Pancreatic D-Cell Recognition of D-Glucose

Studies with D-Glucose, D-Glyceraldehyde, Dihydroxyacetone, D-Mannoheptulose, D-Fructose, D-Galactose, and D-Ribose

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SUMMARY

To investigate how the D-cell recognizes the glucose stimulus, the hormone response to (1) glucose, (2) the trioses glyceraldehyde and dihydroxyacetone, (3) the metabolic blocker, mannoheptulose, and (4) the low- or nonmetabolized sugars galactose, fructose, or ribose were studied using the isolated dog pancreas. We found (1) a sigmoidal relationship between extracellular glucose concentrations and the somatostatin release. The threshold concentration was around 5 mM and the largest increase in somatostatin release occurs between 5 and 10 mM of glucose. (2) Glyceraldehyde at concentrations ranging between 1.25 and 5 mM stimulated the release of somatostatin, whereas the higher concentrations of 10 and 20 mM were suppressive. Dihydroxyacetone (11 mM), also initiated somatostatin release in the absence of glucose. Both of the trioses stimulated B- and inhibited A-cell secretion. (3) Mannoheptulose (5 mM) attenuated somatostatin and insulin secretion to 8.3 mM glucose, while it augmented glucagon output. In contrast, mannoheptulose (5 mM) did not affect D-, A-, or B-cell responses to glyceraldehyde (5 mM) in the absence of glucose. (4) The somatostatin, insulin, and glucagon release remained unchanged when 8.3 mM of either galactose, fructose, or ribose was added. The results suggest that the initiation of glucose-mediated D- as well as A- and B-cell responses depends on the metabolism of the sugar. DIABETES *30*:203–210, March 1981.

It is well known that an increase in the extracellular concentration of glucose stimulates the release of somatostatin from the pancreatic D-cells.[1–5] This glucose-induced somatostatin secretion is dependent on the presence of calcium,[4] and all present evidence points to a key regulatory role for this cation in the events that lead to extrusion of somatostatin from the D-cells.[4–8] Any detailed understanding of the pancreatic D-cell recognition of glucose is, however, still fragmentary. The release mechanisms of the D-cells seem, however, to have much in common with those of the B-cells. Until now, the release responses to a large variety of compounds have thus been found to be similar. In analogy to the suggested models for the B-cell glucoreceptor,[9,10] at least three explanations can be offered concerning the glucose-mediated somatostatin secretion. The somatostatin release may be triggered by the intact glucose molecule itself, or it may be that the metabolism of glucose within the D-cell provides intracellular signals which initiate somatostatin secretion; finally, these two models may function in combination. In an attempt to clarify the question, somatostatin responses were studied in the isolated, perfused canine pancreas to (1) glucose, (2) the trioses glyceraldehyde and dihydroxyactone (which enter the glycolytic pathway at the triose phosphate level), (3) mannoheptulose, which inhibits glucose phosphorylation and consequently the metabolism of glucose[11,12] but not that of glyceraldehyde,[13–15] and (4) non- or low-metabolized sugars (galactose, fructose, ribose). To elucidate and compare the response patterns of the D-, B-, and A-cells, the results of insulin and glucagon measurements will also be discussed briefly.

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MATERIAL AND METHODS

Preparation and perfusion media. Mongrel dogs, fasted overnight, weighing 17–28 kg, were used as pancreas donors. The technique for isolation of the pancreas and the perfusion system has previously been described in detail.[16] In brief, the preparation consisted of the pancreas and the proximal 10 cm of the attached duodenum. A nonrecirculating medium, consisting of a Krebs-Ringer bicarbonate buffer containing 40 g/L dextran (mol. wt. 75,000), 2 g/L bovine albumin, glutamate, fumarate, and pyruvate, each at a concentration of 5 mM, was pumped through the splenic and coeliac arteries, and the total portal effluent was collected every minute. The ionic composition of the standard perfusion medium was as follows: (milliequivalents per

liter): Na^+, 140.0; K^+, 4.4; Ca^{2+}, 2.6; Mg^{2+}, 1.8; Cl^-, 124.0; HCO_3^-, 24.4; SO_4^{2-}, 1.8; and $H_2PO_4^-$, 1.1. Unless otherwise indicated, glucose was not added to the medium.

