Current Topics in Biochemical Research
Vol. 15, *1*, 2013

Review

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

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ABSTRACT

The present review deals mainly with the functional aspects of the response of insulin-producing cells to D-fructose. Attention is drawn to the insulinotropic action of the ketohexose and its modulation by environmental factors, the process of stimulus-secretion coupling involved in fructose-induced insulin release, and the changes evoked by D-fructose in the handling of ^{45}Ca and ^{86}Rb by isolated pancreatic islets. The anomeric specificity of the effects of D-glucose upon the metabolic, cationic and functional response of pancreatic islets to D-fructose, the effects of the ketohexose upon protein biosynthesis in isolated pancreatic islets and its effects upon glucagon release are discussed. An alternative hypothesis concerning the possible role of sweet receptors in the stimulation of insulin release by D-fructose is also discussed.

KEYWORDS: D-fructose, pancreatic islets, insulin secretion, ^{45}Ca and ^{86}Rb handling, D-glucose anomers, sweet taste receptors

INTRODUCTION

In the first article in this series [1], emphasis was placed on the metabolism of D-fructose in pancreatic islets. The present review deals with the functional response of islet cells to this ketohexose, in terms of stimulation of insulin release, alteration of cationic fluxes, effects on protein biosynthesis and glucagon secretion. Attention is also drawn to both the influence of environmental factors such as the anomers of D-glucose upon functional variables, and the possible role of sweet taste receptors in the process of fructose-induced insulin secretion.

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Fructose-induced insulin release

D-fructose only represents a weak insulin secretagogue in mouse islets; a significant increment in insulin output is only observed when D-fructose (20.0 and 33.0 mM) is added to a medium containing both 5.6 mM D-glucose and 1.4 mM theophylline [2]. In rat islets exposed to 3.3 mM D-glucose, D-fructose (20.0 and 33.0 mM) significantly augments insulin output [2]. At intermediate concentrations of D-glucose (5.6 and 7.0 mM), D-fructose, when tested in the 3.3 to 33.0 mM range, causes a dose-related increase in insulin release. However, at a much higher D-glucose level (16.7 mM), D-fructose barely augments insulin output. In the range of D-glucose concentrations up to 11.1 mM, D-fructose (33.0 mM) shifts to the left the curve relating insulin output (y-axis) to D-glucose concentration (x-axis). The magnitude of such a shift indicates that the secretory response to 33.0 mM D-fructose is similar to that evoked by a rise in D-glucose concentration close to 3.7 to 3.9 mM. Yet, the capacity of D-fructose to augment insulin release is much less marked in the presence of D-mannose than in the presence of D-glucose. Indeed, in the presence of 14.0 mM D-mannose, the increment in insulin output attributable to

33.0 mM D-fructose is lower than that evoked by 3.3 mM D-glucose. Moreover, although D-mannose (14.0 mM) stimulates insulin release as efficiently as 7.0 mM D-glucose, the secretory rate reached in the concomitant presence of D-fructose (8.0 or 33.0 mM) is lower in the islets exposed to D-mannose (14.0 mM) than in those exposed to D-glucose (7.0 mM). Likewise, whether in the presence of nutrient secretagogues (e.g. 2-ketoisocapraote 5.0 mM) or non-nutrient secretagogues (e.g. the combination of 2.0 mM Ba^{2+} and 1.4 mM theophylline in the absence of extracellular Ca^{2+}), the insulin output from rat islets remains lower in the presence of 33.0 mM D-fructose than 3.3 mM D-glucose. Last, gliclazide (0.06 mM) augments insulin release in the presence of 3.3 mM D-glucose but not in the presence of 33.0 mM D-fructose [2].

In a further study, it was documented that, in the absence of D-glucose, D-fructose stimulates insulin release with a threshold value for the insulinotropic action of the ketohexose close to 80.0 mM [3]. At this concentration, D-fructose shifts to the left the curve relating insulin output (y-axis) to D-glucose concentration (x-axis) [4]. In the range of D-glucose concentrations up to 11.1 mM, such a shift is similar to that otherwise attributable to a rise in D-glucose concentration close to 7.2 mM. The shift to the left of the sigmoidal curve relating insulin output to D-glucose concentrations itself depends on the concentration of D-fructose. For instance, when D-fructose was tested at a 5.0 mM concentration, the threshold concentration of D-glucose required to detect the enhancing action of the ketohexose was above 6.0 mM and below 8.3 mM [4]. An even higher D-glucose concentration (close to 12.7 mM) is required to allow as little as 3.3 mM D-fructose to significantly augment insulin output [2].

