-stimulated insulin release, (iv) the regulation of nutrient metabolism in islet cells, (v) the pathology of insulin release with emphasis on the deficiency of mitochondrial FAD-glycerophosphate dehydrogenase and (vi) the possible use of the esters of selected dicarboxylic acids as new therapeutic tools in non-insulin-dependent diabetes. Dr. Malaisse has been invited to contribute more than 150 review articles. He was listed among the 20 most prolific researchers between 1981 and 1990. He has attracted to his laboratory about 60 young investigators, more than half of whom were foreign fellows from the five continents.

The beta cell in NIDDM: giving light to the blind

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Summary Impairment of glucose-induced insulin secretion in non-insulin-dependent diabetes mellitus (NIDDM) may be caused by GLUT 2 underexpression in the pancreatic beta cell, a mutation of the glucokinase gene, glucose 6-phosphatase overactivity, FAD-linked glycerophosphate dehydrogenase deficiency, a mitochondrial DNA defect and/or a secondary phenomenon of so-called glucotoxicity possibly involving glycogen accumulation in the beta-cell. It is proposed that the methyl esters of succinic acid and related molecules may represent new tools with which to bypass these defects in glucose transport, phosphorylation and further catabolism and, hence, to stimulate both proinsulin biosynthesis and insulin release in NIDDM. [Diabetologia (1994) 37 [Suppl 2]: S36–S42]

Key words Beta cell, insulin secretion, glucose metabolism, succinic acid esters.

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Abbreviations: GLUT, Glucose transporter; FAD, flavin adenine dinucleotide; m-GDH, mitochondrial glycerophosphate dehydrogenase; NIDDM, non-insulin-dependent diabetes mellitus; IDDM, insulin-dependent-diabetes mellitus; BB, bio-breeding; NOD, non-obese diabetic; GOT, glutamate-oxalacetate transaminase; GPT, glutamate-pyruvate transaminase.

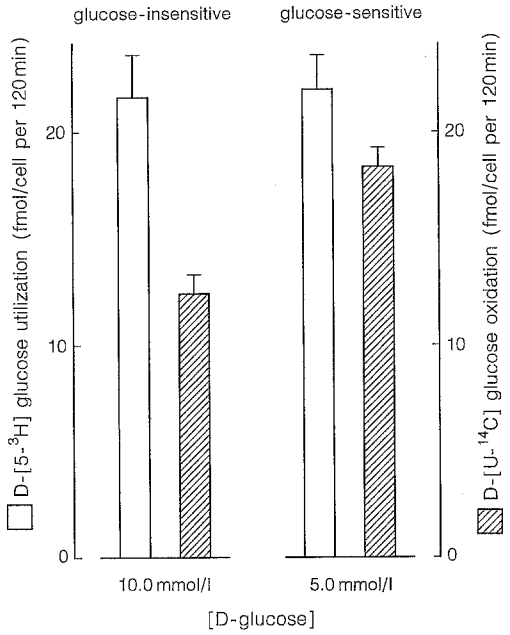

Fig. 1. D-glucose metabolism in subpopulations of glucose-insensitive purified beta cells incubated in the presence of 10 mmol/l D-glucose and glucose-sensitive beta cells incubated in the presence of only 5 mmol/l D-glucose. Despite virtually identical rates of D-[5-^{3}H]glucose conversion to ^{3}HOH in the two subpopulations, the oxidation of D-[U-^{14}C]glucose is much higher ($p < 0.001$) in the glucose-sensitive than glucose-insensitive cells

Non-insulin-dependent diabetes mellitus is currently looked upon as a syndrome of variable aetiology rather than a well-defined nosological entity. Moreover, even in individual cases, its determinism often appears multifactorial, including inherited and acquired factors of pancreatic beta-cell dysfunction and/or extrapancreatic insulin resistance. The present review is restricted to selected aspects of beta-cell impaired secretory behaviour in NIDDM. Emphasis is placed both on possible causes of beta-cell insensitivity to D-glucose and on a novel approach to bypass the latter defect.

