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Review

D-fructose metabolism and insulinotropic action in pancreatic islets: metabolic aspects

W. J. Malaisse*

Department of Biochemistry, Université Libre de Bruxelles, 808 Route de Lennik, B-1070 Brussels, Belgium

ABSTRACT

Despite extensive investigations, the determinants of the insulinotropic action of D-fructose still remain elusive. The major aim of the present article concerns several aspects of D-fructose metabolism in pancreatic islets. Emphasis is first placed on the possible participation of distinct enzymes, low-Km hexokinase, high-Km glucokinase and fructokinase in the phosphorylation of D-fructose by pancreatic islet homogenates. The uptake of D-fructose by intact islets and the generation of sorbitol by islets exposed to D-fructose are then briefly discussed. A detailed review of the metabolic fate of D-fructose in the islets is then presented based on the measurements of such variables as the conversion of D-[3-^{3}H] fructose and D-[5-^{3}H]fructose to either ^{3}HOH or tritiated acidic metabolites and the paired ratio between the oxidation of ^{14}C-labelled D-fructose and generation of ^{3}HOH from tritiated D-fructose. Other variables under consideration include the oxidation of D-[1-^{14}C]fructose, D-[2-^{14}C]fructose, D-[3,4-^{14}C]fructose, D-[6-^{14}C]fructose and D-[U-^{14}C] fructose and their conversion to either ^{14}C-labelled acidic metabolites or amino acids. Complementary information is also provided on the concentration-related effects of D-glucose on these variables and the effects of D-fructose on D-glucose metabolism. Attention is also paid on the interference of D-glyceraldehyde, on one hand, and D-mannoheptulose on the other hand, upon the metabolism of D-glucose and/or D-fructose. Finally, attention is drawn to the effects of D-fructose on O_2 uptake and either the total or cytosolic content of ATP and ADP in pancreatic islets.

KEYWORDS: D-fructose and D-glucose phosphorylation and metabolism, pancreatic islets, O_2 uptake, total and cytosolic ATP and ADP content

INTRODUCTION

Under suitable experimental conditions, D-fructose stimulates insulin release from pancreatic islets. Despite extensive investigations, the determinants of such insulinotropic action still remain elusive. The present series of three articles aims at reviewing available information on the metabolic, functional and pathological aspects of D-fructose fate and action in pancreatic islet cells. The major aim of the first contribution in this series concerns the phosphorylation, uptake and catabolism of D-fructose and its effects upon O_2 uptake and both the total and cytosolic content of ATP and ADP in pancreatic islets.

D-fructose phosphorylation

Fructokinase

Rat pancreatic islets display fructokinase activity [1, 2]. It was first observed that homogenates of rat pancreatic islets that had been heated for 5 min at 70 °C to inactivate hexokinases catalyze the ATP-dependent phosphorylation of D-fructose.

*malaisse@ulb.ac.be

This reaction was dependent on the presence of K^+ and was inhibited by D-tagatose, but not by D-glucose 6-phosphate. The phosphorylation product was identified as fructose 1-phosphate through its conversion to a bisphosphate ester product by *Clostridium difficile* fructose 1-phosphate kinase. These findings allowed the conclusion that fructokinase (ketohexokinase) was responsible for this process. Similar results were observed with tumoral insulin-producing cells (RINm5F line) [1]; D-mannoheptulose does not inhibit the phosphorylation of D-fructose in rat pancreatic islet homogenates first heated for 5 min at 70 °C [2]. Whether in non-heated or heated homogenates, the paired ratio between the phosphorylation of D-glucose (1.0 mM) and that of D-fructose (also 1.0 mM) does not differ significantly in purified B-cells and non-B islet cell homogenates [2].