Oxygenation of the Krebs-Ringer bicarbonate buffer was achieved by means of a rotating roller screen in an atmosphere of 94.4% O_2 and 5.6% CO_2. During the experiments, the perfusion fluid had a constant pH of 7.4 and a temperature of 37°C. The perfusion pressure was 30–40 mm Hg, and the perfusion flow was 20 ml/min.

Experimental procedure. Samples were taken every minute from the efflux. To prevent possible degradation of glucagon and somatostatin, 3 mg/ml EDTA was added to the tubes collecting the efflux. The samples were stored immediately at −18°C until assayed.

The pancreas was perfused for an equilibration period of 20–30 min. Thereafter, the substances to be studied were infused for 10–30 min, with 15–20-min recovery periods in between. The total perfusion averaged 3 h.

In the dose-response studies, glucose was administered at increasing concentrations to four pancreata, while in one pancreas, it was infused at decreasing concentrations. As for glyceraldehyde, two of the pancreata received the triose at increasing doses, whereas the reverse was the case in one pancreas. In the study of the effects of 8.3 mM of glucose, galactose, fructose, and ribose, the four sugars were given in random order to each of four pancreata.

Reagents. The sugars applied were all D-isomers. D-glucose, D-glyceraldehyde, dihydroxyacetone, D-mannoheptulose, D-galactose, D-fructose, and D-ribose were purchased from Sigma Chemical Co. (St. Louis, Missouri).

Radioimmunoassays. Somatostatin was measured by radioimmunoassay as previously described,[5,8] with the modification that the tyrosin[11] instead of the tyrosin[1] analogue of somatostatin was iodinated with ^{125}I. The perfusion buffer was used as diluent for the standards. The detection limit was 2 pg/ml.

Incubation damage was estimated in individual incubation tubes in which the addition of antibody was omitted; it was found to be negligible (1%–2%) and identical in standards and effluent buffer medium. Thus, methodologic errors due to differences in the immunoreactivity of labeled somatostatin as well as to the stability of endogenous somatostatin during storage and incubation in various solutions are not likely. Furthermore, determinations in dilutions of the endogenous somatostatin demonstrated decreases in binding percentages parallel to those of synthetic standard solutions. The somatostatin immunoreactivity was eluted from Sephadex G-25 superfine gel in a single peak at an elution volume corresponding to that of synthetic cyclic somatostatin. The recovery of synthetic somatostatin added to the efflux medium averaged 103 ± 6% (mean ± SEM) at concentrations between 50 (N = 4) and 100 pg/ml (N = 4). At the somatostatin levels of 40 and 145 pg/ml the intraassay coefficient of variation was 6% (N = 10) and 7% (N = 10), respectively. At the same level of somatostatin, the interassay coefficient was 7% (N = 9) and 13% (N = 9), respectively. The antibody employed had no cross-reactivity with any of the other pancreatic hormones (insulin, glucagon, VIP, or pancreatic polypeptide). Neither did any of the above-mentioned infused reagents interfere in the somatostatin assay.

Insulin and glucagon were both measured in the perfusate by specific and sensitive radioimmunoassays, as previously described in detail.[17] A pancreatic glucagon-specific antiglucagon serum (Lise Heding, NOVO Research Institute, Copenhagen) was used.