Preferential alteration of glucose-stimulated insulin release in NIDDM

It is currently believed, albeit not universally accepted [1], that, in NIDDM patients, the secretory response of the pancreatic beta-cell to D-glucose is more severely affected than that evoked by other secretagogues. If so, a perturbation of the beta-cell glucose-sensing device could represent an essential factor in the pathogenesis of the disease.

The stimulation of insulin secretion by D-glucose is thought to be causally linked to the catabolism of the hexose in the beta cell. An increased rate of ATP generation apparently participates in the coupling of metabolic to more distal ionic events in the process of glucose-stimulated insulin release.

The regulation of D-glucose metabolism in the islet beta cell displays several unusual features which optimalize its glucose-sensing function [2, 3]. They include a rapid equilibration of D-glucose concentration across the plasma membrane, resulting from the efficient transport of the hexose by the GLUT 2 carriers, the participation of the low affinity glucokinase enzyme to the phosphorylation of D-glucose, and a preferential stimulation of oxidative mitochondrial events relative to total glycolysis in islets exposed to high concentrations of D-glucose [4].

The latter attribute represents, in my opinion, an essential feature of the beta-cell glucose-sensing device. It indeed accounts for a considerable increase in ATP generation rate at increasing concentrations of D-glucose. It represents an intrinsic property of purified beta, as distinct from non-beta, islet cells [5, 6]. It may even participate in the well-known heterogeneity in the metabolic and functional response of individual beta cells to D-glucose. Thus, as documented in Figure 1, the ratio between D-glucose oxidation and utilization is higher in glucose-sensitive, rather than glucose-insensitive, purified beta cells [7, 8].

The efforts made to elucidate the regulation of D-glucose metabolism in normal beta-cells have paved the way to identify possible site-specific defects of such a metabolism in NIDDM.

Altered D-glucose metabolism in the beta cell: the G quintet

In a recent review [9], five candidates for altered D-glucose metabolism in the beta cell of NIDDM patients were taken into consideration. They include GLUT 2 underexpression, glucokinase gene mutation, glucose 6-phosphatase hyperactivity, glycerophosphate dehydrogenase (FAD-linked) deficiency

Table 1. Alteration of islet m-GDH activity and GOT/GPT ratio in animal models of diabetes

Type of diabetes and species	Enzymatic activity	
	m-GDH	GOT/GPT ratio
pre-IDDM		
BB rats	high	N.D.
NOD mice	normal	high
pre-NIDDM		
Protein malnutrition (rats)	low	low
NIDDM		
STZ rats	low	low
GK rats	low	low
fa/fa rats	low	low
db/db mice	low	N.D.
ob/ob mice	normal	high
Golden spiny mice	high	normal

N.D., Not determined

and glycogen accumulation. These candidates were presented as a G quintet. It should be realized, however, that further candidates may well be identified in the near future. For instance, a defect of mitochondrial DNA was recently reported to represent an uncommon cause of NIDDM [10–12].

Underexpression of GLUT 2 was documented in several animal models of NIDDM [13–16]. It coincides with an altered time course for the net uptake of 3-O-methyl-D-glucose by islet cells. In addition to a decreased initial rate for the uptake of the D-glucose analogue, however, the later close-to-equilibrium value is also severely decreased in islets of diabetic animals [17]. This suggests that the major defect consists in a reduction of the intracellular space readily accessible to the hexose. This defect may reflect both a decreased contribution of beta-cells relative to total islet mass [17] and a lowered percentage of GLUT 2-positive true beta-cells [16]. Thus, the available data can only be considered as a cause of beta-cell dysfunction in the framework of severe cell-to-cell heterogeneity, virtually of the all or nothing type [18].

A defect in the phosphorylation of D-glucose by glucokinase was already considered as a possible cause of impaired insulin release 25 years ago when the parallel inhibition by D-mannoheptulose of both D-glucose phosphorylation in islet homogenates and glucose-stimulated insulin secretion in intact islets was first documented [19]. Several converging reports [20–23] now suggest that a mutation of the glucokinase gene represents an uncommon finding in the vast majority of NIDDM patients. It remains conceivable, however, that an impaired phosphorylation of D-glucose in the beta cell of these patients is attributable to an altered contribution of the glucokinase regulatory protein, the presence of which was indeed recently documented in pancreatic islets [24].