Low-Km hexokinase

In non-heated islet homogenates, the phosphorylation of D-fructose (1.0 mM) averaged to 89 ± 6% of the paired value found with D-glucose (1.0 mM). At variance with the situation found in heated islet homogenates, the phosphorylation of D-fructose by non-heated islet homogenates was decreased to 8 ± 2% of its control value by D-mannoheptulose (20.0 mM) and was not significantly affected in the absence of K^+ [2, 3]. In the non-heated islet homogenates, the data obtained at increasing concentrations of D-fructose (0.25-10.0 mM) were compatible with the participation of a single enzyme, presumably the low-Km hexokinase, with a Km for D-fructose close to 6.0 mM, as distinct from 0.04-0.05 mM in the case of D-glucose or D-mannose [3]. At a low concentration (0.25 mM), the phosphorylation of D-fructose by non-heated islet homogenates was much lower than that of D-glucose or D-mannose. An inverse situation prevailed at a 10.0 mM concentration, despite the participation of glucokinase at this high concentration of hexoses [3]. The phosphorylation of D-fructose by non-heated homogenates was inhibited by D-glucose, D-mannose and D-glucose 6-phosphate [3], whilst D-fructose failed to affect significantly the phosphorylation of D-glucose [3].

High-Km glucokinase

Native human B-cell glucokinase displays a low affinity for D-fructose (apparent Km: 158 mM) as distinct from either D-glucose (3.8 mM) or D-mannose (4.6 mM). However, the maximal velocity for the phosphorylation of D-fructose (99 $\mu mol.min^{-1}.mg^{-1}$) largely exceeds that found, within the same experiments, for D-glucose or D-mannose (about 37 $\mu mol.min^{-1}.mg^{-1}$) [4]. At variance with the situation found with either D-glucose or D-mannose, no evidence of positive cooperativity was observed when the phosphorylation of D-[U-^{14}C]fructose by human B-cell glucokinase was measured over a wide range of concentrations ranging from 2.5 to 320.0 mM [5]. In the same study, D-fructose in the 0.5 to 20.0 mM range virtually failed to affect the phosphorylation of either D-[U-^{14}C]glucose or D-[U-^{14}C]mannose, each tested at an 0.5 mM concentration. The sole significant effect of D-fructose upon D-glucose phosphorylation consisted in a modest inhibition, which only occurred at high concentrations of the ketose (20.0 mM or more), and when the aldose was tested at a concentration (6.0 mM) above the range of values in which the phenomenon of positive cooperativity was otherwise observed [5]. Despite the much greater affinity of glucokinase for D-glucose than D-fructose, the aldose, when tested at concentrations up to 10.0 mM, failed to adversely affect D-fructose phosphorylation. On the contrary, D-glucose increased the phosphorylation of D-fructose, this effect being most marked at concentrations of the aldose in the 2.0-6.0 mM range. The concentration of D-glucose had to be raised in excess of 20.0 mM to cause sizeable inhibition of D-fructose phosphorylation. The stimulatory effect of D-glucose on D-fructose phosphorylation was observed at all concentrations of the ketose (0.1, 1.0, 5.0, 10.0, 20.0 or 50.0 mM). In relative terms, it was most marked at low concentrations of D-fructose. D-mannose and 2-deoxy-D-glucose, but not 3-O-methyl-D-glucose (6.0 mM), mimicked the effect of D-glucose (also 6.0 mM) to increase the phosphorylation of D-fructose, albeit to a lesser extent than that observed with D-glucose [5]. The enhancing action of D-glucose on the phosphorylation of D-fructose by human liver glucokinase displays an obvious anomeric preference for α-D-glucose, and such an anomeric specificity remains operative in intact pancreatic islets [6]. The phosphorylation of D-[U-^{14}C]glucose (10.0 mM)

by human liver glucokinase was decreased by about 90% in the presence of D-mannoheptulose (20.0 mM), whether in the absence or presence of D-fructose (also 10.0 mM). The heptose decreased the much lower phosphorylation rate of D-[U-^{14}C] fructose (10.0 mM) by about 60 and 90% in the absence and presence of D-glucose (also 10.0 mM), respectively. In these experiments, D-glucose (10.0 mM) increased about 9-fold the phosphorylation of D-[U-^{14}C]fructose (10.0 mM) in the absence of D-mannoheptulose, as distinct from a close-to only 3-fold increase in the presence of the heptose [7].

