科技资料

Diabetes, Obesity and Hyperlipidemias-IV

DIABETES, OBESITY AND HYPERLIPIDEMIAS - IV

Proceedings of the 5th European Symposium on Metabolism, Padova, 15–17 May 1989

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PREFACE

This volume contains the papers presented at the 5th European Symposium on Metabolism (Padova, 15–17 May 1989) by the invited speakers, and some selected oral presentations. These Symposia, held in Padova every four years, are a must for all scientists interested in lipoprotein, adipose tissue metabolism, and diabetes.

The current Symposium focused on genetics and the role of apoprotein on lipid metabolism, the disorders of lipoprotein metabolism in diabetes mellitus, and the enzymes involved in lipid metabolism. With respect to obesity, the papers deal with the development and differentiation of adipose tissue, the new trends in pathogenesis, and in the importance of different fat distribution. Furthermore, fuel substrate utilization and interaction in diabetes mellitus and the pathogenesis and treatment of diabetic nephropathy are discussed.

For the second time, the Morgagni Prize, endowed by Fidia Research Laboratories under the auspices of the Faculty of Medicine of the University of Padova, was awarded during the Symposium. Dr. Willy J. Malaisse, whose lecture opens this book, was the recipient of what is today one of the most important prizes offered to scientists working in the field of metabolism.

This volume contains some really up-to-date work on different, but at the same time related, aspects of metabolism, and we hope it will prove to be a valuable addition to International literature.

GAETANO CREPALDI
Chairman of
the 5th European
Symposium on Metabolism

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PHYSIOLOGY AND PATHOLOGY OF THE PANCREATIC B-CELL GLUCOSE-SENSOR DEVICE[1]

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INTRODUCTION

Insulin secretion plays an essential role in the control of fuel homeostasis. The major theme of this contribution represents a complementary proposal, namely that fuel metabolism in the pancreatic B-cell plays an essential role in the control of insulin secretion. The capacity of D-glucose and other nutrient secretagogues to stimulate insulin release may indeed reflect their capacity to act as a fuel and, hence, to accelerate ATP generation rate in islet B-cells. This fuel concept was first formulated ten years ago (1, 2), after almost two decades of debate between the defenders of the glucoreceptor theory and those of the metabolic theory for insulin release. The essential findings in support of this fuel concept consist in the observation that the higher insulinotropic capacity of α- than ß-D-glucose (or D-mannose) coincides with a more efficient utilization of the α- than ß-anomers in pancreatic islets (3, 4) and the elucidation of the mode of action of non-metabolized or poorly metabolized nutrient secretagogues, especially the activation of glutamate dehydrogenase by the non-metabolized analogue of L-leucine, 2-amino[2,2,1]heptane-2-carboxylic acid (5, 6), and the role of 3-phenylpyruvate as a transamination partner in islet cells (7, 8).

When this fuel concept had been documented, it was considered that a further task, in order to progress in our understanding of the cytophysiology of insulin release, should aim at characterizing both the regulation of nutrient catabolism in normal B-cells and its perturbation in experimental models of B-cell dysfunction.The present account, which complements prior reports on the same theme (9, 10),

[1]The Morgagni Prize Lecture delivered on May 16, 1989, at the 5th European Symposium on Metabolism in Padova.

aims at reviewing recent acquisitions dealing with the physiology and pathology of the pancreatic B-cell glucose-sensor device (Table I).

TABLE I

THE PANCREATIC B-CELL GLUCOSENSOR DEVICE

1. D-glucose transport
2. D-glucose phosphorylation
   - Hexokinase isoenzymes
   - Synarchistic regulation
   - Hexokinase binding
   - Glucokinase regulation
3. Hexose phosphates channelling
   - Anomeric specificity
   - Diastereomeric specificity
4. Phosphofructokinase activation
5. Mitochondrial oxidative events
   - Glycerol phosphate shuttle
   - Pyruvate decarboxylation
   - Acetyl coenzyme A oxidation
6. Anomeric specificity

GLUCOSE TRANSPORT

The transport of D-glucose and other hexoses into the B-cell (but not into purified non-B islet cells) is sufficiently efficient to ensure a rapid equilibration of D-glucose concentrations across the plasma membrane (11, 12). This represents a first essential attribute of the B-cell glucose-sensor device. A site-specific defect in hexose transport was first identified in islet cells of the RINm5F line (13). In these tumoral cells, as distinct from normal B-cells, no rapid equilibrium of the extracellular and intracellular concentrations of D-glucose takes place especially at low temperatures or high hexose concentrations (14-16). Whether a comparable defect may be found in the B-cell of animals prone to become diabetic or affected by this disease remains a matter of debate (17).

GLUCOSE PHOSPHORYLATION

Although the B-cell is equipped with both a low-Km hexokinase and high-Km glucokinase, the phosphorylation of D-glucose under physiological conditions occurs mainly at the intervention of the latter enzyme, hexokinase being largely inhibited in intact cells by glucose 6-phosphate and, to a lesser extent, by glucose 1,6-bisphosphate (18).

The rate of D-glucose phosphorylation is not solely dependent, however, on the concentration of the hexose inside the B-cell.

First, it depends on the hexokinase isoenzyme pattern, which may be altered by environmental factors (e.g. in fasting) or in pathological situations (19, 20).

Second, ATP participates in a synarchistic and sequential-type regulation of glucose phosphorylation in islet cells (21).