In the absence of any other exogenous nutrient, the threshold value for the insulinotropic action of D-fructose is close to 80.0 mM and a maximal secretory response is recorded in the 240.0 to 320.0 mM range [5]. D-glucose, when tested in the 1.0 to 4.0 mM range, increases the release of insulin from islets exposed to 80.0 mM D-fructose in a sigmoidal manner. When islets are first exposed for 90 min to 240.0 mM D-fructose and then incubated for another 90 min period in the absence of any exogenous nutrient, the rate of insulin release during the second incubation (38.2 ± 2.6 μU/islet) remains higher than that recorded at the same time in islets deprived of any exogenous nutrient during the two successive incubations (5.3 ± 0.7 μU/islet). Likewise, when D-glucose (16.7 mM) is present in the medium during the second incubation, the output of insulin is higher in the islets first incubated in the presence of 240.0 mM D-fructose (146.1 ± 13.1 μU/islet) than in the islets first incubated in the absence of any exogenous nutrient (102.1 ± 7.6 μU/islet). Thus, prior exposure of the islets to a high concentration of the ketohexose does not impair, but on the contrary may improve, their functional responsiveness to D-glucose [5].

Lastly, whilst D-fructose (10.0 mM) fails to increase insulin output in the absence of any exogenous nutrient, it was found to significantly augment insulin release evoked by 10.0 mM D-glucose [6].

Stimulus-secretion coupling of fructose-induced insulin release

The stimulation of insulin release by high concentrations of D-fructose (e.g. 240.0 mM) corresponds to an active process modulated by the metabolic fate of the hexose (inhibition by D-mannoheptulose), the availability of ATP (inhibition by KCN), the activity of ATP-sensitive K^+ channels (potentation by glibenclamide), the extracellular concentration of Ca^{2+} (suppression in the absence of Ca^{2+}), the cell content in cyclic AMP (potentiation by forskolin or theophylline) and the motile events under the control of the microfilamentous cell web (potentiation by cytochalasin B) [5].

The effects of D-fructose (33.0 mM) on ^{45}Ca net uptake and ^{45}Ca outflow from islets prelabelled with ^{45}Ca during 60 min preincubation in the presence of 16.7 mM D-glucose were first investigated [7]. Over 90 min incubation, D-fructose (33.0 mM), but not D-glucose (3.3 mM) significantly augmented ^{45}Ca net uptake above basal value. A further increase in ^{45}Ca net uptake was observed in the concomitant presence of the ketohexose (33.0 mM) and the aldohexose (3.3 mM). Under these experimental conditions, the relationship between insulin output and ^{45}Ca net

uptake was virtually identical to that otherwise found at increasing concentration of D-glucose (zero, 3.3, 7.0 and 16.7 mM). The threshold value for stimulation of insulin output corresponded to a value for ^{45}Ca net uptake, in between that found in the presence of 33.0 mM D-fructose on one hand and those recorded either in the presence of 7.0 mM D-glucose or in the concomitant presence of D-fructose (33.0 mM) and D-glucose (3.3 mM) on the other hand. The ^{45}Ca fractional outflow rate from prelabelled islets perifused in the presence of 7.0 mM D-glucose displayed a biphasic change in response to the administration of D-fructose (33.0 mM), first decreasing within one to two minutes of exposure to the ketohexose and then ascending to a peak value at about 5 min after the onset of D-fructose administration [7]. Such a biphasic pattern is similar to that observed in response to the administration of 11.1 mM D-glucose to islets first perifused in the absence of any exogenous nutrient [8]. In both cases, a rapid and sustained stimulation of insulin release is observed.

The cationic determinants of the insulinotropic action of D-fructose, in high concentration (240.0 mM) are comparable, if not identical to those currently incriminated in the stimulation of insulin release by D-glucose (11.1 mM). Thus, both hexoses decrease ^{86}Rb fractional outflow rate from prelabelled islets, cause a decrease of ^{45}Ca fractional outflow rate from islets perifused in the absence or presence of extracellular Ca^{2+} and, in the latter situation provoke a secondary rise in the efflux of the radioactive divalent cation; these cationic effects coincide with stimulation of insulin output from the perifused islets. The sole obvious differences between the two series of experiments consisted, in the islets exposed to D-fructose, in the occurrence of an early and transient increase in ^{45}Ca efflux at normal extracellular Ca^{2+} concentration and of a dramatic off-response in both ^{86}Rb and ^{45}Ca outflow as well as insulin release after removal of the ketohexose from the perifusate [8].

In dispersed islet cells incubated for 90 min at increasing concentrations of D-glucose, the concentration-response relationship for the enhancing action of the aldohexose on ^{86}Rb net uptake represents a mirror image of that characterizing the concentration-related effect of D-glucose on ^{86}Rb fractional outflow rate from prelabelled and perifused islets. This is in agreement with the knowledge that D-glucose increases K^+ content of islet cells by decreasing K^+ conductance, without any obvious effect on the rate of K^+ inflow into islet cells. In the absence of D-glucose, D-fructose at a 100.0 mM concentration, but not at a 10.0 mM concentration, also increases ^{86}Rb net uptake by dispersed islet cells. In the presence of D-glucose (10.0 mM), as little as 10.0 mM D-fructose again increases ^{86}Rb net uptake by the dispersed islet cells [9].