Incidentally, in the post-microsomal supernatant of pancreatic islets, D-fructose 1-phosphate increases the activity of glucokinase as measured in the presence of D-glucose 6-phosphate and D-fructose 6-phosphate. The islet cytosol inhibits purified liver glucokinase activity, an effect antagonized by D-fructose 1-phosphate. In the presence of hexose 6-phosphates, partially purified islet glucokinase is inhibited by the hepatic glucokinase regulatory protein in a D-fructose 1-phosphate sensitive manner. In intact islets, D-glyceraldehyde stimulates the generation of ^{14}C-labelled D-fructose 1-phopshate from D-[U-^{14}C]glucose and increases the production of ^{3}HOH from D-[5-^{3}H]glucose. These findings suggest that the activity of glucokinase in islet cells may be regulated by a protein mediating the antagonistic effect of D-fructose 6-phosphate and D-fructose 1-phosphate in a manner qualitatively similar to that operative in hepatocytes [8].

D-Fructose uptake

After only 5 min incubation, the apparent distribution spaces of either D-[U-^{14}C]glucose (20.0 mM) or D-[U-^{14}C]fructose (also 20.0 mM) in rat pancreatic islets do not differ significantly from one another and are both significantly higher than that of L-[1-^{14}C]glucose (2.0 mM) used as an extracellular marker. The distribution space of D-[U-^{14}C]fructose (20.0 mM) is virtually identical after either 5 or 20 min incubation, whilst that of D-[U-^{14}C]glucose (also 20.0 mM) increases significantly between the 5th and 20th min of incubation. This difference is probably attributable, at least in part, to the higher rate of D-glucose than D-fructose catabolism, resulting in a larger intracellular accumulation of radioactive metabolites generated from D-[U-^{14}C]glucose as distinct from D-[U-^{14}C]fructose [9].

Generation of sorbitol

After 90 min incubation of rat pancreatic islets in the presence of 16.7 mM D-fructose, no significant formation of sorbitol could be detected, in sharp contrast to the situation found after 90 min incubation in the presence of D-glucose (also (16.7 mM) [10].

D-Fructose catabolism

In a first study, the metabolic fate of D-fructose (33.3 mM) was examined in rat pancreatic islets incubated for 90 min in the presence of the ketohexose [11]. The measurement of D-[5-^{3}H] fructose conversion to either ^{3}HOH or tritiated acidic metabolites and that of either D-[1-^{14}C] fructose or D-[U-^{14}C]fructose to $^{14}CO_2$ and ^{14}C-labelled lactic acid allowed to present a tentative scheme for the catabolism of the ketohexose. The flux through the pentose phosphate pathway was much higher than the net rate of conversion of D-fructose 6-phosphate to D-fructose 1,6-bisphopshate. The stepwise generation of pyruvate from triose phosphates nevertheless accounted for about 75% of D-fructose phosphorylation. The conversion of pyruvate generated from exogenous D-fructose to lactate was about twice higher than the corresponding oxidation of pyruvate-derived acetyl CoA in the Krebs cycle. In the same study, the ketohexose (33.3 mM) failed to affect the oxidation of D-[U-^{14}C]glucose (3.3 mM), whilst the aldohexose (3.3 mM) decreased the D-[1-^{14}C]fructose/ D-[U-^{14}C]-fructose oxidation ratio from about 1.44 ± 0.06 to about 0.83 ± 0.06, the latter ratio being virtually identical to that found when comparing D-[1-^{14}C]glucose oxidation to D-[U-^{14}C] glucose oxidation [11]. The only two significant effects of D-fructose (33.3 mM) on the catabolism of D-glucose (3.3 mM) consisted in a slight decrease in ^{3}HOH generation from D-[5-^{3}H] glucose and a modest increase of the ^{14}C-labelled metabolites generated from D-[U-^{14}C]glucose through aerobic glycolysis [12].