An increased activity of glucose 6-phosphatase in the beta cell, leading to operation of an ATP-wasting futile cycle between D-glucose and D-glucose 6-phosphate could theoretically also account for a preferential alteration of glucose-stimulated insulin release [25]. I recommend, as an easy screening procedure to document this potential anomaly, searching for an abnormally high ratio between D-[2-^{3}H]glucose and D-[5-^{3}H]glucose conversion to ^{3}HOH in intact islets.

FAD-glycerophosphate dehydrogenase deficiency

As first proposed a few years ago [26], a further candidate for altered beta-cell glucose metabolism in NIDDM consists in an impaired activity of the mitochondrial FAD-linked enzyme glycerophosphate dehydrogenase (m-GDH). This enzyme plays a key role in the glucose-sensing device of the beta cell. In the process of glucose-stimulated insulin release, its activation by cytosolic Ca^{2+} accounts for a preferential stimulation of the oxidative modality of glycolysis, as coupled with both the reoxidation of cytosolic NADH by the glycerol phosphate shuttle and the mitochondrial oxidation of glucose-derived pyruvate [27, 28]. These coupled processes optimalize the yield of ATP generated through the catabolism of D-glucose [4].

A deficiency of m-GDH in islets was first documented in adult rats which had been injected with streptozotocin during the neonatal period [29]. It was then observed in several other animal models of NIDDM (Table 1), including models in which the disease is hereditary such as in GK rats [30], db/db mice [31] or fa/fa rats [32]. It was also found in rats which underwent protein malnutrition early in life [33]. It was not observed, however, in either ob/ob mice [34] or diabetic Golden spiny mice [35]. It was also absent in animal models of IDDM, such as BB rats [36] or NOD mice [37] examined prior to the onset of frank hyperglycaemia. Whenever present, the decrease in m-GDH activity was often associated with a low ratio between the activity of glutamate-oxalacetate transaminase (GOT) and glutamate-pyruvate transaminase (GPT) in the islet homogenates (Table 1). As reviewed elsewhere [38, 39], these findings suggest that a beta-cell deficiency in m-GDH may represent a far-from-uncommon, albeit not universal, contributive factor in the pathogenesis of NIDDM.

Preliminary data collected in either lymphocytes [40, 41] or freshly-isolated pancreatic islets [42, 43] suggest that a deficiency of m-GDH may also be encountered in NIDDM, but not IDDM patients.

Primary and secondary beta-cell lesions

The four defects so far considered in this report could represent primary causes of beta-cell dysfunction in NIDDM. In addition, chronic hyperglycaemia may lead to a secondary alteration of the beta-cell secretory potential in a phenomenon of so-called desensitization or glucotoxicity.

We have previously proposed that two specific features of this phenomenon of glucotoxicity consist in a paradoxical and transient inhibition of insulin release and the perturbation of its anomeric specificity in response to the intravenous administration of D-glucose to NIDDM patients [44–46]. These two features are also encountered in several animal models of NIDDM [47, 48].

Several mechanisms may participate in the phenomenon of beta-cell glucotoxicity. They include the accumulation of sorbitol in the beta cell, the non-enzymatic glycation of beta-cell proteins, even those located in the cytosolic domain and, most naively, the sustained state of secretory hyperactivity, resulting in apparent beta-cell exhaustion [49]. Over recent years, attention was also paid to the possible role of