Another analogy between the secretory responses to either D-glucose alone (8.3 mM) or the combination of D-glucose (8.3 mM) and D-fructose (20.0 mM), in terms of their modulation by environmental factors consisted, in both cases, in an inhibition of insulin output in response to either a fall of extracellular pH (from 7.4 to 6.9) or a rise in extracellular pH (from 7.4 to 8.0). Nevertheless, whilst the decrease in secretory rate provoked by the rise in pH displayed a comparable relative magnitude in the sole presence of D-glucose or in the presence of both D-glucose and D-fructose, the decrease in extracellular pH affected more severely, in relative terms, the secretory response to the combination of D-glucose and D-fructose (39.9 ± 9.0% inhibition) than that to D-glucose alone (17.8 ± 6.9%) [10].

Anomeric specificity of the effects of D-glucose on the metabolic, cationic and functional response of pancreatic islets to D-fructose

Another example of the modulation of D-fructose metabolism and insulinotropic action concerns the anomeric specificity of the effects of D-glucose on the metabolic, cationic and functional response of pancreatic islets to D-fructose. In intact islets incubated for 60 min at 4 °C, α-D-glucose (5.6 mM) increases the conversion of D-[U-^{14}C]fructose (5.0 mM) to both $^{14}CO_2$ and ^{14}C-labelled acidic metabolites above basal value (no D-glucose anomer); such increases are higher than those recorded in the presence of β-D-glucose (also 5.6 mM) [11]. In islets prelabelled with ^{45}Ca and perifused in the presence of 5.6 mM α-D-glucose, the administration of D-fructose (20.0 mM)

between the 45th and 70th minutes of perifusion opposed the slow and progressive decrease in ^{45}Ca outflow recorded between 30 and 45 minutes and, in most cases, increased ^{45}Ca fractional outflow rate [11, 12]. However, when comparable experiments were conducted in the presence of β-D-glucose (also 5.6 mM), D-fructose decreased ^{45}Ca fractional outflow rate in most cases; this effect was rapidly reversed upon removal of D-fructose from the perifusate [11, 12]. The prevailing effect of D-fructose in the islets exposed to β-D-glucose was thus comparable to that otherwise observed in response to the administration of equilibrated D-glucose in concentrations not exceeding 7.0 mM [13]. Such an effect is currently ascribed to the effect of the hexose upon both the sequestration of Ca^{2+} by intracellular organelles and Na^{+}-Ca^{2+} countertransport at the level in the B-cell plasma membrane [14, 15]. Likewise, in the presence of α-D-glucose, D-fructose provoked a typical biphasic increase in insulin output, in contrast with a modest and sluggish increase in insulin release evoked by D-fructose in the presence of β-D-glucose [11]. Under these experimental conditions, the stimulation of insulin release by D-fructose was apparently not rapidly reversible [11].

Protein biosynthesis

In one study, D-fructose (16.7 mM) exerted a minor stimulation of (pro)insulin and total protein biosynthesis in rat islets exposed to this ketohexose for 90 min [16]. However, the paired ratio between these two variables remained lower than that found in islets exposed to as little as 3.9 mM D-glucose. Moreover, at variance with the stimulation of protein biosynthesis observed in rat pancreatic islets exposed to 16.7 mM D-glucose, no stimulation of biosynthetic activity was observed in islets exposed to 80.0 or 240.0 mM D-fructose. The latter finding was again considered to support the view that the insulinotropic action of the ketohexose does not entail the same metabolic determinants as those operative in glucose-stimulated islets [17].

Glucagon secretion

In rat pancreases perfused in the presence of 3.3 mM D-glucose, the administration of either 17.0 or 40.0 mM D-fructose affected both insulin and glucagon output in a manner comparable to that otherwise recorded in response to an increment in D-glucose concentration of either 1.7 or 4.0 mM. Thus, under these experimental conditions, a concentration-related stimulation of insulin release, with a typical biphasic pattern at the highest concentrations of these hexoses, coincided in all cases with a sizeable decrease in glucagon output [18]. The positive glucagon secretory response to L-arginine (5.0 mM) administered 25 min after restoration of the basal concentration of D-glucose (3.3 mM) was more markedly reduced after prior administration of D-fructose than after a prior increase in D-glucose concentration.