Comparable results were recorded in a further study dealing with the effects of D-fructose

(5.0, 20.0 and 80.0 mM) on the utilization of D-[5-^{3}H]glucose and conversion of D-[U-^{14}C] glucose (6.0 or 8.3 mM) to $^{14}CO_2$ and ^{14}C-labelled acidic metabolites or amino acids. At a concentration of 80.0 mM, the oxidation of D-[U-^{14}C]fructose was close to that found for the oxidation of 6.0 mM D-[U-^{14}C]glucose [13]. In the same study, a dramatic dissociation between the oxidation and insulinotropic action of D-glucose and D-fructose was documented. Thus, the generation of $^{14}CO_2$ from 8.3 mM D-glucose exceeded that recorded in islets concomitantly exposed to 6.0 mM D-[U-^{14}C]glucose and 80.0 mM D-[U-^{14}C]fructose. Yet, the release of insulin recorded in the sole presence of 8.3 mM D-glucose was 4-times lower than that found in the presence of both 6.0 mM D-glucose and 80.0 mM D-fructose [13].

In further investigations dealing with the effects of D-glucose on the metabolism of D-fructose, it was first shown that as little as 1.0 mM D-glucose inhibits significantly the utilization of D-[5-^{3}H]fructose (1.0 or 20.0 mM) by rat islets incubated for 120 min in the presence of both the aldohexose and ketohexose [14]. Such an inhibitory effect of the aldohexose was opposed when its concentration was raised to 20.0 mM. A comparable situation prevailed in terms of D-[U-^{14}C]fructose oxidation, except that in the presence of 20.0 mM D-glucose, the oxidation of the ketohexose (1.0 or 20.0 mM) was now higher than that found in the absence of the aldohexose. As a result of these changes, the paired ratio between D-[U-^{14}C]fructose oxidation and D-[5-^{3}H]fructose utilization progressively increased, whether at a 1.0 or 20.0 mM concentration of the ketohexose, as the concentration of D-glucose was raised from zero to 1.0 and 20.0 mM. As a matter of fact, the oxidation of D-[U-^{14}C]fructose (10.0 mM) progressively increased to more than twice the value found in the absence of D-glucose as the concentration of the aldohexose was raised up to 10.0 mM, a progressive decrease below the latter peak value being then observed at higher concentrations of D-glucose (20.0 and 40.0 mM). At a 10.0 mM concentration of the ketohexose, the paired ratio between the oxidation of ^{14}C-labelled D-fructose and D-[5-^{3}H]fructose conversion to ^{3}HOH yielded the following hierarchy with distinct ^{14}C-labelled tracers of the ketohexose: D-[6-^{14}C]fructose ≤ D-[2-^{14}C]fructose < D-[1-^{14}C] fructose < D-[U-^{14}C]fructose ≤ D-[3,4-^{14}C]fructose. The enhancing action of D-glucose (10.0 mM) on the same ratio was lowest in the case of D-[1-^{14}C] fructose and highest in the case of D-[U-^{14}C]fructose or D-[3,4-^{14}C]fructose. These findings indicated that D-glucose decreases the metabolic flux of exogenous D-fructose through the pentose phosphate pathway, whilst stimulating preferentially the oxidative decarboxylation of fructose-derived pyruvate relative to the conversion of the latter 2-keto acid to either L-alanine or L-lactate. For purpose of comparison, the effect of 10.0 mM D-fructose on the catabolism of D-glucose (also 10.0 mM) was also examined. The ketohexose did not affect significantly D-[5-^{3}H]glucose utilization, D-[U-^{14}C]glucose oxidation to either $^{14}CO_2$ or ^{14}C-labelled acidic metabolites and amino acids or the ratio between D-[U-^{14}C]glucose oxidation and D-[5-^{3}H]glucose utilization [14].

Further information was obtained from the data collected from islets in control rats in investigations dealing with a comparison between control rats and either Goto-Kakizaki rats or adult rats injected with streptozotocin during the neonatal period. In fair agreement with prior findings, D-fructose (10.0 mM) did not affect significantly the catabolism of D-glucose (also 10.0 mM), as judged from either D-[5-^{3}H]glucose utilization or D-[U-^{14}C]glucose oxidation. Inversely, D-glucose (10.0 mM) decreased the generation of ^{3}HOH from D-[5-^{3}H]fructose (10.0 mM) and increased the oxidation of D-[U-^{14}C]fructose (10.0 mM), such changes resulting in a close to two-fold increase of the $^{14}CO_2/^{3}$HOH ratio. Once again, the peak value for such a ratio was reached at a 10.0 mM concentration of D-glucose [9].