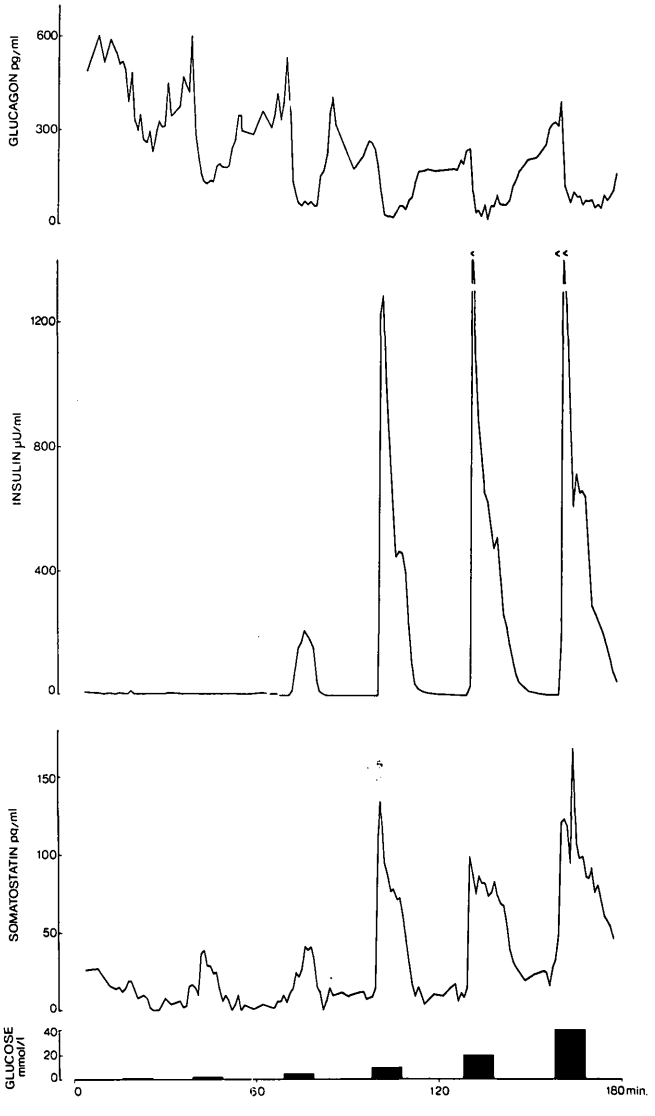
It is unlikely that the attached duodenum has any significant regulatory role in islet hormone secretion, since exclusion of the duodenal circulation by clamping induces no alteration in the shape or magnitude of the somatostatin, insulin, and glucagon responses to Ca^{2+},[18] tolbutamide, or glucose (unpublished observations).

Calculations. Percentage change in hormone secretion (Δ%): The mean of the 1-min hormone values during the entire sugar infusion (B) is related to the average of the last five 1-min values just before the addition of the sugar (A), i.e., $\Delta\% = [(B - A)/A] \times 100\%$.

Since the control values (A) for insulin were 0 or almost 0, the percentage changes have not been recorded.

Statistical analyses were made by Student's *t* test for paired comparisons using a 5% confidence limit.

FIGURE 1. Dynamics of somatostatin, insulin, and glucagon release in response to 10-min infusions of glucose at concentrations of 1.25, 2.5, 5, 10, 20, and 40 mM. One of five perfusions (included in Figure 2).