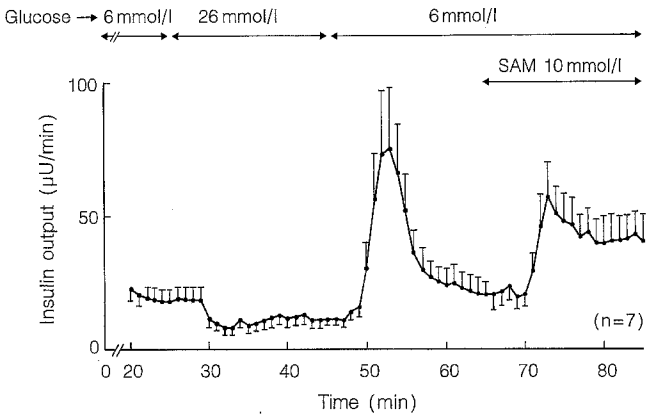

Fig. 2. Insulin release by the perfused pancreas from rats injected 13 days before with streptozotocin (40 mg/kg body weight). This figure documents the paradoxical decrease in insulin output observed in response to a rise in D-glucose concentration from 6 to 26 mmol/l, the paradoxical stimulation of insulin secretion later recorded when the hexose concentration was lowered back to its initial value, and the positive secretory response evoked by succinic acid monomethyl ester (10 mmol/l) at the low concentration of D-glucose

glycogen accumulation in the beta cell as a factor of glucotoxicity.

Glycogen accumulation and beta-cell glucotoxicity

The latter hypothesis is based on the knowledge that beta cells are normally devoid of glycogen which, however, accumulates in the islet cells whenever the latter are exposed to abnormally high concentrations of D-glucose [47, 50]. The extent of glycogen accumulation is related to the severity and duration of hyperglycaemia, and this situation can be mimicked in vitro [51, 52].

The two phenomenological secretory features of beta-cell glucotoxicity, namely the paradoxical inhibition of insulin output and the anomeric malaise, can both be accounted for by interference of glycogenolysis with the glycolytic response of the beta cell to a rise in D-glucose concentration [49]. Thus, inhibition by D-glucose of glycogenolysis [52], a phenomenon characterized by anomeric α-stereospecificity [53], may either transiently overcome the acceleration of glycolysis otherwise expected from the rise in extracellular hexose concentration [54] or mask the normal preference of glucose-induced insulin release for α-D-glucose [48].

In fair agreement with such a proposal, it was recently reported that, at variance with D-glucose, 2-ketoisocaproate fails to provoke a paradoxical secretory response in the pancreas removed from glucose-infused rats [55]. Likewise, in the pancreas from streptozotocin-injected rats, the monomethyl ester of succinic acid evokes a positive secretory response, despite the paradoxical inhibition of insulin release caused by a rise in D-glucose concentration (Fig. 2). These converging findings indicate that the phenomenon of beta-cell glucotoxicity is indeed attributable to a paradoxical glycolytic response to D-glucose, rather than altered coupling between ATP availability and subsequent events in the secretory sequence.

Beta-cell blindness to D-glucose

The findings so far reviewed indicate that, in NIDDM, a preferential impairment of the insulin secretory response to D-glucose might be due to a number of primary or secondary alterations in the metabolism of the hexose in the beta cell. Whatever their precise nature and cause, such metabolic defects would indeed result in an altered identification of D-glucose as a stimulus for both proinsulin biosynthesis and insulin release.

In other words, the beta cell in NIDDM may be considered as suffering from a kind of blindness to D-glucose. If so, the question comes to mind as to how to provide light to this blind cell.

Non-glucidic nutrient secretagogues as possible tools in the treatment of NIDDM

Whatever its precise determinism – e.g. an anomaly in D-glucose transport, phosphorylation or further metabolism – and whether it is attributable to a primary or secondary lesion of the beta-cell, the preferential impairment of glucose-induced insulin release in NIDDM raises the idea that, in this disease, non-glucidic secretagogues may be helpful to increase insulin output.

Candidates for such a purpose include, in addition to hypoglycaemic sulphonylureas, calcium agonists [56], potential precursors of adenine nucleotides such as AICA riboside [57] and peptides causing adenylate cyclase activation in the beta cell [50]. Non-glucidic nutrients should also be considered since they are likely to mimic the effect of D-glucose not only upon insulin release but also upon other beta-cell functional variables, such as proinsulin biosynthesis.

In this perspective, we have recently initiated a study on the possible use of succinic acid esters as new tools in the treatment of NIDDM. The insulinotropic action of the monomethyl and dimethyl esters of succinic acid was first revealed by MacDonald and Fahien [58]. At variance with unesterified succinic acid, these esters penetrate efficiently into the beta cell in which they undergo de-esterification so that succinic acid becomes readily available to support mitochondrial respiration [59].