Three novel sets of information were provided in a later report [7]. First, in islets exposed for 120 min to 10.0 mM D-glucose, the production of ^{3}HOH from D-[5-^{3}H]glucose exceeded that from D-[3-^{3}H]glucose. When the same measurements were made in islets incubated in the absence of extracellular Ca^{2+} (i.e. in the absence of $CaCl_2$ and presence of 1.0 mM EGTA), the ratio between D-[5-^{3}H]glucose/D-[3-^{3}H]glucose utilization was even higher than that otherwise found at normal extracellular Ca^{2+} concentration (1.0 mM). The oxidation of D-[U-^{14}C]glucose relative to the

paired value for D-[5-^{3}H]glucose utilization was lower in the absence rather than presence of extracellular Ca^{2+}, whilst such was not the case for the paired ratio between D-[U-^{14}C]glucose oxidation and D-[3-^{3}H]glucose utilization. A possible interpretation of these findings could be that a fraction of tritiated dihydroxyacetone phosphate generated from D-[3-^{3}H]glucose escapes detritiation, for instance being converted to L-glycerol 3-phosphate, which is then incorporated into triglycerides and phospholipids [15, 16]. It might be expected that the relative magnitude of such an escape phenomenon will be increased whenever the metabolism of D-glucose is inhibited. Such was indeed the case in the islets deprived of extracellular Ca^{2+}. Second, a comparable situation prevailed when the islets were exposed concomitantly to D-glucose (10.0 mM) and D-glyceraldehyde (also 10.0 mM). In the islets exposed to D-glucose, D-glyceraldehyde, which inhibited D-glucose catabolism, indeed augmented the paired ratio between D-[U-^{14}C]glucose oxidation and D-[3-^{3}H]glucose utilization, whilst failing to affect the paired ratio between D-[U-^{14}C]glucose oxidation and D-[5-^{3}H]glucose utilization. Thus, as already observed in the absence of extracellular Ca^{2+}, the decrease in D-glucose catabolism caused by D-glyceraldehyde coincided with a more severe alteration of D-[3-^{3}H]glucose utilization as compared to D-[5-^{3}H]glucose utilization. Likewise, in the islets exposed to D-fructose (10.0 mM), the impairment of the catabolism of the ketohexose caused by D-glyceraldehyde coincided with a more severe relative decrease of D-[3-^{3}H]fructose utilization, as distinct from D-[5-^{3}H]fructose utilization [16]. Lastly, contrasting with the severe decrease in the catabolism of D-glucose (10.0 mM) caused by D-mannoheptulose (20.0 mM), whether in terms of D-[5-^{3}H]glucose conversion to ^{3}HOH or D-[U-^{14}C]glucose conversion to $^{14}CO_2$ and ^{14}C-labelled amino acids, the heptose only provoked a modest decrease in D-[5-^{3}H]fructose utilization and no significant effect upon D-[U-^{14}C]fructose conversion to $^{14}CO_2$ and labeled amino acids in islets exposed to 10.0 mM D-fructose. Moreover, in the concomitant presence of D-glucose and D-fructose (10.0 mM each), the inhibitory action of D-mannoheptulose on D-glucose catabolism was again quite obvious, but the heptose now severely decreased D-[5-^{3}H] fructose utilization as well as D-[U-^{14}C]fructose oxidation. These findings are consistent with the knowledge that D-glucose augments D-fructose phosphorylation by glucokinase and the finding that D-mannoheptulose, which fails to affect D-fructose phosphorylation by fructokinase, inhibits the phosphorylation of D-fructose by glucokinase, the relative magnitude of the latter inhibition being much more pronounced in the concomitant presence of D-glucose than in the absence of the aldohexose [7].