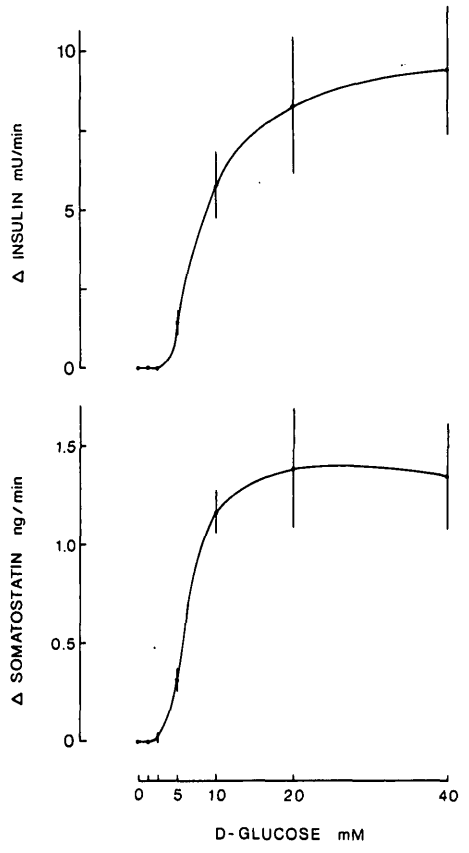


FIGURE 2. Relationship between perfusate glucose levels and increases in output of somatostatin (ng/min) and insulin (mU/min). The individual Δ values have been calculated as B − A; B representing the mean hormone output/min during the 10-min glucose infusion and A the average output/min the last 5 min preceding the glucose administration. Data expressed as mean ± SEM of five perfusion experiments.

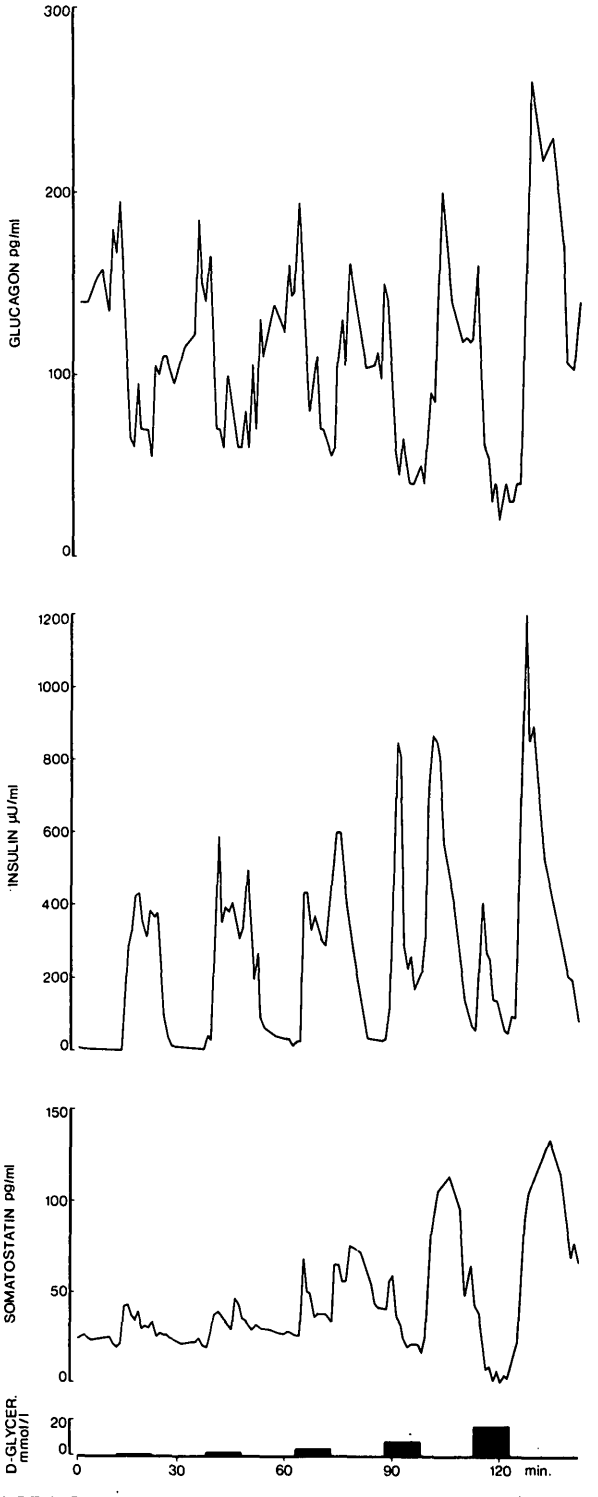


FIGURE 3. Dynamics of somatostatin, insulin, and glucagon release in response to 10-min infusion of glyceraldehyde at concentrations of 1.25, 2.5, 5, 10, and 20 mM. One of three perfusions (included in Figure 4).