The information gathered so far indicates that the succinate esters indeed display several advantages as potential tools in the treatment of NIDDM (Table 2).

Table 2. Potential advantages of succinic acid methyl esters as insulinotropic agents in NIDDM

Succinic acid methyl esters
1. Bypass metabolic defects in glucose transport and phosphorylation or oxidative glycolysis
2. Stimulate both proinsulin biosynthesis and insulin release
3. Augment insulin output at high glucose concentrations
4. Are still efficient when the beta cell displays a paradoxical negative secretory response to glucose
5. Enhance the insulinotropic action of hypoglycaemic sulphonylureas
6. May improve the beta-cell secretory potential in long-term treatment
7. Protect the beta cell against cytotoxic aggressions
8. Display no glucagonotropic action

First, the succinate esters owe their insulinotropic action to a concerted increase in the supply of succinic acid and acetyl CoA to the Krebs cycle [59]. They are well suited, therefore, to bypass site-specific defects in D-glucose transport, phosphorylation and further catabolism.

Second, acting as nutrient secretagogues, the succinic acid esters stimulate both proinsulin biosynthesis and insulin release [60]. In experiments conducted in vivo in normoglycaemic rats, they were even found to display a higher insulinotropic efficiency, on a molar basis, than D-glucose [61].

Third, they cause a sizeable increase in insulin output at very high concentrations of D-glucose, whether in the absence or concomitant presence of a hypoglycaemic sulphonylurea [62, 63]. Such is also the case when the pancreas is removed from rats first infused for 48 h with a hypertonic solution of D-glucose [63].

Fourth, in the latter model of beta-cell glucotoxicity or in animals first injected with a submaximal amount of streptozotocin, the esters of succinic acid remain able to efficiently stimulate insulin release, even when the beta cell displays a paradoxical secretory response to rapid changes in D-glucose concentrations (Fig. 2).

Fifth, the succinate esters were found to enhance the insulinotropic action of hypoglycaemic sulphonylureas both in vitro [64] and in vivo [65]. In the latter situation, they also enhance the hypoglycaemic action of glibenclamide.

Sixth, preliminary results suggest that the succinate esters may improve the secretory potential of the endocrine pancreas when administered for several days to rats first injected with submaximal amounts of streptozotocin [62].

Seventh, the succinate esters appear to protect the beta cell against cytotoxic aggression such as those caused by either streptozotocin [66] or interleukin-1 [67].

Last, the succinate esters fail to display any glucagonotropic action, whether in vitro [63] or in vivo [65].

Moreover, recent experiments conducted in our laboratory have revealed that insulin release is also stimulated by the dimethyl ester of glutamic acid (unpublished observation). This represents a second example of a dicarboxylic acid known not to penetrate efficiently into the beta cell in its ionized form [68], but converted by esterification to a fully potent insulin secretagogue. The latter finding duly illustrates, therefore, that the use of the esters of selected dicarboxylic acids as insulinotropic agents remains a field largely open to further developments.

Concluding remarks

The present review emphasizes the concept that, in NIDDM, a preferential impairment of the beta-cell secretory response to D-glucose, as distinct from other secretagogues, may be accounted for by site-specific defects in either the transport of the hexose across the beta-cell plasma membrane, its phosphorylation and further dephosphorylation or its catabolism by oxidative glycolysis. Likewise, the secondary phenomenon of beta-cell glucotoxicity in NIDDM may also involve an altered glycolytic response to a rise in D-glucose concentration, due to the interference of changes in glycogenolytic flux.

In the light of such concepts, it is proposed that nutrient secretagogues able to bypass these anomalies in the glycolytic pathway, such as the esters of succinic or glutamic acids, may represent novel tools with which to stimulate proinsulin biosynthesis and insulin release, to enhance the insulinotropic action of hypoglycaemic sulphonylureas and, possibly, to exert a long-term favourable influence upon the secretory potential of the endocrine pancreas in NIDDM. The esters of dicarboxylic acid may even protect the beta cell against cytotoxic aggressions conceivably involved in the pathogenesis of both IDDM and NIDDM.

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