The failure of D-fructose (10.0 mM) to affect the catabolism of D-glucose (also 10.0 mM), in terms of D-[5-^{3}H]glucose utilization, D-[U-^{14}C]glucose oxidation and paired $^{14}CO_2/^{3}$HOH ratio, as well as the enhancing action of D-glucose (10.0 mM) on the oxidation of D-[U-^{14}C]fructose and ratio between such an oxidation and the utilization of D-[5-^{3}H]fructose were confirmed in the islets from rats serving as control in the study of adult rats injected with streptozotocin during the neonatal period [17].

Energy yield

It was first reported that, in rat pancreatic islets, D-fructose (33.0 mM) and D-glucose (3.3 mM), when tested separately, slightly augment O_2 uptake but do not enhance insulin release above basal value [18]. In the simultaneous presence of both hexoses, the O_2 uptake was further increased, thus coinciding with a significant stimulation of insulin release. The increase in O_2 uptake caused by D-fructose (33.3 mM) and/or D-glucose (3.3 mM) occurred despite the fact that, under these three experimental conditions, the hexose(s) caused a sparing action upon the oxidation of endogenous fatty acids as judged from the production of $^{14}CO_2$ by islets preincubated for 120 min with [U-^{14}C]palmitate (0.1 mM) in the presence of 8.3 mM D-glucose. Neither D-fructose (33.0 mM) nor D-glucose (3.3 mM) affected significantly the production of $^{14}CO_2$ from islets preincubated for 30 min with L-[U-^{14}C]glutamine (1.0 mM) [18].

The ATP, ADP and (ATP + ADP) content, as well as ATP/ADP ratio were then measured in rat pancreatic islets incubated for 60 min in either the absence of any exogenous nutrient or in the presence of D-glucose (10.0 mM), D-fructose (10.0 mM and 100.0 mM) and both D-glucose

(10.0 mM) and D-fructose (10.0 mM) [10]. D-glucose (10.0 mM) augmented the ATP and (ATP + ADP) content and ATP/ADP ratio above the basal value. D-fructose (10.0 and 100.0 mM), however, lowered in a concentration-related manner the ATP, ADP and (ATP + ADP) content, whilst failing to affect significantly the ATP/ADP ratio. Likewise, in the presence of 10.0 mM D-glucose, D-fructose (10.0 mM) lowered the ATP content and ATP/ADP ratio below the level found in the sole presence of D-glucose, such variables remaining nevertheless higher than the basal values found in the absence of both hexoses. These findings obviously contrasted with the fact that D-fructose (100.0 mM) augments insulin release above basal value and with the fact that, in the presence of D-glucose (10.0 mM), D-fructose (also 10.0 mM) augments insulin secretion above the value found in the sole presence of the aldohexose [19]. A different picture prevailed for the cytosolic content of adenine nucleotides, as measured after exposure of dispersed islet cells to digitonine. Once again, D-glucose (10.0 mM) augmented significantly the cytosolic ATP and (ATP + ADP) content, as well as the ATP/ADP ratio. Whether in the absence or presence of the aldohexose, D-fructose (10.0 mM) did not affect significantly these three variables, whilst at a higher concentration (100.0 mM) the ketohexose augmented significantly the ATP content and ATP/ADP ratio above basal value. Under these five experimental conditions, significant positive correlations were found between the mean values for either cytosolic ATP content or ATP/ADP ratio in the dispersed islet cells and the corresponding values for insulin output from isolated islets. The relationships between either insulin output from isolated islets or ^{86}Rb net uptake by the dispersed islet cells and the cytosolic ATP/ADP ratio in the dispersed islet cells displayed a sigmoidal pattern, with a threshold value for the increase in functional variables above basal value at an ATP/ADP ratio in excess of that found in the sole presence of 10.0 mM D-fructose. Nevertheless, the present data afford, to our knowledge, the first example of a dramatic dissociation between the effects of a given nutrient secretagogue, i.e. D-fructose, on total and cytosolic adenine nucleotide content [19].

CONCLUSION

The information provided by this first review article sets the scene to consider both the possible link between the metabolism of D-fructose and its functional effects in pancreatic islets [20] and the alteration of these processes in models of pancreatic islet cell dysfunction [21].

CONFLICT OF INTEREST STATEMENT

No conflict of interest.

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