RESULTS

The effects of glucose. The effects on somatostatin, insulin, and glucagon release of 10-min increases in the glucose concentration from 0 to 1.25, 2.5, 5, 10, 20, and 40 mM were studied. The dynamics of the hormone release are illustrated in Figure 1. Somatostatin release is biphasic at high concentrations of glucose and is characterized by immediate increases and decreases in response to infusion and withdrawal of the stimulus. Figure 2 demonstrates the relationship between perfusate glucose levels and the increase in somatostatin output. Glucose stimulates the somatostatin release in a dose-dependent way (Figure 2 and Table 1). The D-cell threshold for glucose is close to 5 mM ($2P < 0.05$). The half-maximal somatostatin release occurs at a glucose dose between 5 and 10 mM, the latter dose giving a significantly higher response than the former ($2P < 0.001$). Maximal release is reached at about 20 mM glucose. No significant difference was found, however, between the increase in somatostatin release at the highest three glucose doses of 10, 20, and 40 mM. As regards insulin, glucose stimulated the release dose-dependently as expected (Figure 2). In contrast, glucagon release was significantly suppressed at all the employed glucose doses, even at the lowest of 1.25 mM ($2P < 0.01$) (Table 1).

Effects of glyceraldehyde and dihydroxyacetone. The effect of increasing glyceraldehyde concentrations was studied in the absence of extracellular glucose. Glyceraldehyde was infused for 10-min periods at doses of 1.25, 2.5, 5, 10, and 20 mM. Figure 3 illustrates that low doses of glyceraldehyde elicited an immediate augmentation in the somatostatin release. By increasing the triose concentration to 10 and 20 mM, the somatostatin release is, however, suppressed.

TABLE 1
Percentage changes in glucagon and somatostatin output in response to glucose and glyceraldehyde

Concentration (mM)	Glucose (N = 5)		Glyceraldehyde (N = 3)	
	Glucagon (%)	Somatostatin (%)	Glucagon (%)	Somatostatin (%)
1.25	−48 ± 8*	−7 ± 7 NS	−39 ± 9*	33 ± 7*
2.5	−53 ± 2†	6 ± 13 NS	−52 ± 2†	73 ± 15*
5	−64 ± 5†	75 ± 24*	−49 ± 10*	45 ± 10*
10	−75 ± 5†	181 ± 69*	−64 ± 8*	−53 ± 17*
20	−68 ± 10†	188 ± 66*	−74 ± 9*	−79 ± 2‡
40	−61 ± 9*	171 ± 55*	—	—

Significance levels of changes in hormone release induced by the carbohydrates. * $2P < 0.05$, † $2P < 0.01$, and ‡ $2P < 0.001$. For calculations see MATERIALS AND METHODS.

After withdrawal of glyceraldehyde, at doses above 1.25 mM, a transitory rebound phenomenon appears. Glyceraldehyde also stimulates insulin, while it inhibits glucagon secretion. It is noteworthy that the insulin responses at the high doses of the triose of 10 and 20 mM are also followed by prominent off responses.

Figure 4 and Table 1 demonstrate that the D-cell threshold for glyceraldehyde is below 1.25 mM, and a clearcut stimulation of somatostatin release is induced in the range between 1.25 and 5 mM ($2P < 0.05$), while 10 and 20 mM block the secretory process of the D-cells ($2P < 0.05$ and $2P < 0.001$, respectively). Insulin secretion is stimulated by all the glyceraldehyde concentrations applied, however, with decreasing responses at the higher concentrations of 10 and 20 mM. Glucagon release is suppressed by all the glyceraldehyde concentrations applied (Table 1).