Third, in islets, a major fraction of hexokinase isoenzymes is bound to mitochondria (22, 23). The binding of hexokinase is inhibited by D-glucose 6-phosphate and enhanced by spermidine. This ambiquity of hexokinase may play a propitious role in the glucose-sensing function of the B-cell, and this for several reasons. Bound hexokinase is indeed more resistant than the cytosolic enzyme to inhibition by D-glucose 6-phosphate (22). The mitochondrial binding of hexokinase also provides a direct pathway for the coupling of hexose phosphorylation to mitochondrial respiration (24). Most importantly, mitochondria-bound hexokinase uses mitochondrial rather than cytosolic ATP as a substrate for D-glucose phosphorylation. This was documented in isolated islet mitochondria incubated in the presence of D-[U-^{14}C]glucose and [γ-^{32}P]ATP (Fig. 1). In the absence of any other agent, only 40 % of the rate of D-glucose phosphorylation is accounted for by the contribution of exogenous ATP, the major fraction of the phosphorylation process being supported by endogenous ATP. The fractional contribution of exogenous ATP is further decreased in the presence of ADP and succinate and, inversely, increased to close-to-unity in the presence of metabolic poisons including inhibitors of either adenine nucleotide translocation or adenylate kinase activity. This novel experimental approach unambiguously documents that

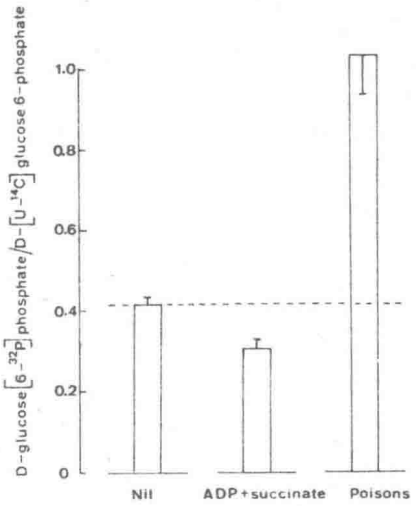

Fig. 1. Phosphorylation of D-[U-^{14}C]glucose (1.0 mM) by islet mitochondria exposed to [γ-^{32}P]ATP (0.4 mM) in the absence (Nil) or presence of either ADP (0.2-2.0 mM) and succinate 10.0 mm) or KCN (1.0 mM), rotenone (10 μM), carboxyactractyloside (12 μM) and P^1,P^5-di-(adenosine-5')-pentaphosphate (10 μM). The results refer to the fractional contribution of exogenous ATP to the total rate of hexose phosphorylation

mitochondria-bound hexokinase uses preferentially mitochondrially formed ATP as a substrate for D-glucose phosphorylation (25). This may help to maintain a high concentration of cytosolic ATP. At this point, it seems appropriate to recall that cytosolic ATP is currently considered as the key factor coupling the metabolism of nutrients to more distal cationic events in the secretory sequence (26).

Last, the activity of glucokinase may be modulated by a cytosolic regulatory protein mediating the antagonistic and competitive effects of D-fructose 1-phosphate and D-fructose 6-phosphate, as recently reported in hepatocytes (27, 28). The same mechanism may be operative in islet cells, provided that the latter are equipped with fructokinase in order to catalyze the formation of D-fructose 1-phosphate (Fig. 2). In prior reports, it was proposed that the phosphorylation of D-fructose in islet cells is catalyzed mainly by hexokinase

rather than fructokinase (29, 30). However, recent experiments indicate that fructokinase is nevertheless present in islet cells (31). In these experiments, islet homogenates were heated for 5 min at 70°C in order to abolish their capacity to catalyze the phosphorylation of D-glucose. A residual rate of D-fructose phosphorylation was still

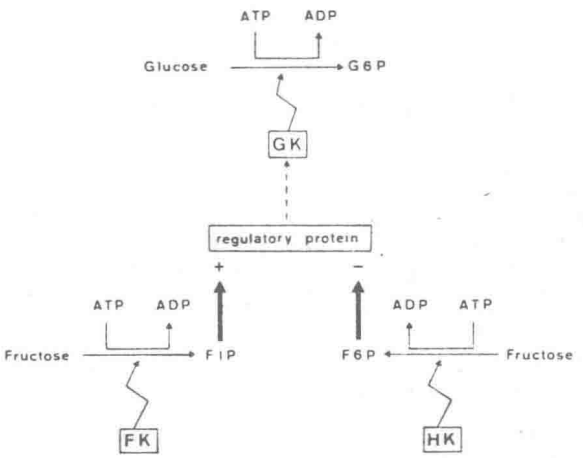

Fig. 2. Schematic view for the role of a regulatory protein mediating the antagonistic effects of D-fructose 1-phosphate (F1P) and D-fructose 6-phosphate (F6P), generated respectively in the fructokinase (FK) and hexokinase (HK) reaction, upon glucokinase (GK) activity.

observed, however, in the heated homogenates (Fig. 3, left panel). Moreover, the phosphorylation of D-fructose by the heated homogenate was strictly resistant to the presence of either D-glucose or D-glucose 6-phosphate and was abolished in the absence of K^+, all features characteristic of the participation of fructokinase (Fig. 3, right panel). Further work made it possible to document the presence in pancreatic islet of a regulatory protein indeed conferring to glucokinase the property of being antagonistically affected by D-fructose 1-phosphate and D-fructose 6-phosphate (32).

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