An alternative hypothesis

Investigations concerning the effects of artificial sweeteners on insulin release and cationic fluxes in rat pancreatic islets [19], as well as findings dealing with the insulinotropic action of L-glucose pentaacetate [20] drew attention to the possible role of sweet or bitter taste receptors in the insulin secretory response to these agents. As a matter of fact, the abnormal identification of the sweet taste of D-glucose anomers in certain human subjects had led to the speculation that diabetes mellitus could represent a glucoreceptor disorder [21, 22]. Quite recently, it was documented that insulin-producing cells express sweet taste receptors and that their activation by artificial sweeteners stimulates insulin release through the generation of diverse intracellular signals and promotion of D-glucose metabolism [23-25]. Likewise, it was proposed that, both *in vitro* and *in vivo*, sweet taste receptor signaling in insulin-producing cells mediates the fructose-induced potentiation of glucose-stimulated insulin secretion [26].

CONCLUSION

The extensive information on the functional response of pancreatic islet cells to D-fructose considered in this report complements what was reviewed in the preceding article in this series dealing with the metabolism of the ketohexose in the same cells [1]. As such, these two publications may set the scene for further considerations on the perturbation of these processes in experimental

models of pancreatic islets dysfunction, as documented in the last contribution in this series.

CONFLICT OF INTEREST STATEMENT

No conflict of interest.

REFERENCES

1. Malaisse, W. J. 2013, Curr. Top. Biochem. Res., 15(1), 87-93.
2. Sener, A. and Malaisse, W. J. 1988, Arch. Biochem. Biophys., 261, 16-26.
3. Sener, A. and Malaisse, W. J. 1996, Biochim. Biophys. Acta, 1312, 73-78.
4. Sener, A. and Malaisse, W. J. 1996, Biochem. Mol. Med., 59, 182-186.
5. Sener, A. and Malaisse, W. J. 1998, Acta Diabetol., 35, 74-76.
6. Scruel, O., Sener A. and Malaisse, W. J. 1999, Mol. Cell Biochem., 197, 209-216.
7. Sener, A., Blachier, F. and Malaisse, W. J. 1990, Turk. J. Med. Biol. Res., 1, 5-12.
8. Jijakli, H. and Malaisse, W. J. 2000, Acta Diabetol., 37, 27-32.
9. Giroix, M.-H., Agascioglu, E., Oguzhan, B., Louchami, K., Zhang, Y., Courtois, P., Malaisse, W. J. and Sener, A. 2006, Biochim. Biophys. Acta, 1757, 773-780.
10. Sener, A. and Malaisse, W. J. 2010, Metab. Funct. Res. Diab., 3, 40-41.
11. Jijakli, H., Courtois, P., Zhang, H.-X., Sener, A. and Malaisse, W. J. 2003, J. Biol. Chem., 278, 4531-4535.
12. Jijakli, H., Zhang, H.-X., Sener, A. and Malaisse, W. J. 2003, Int. J. Mol. Med., 12, 513-515.
13. Malaisse, W. J., Lebrun, P., Yaylali, B., Camara, J., Valverde, I. and Sener, A. 1990, Am. J. Physiol., 259, E117-E122.
14. Herchuelz, A., Sener, A. and Malaisse, W. J. 1980, J. Membrane Biol., 57, 1-12.
15. Gylfe, E. 1988, J. Biol. Chem., 263, 13750-13754.
16. Pipeleers, D. G., Marichal, M. and Malaisse, W. J. 1973, Endocrinology, 93, 1001-1011.
17. Viñambres, C., Villanueva-Peñacarrillo, M. L., Valverde, I. and Malaisse, W. J. 1997, Biochem. Mol. Biol. Int., 41, 571-574.
18. Sener, A., Leclercq-Meyer, V. and Malaisse, W. J. 2004, Endocrine, 24, 73-81.
19. Malaisse, W. J., Vanonderbergen, A., Louchami, K., Jijkli, H. and Malaisse-Lagae, F. 1998, Cell Signal, 10, 727-733.
20. Malaisse, W. J. 1998, Int. J. Mol. Med., 2, 383-388.
21. Malaisse-Lagae, F. and Malaisse, W. J. 1986, Diabetologia, 29, 344-345.
22. Niki, A. and Niki, H. 1975, Lancet, 2, 658.
23. Nakagawa, Y., Nagasawa, M., Yamada, S., Hara, A., Mogami, H., Nikolaev, V. O., Lohse, M. J., Shigemura, N., Ninomiya, Y. and Kojima, I. 2009, PLoS ONE, e5106.
24. Nakagawa, Y., Nagasawa, M., Mogami, H., Lohse, M., Ninomiya, Y. and Kojima, I. 2013, Endocr. J., 60, 1191-1206.
25. Nakagawa, Y., Ohtsu, Y., Nagasawa, M., Shibata, H. and Kojima, I. 2013, Endocr. J., doi: 10.1507.
26. Kyriazis, G. A., Soundarapandian, M. M. and Tyrberg, B. 2012, Proc. Natl. Acad. Sci. USA, 109, E524-E532.