The effect of the other triose, dihydroxyacetone (11 mM), was investigated in four perfusions. Also, dihydroxyacetone elicited an augmentation in the release of somatostatin (40% ± 12%, $2P < 0.05$) and insulin and a decrease in glucagon secretion by 37% ± 6% ($2P < 0.01$) (Figure 5). However, the D- and B-cell responses to dihydroxyacetone are quite different from those to glyceraldehyde. Both somatostatin and insulin increases are more gradual. Furthermore, the release during equimolar dihydroxyacetone infusions was smaller than that observed during glyceraldehyde.

FIGURE 4. Relationship between glyceraldehyde concentrations and changes in output of somatostatin (ng/min) and insulin (mU/min). The individual Δ values have been calculated as described in Figure 2. Data expressed as mean ± SEM of three perfusion experiments.

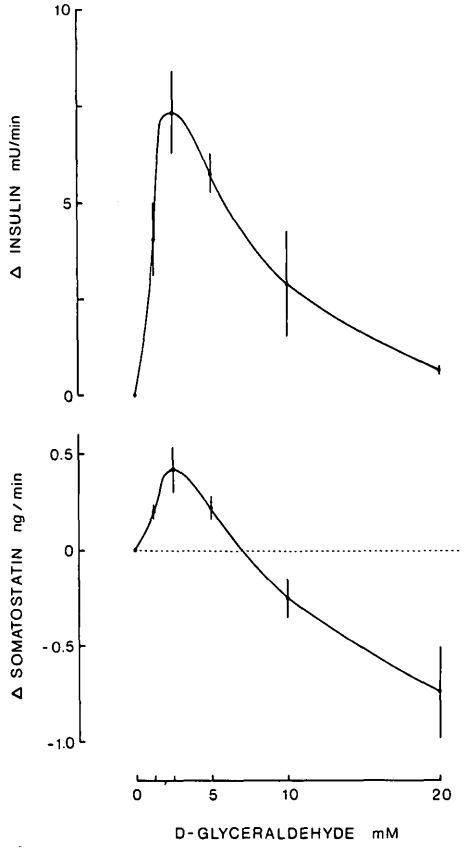
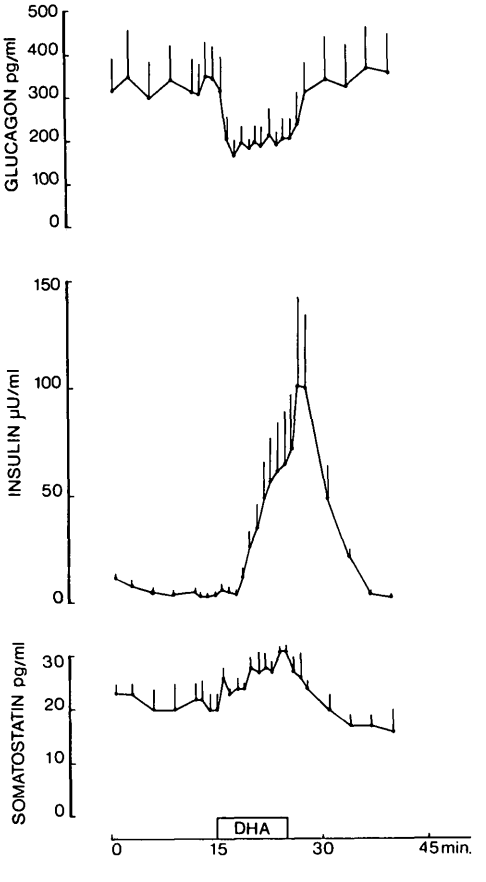


FIGURE 5. The effects of 11 mM dihydroxyacetone on the somatostatin, insulin, and glucagon release. Data expressed as mean ± SEM of four perfusion experiments.



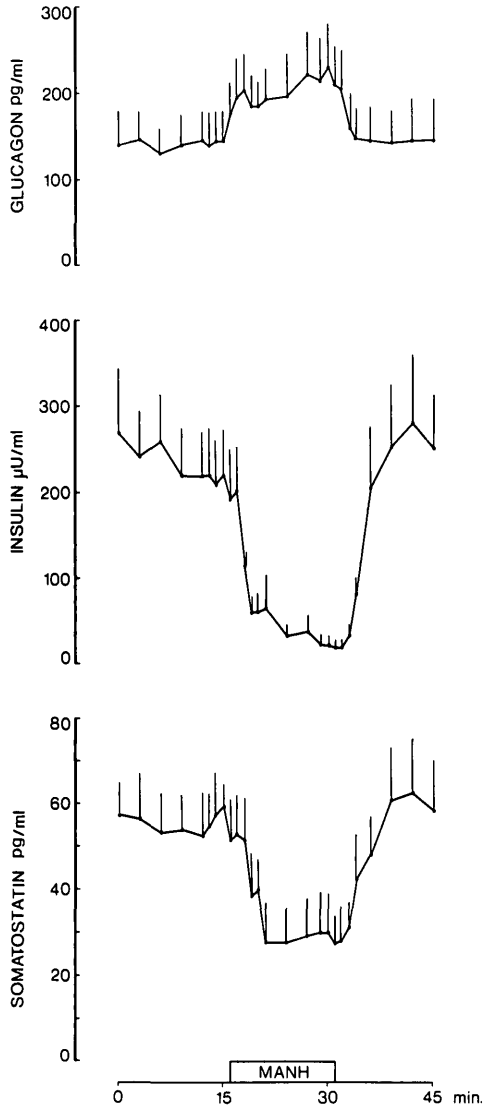


FIGURE 6. The effects of 5 mM mannoheptulose on the somatostatin, insulin, and glucagon release during perfusion with 8.3 mM glucose. Mean results ± SEM of four perfusion experiments.

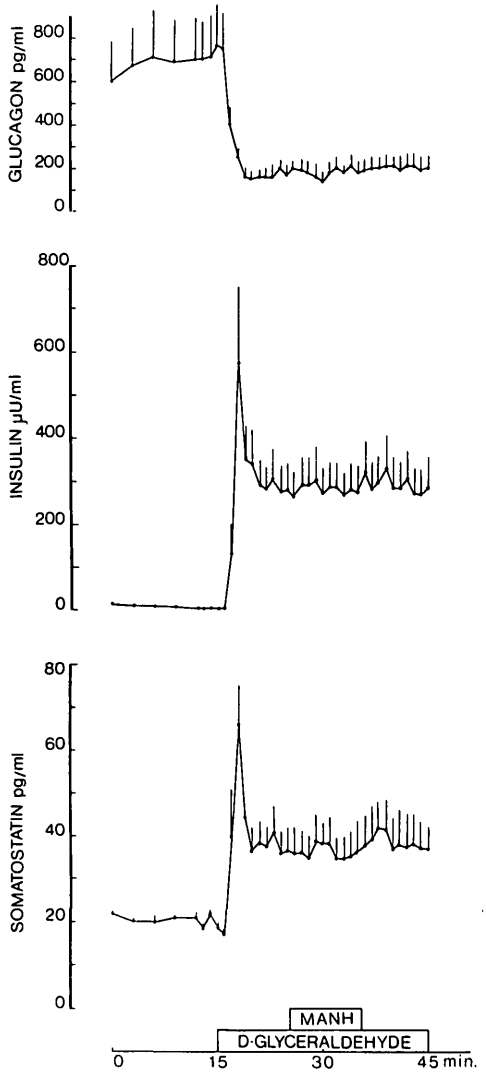


FIGURE 7. The effects of 5 mM mannoheptulose on the secretion of somatostatin, insulin, and glucagon during perfusion with 5 mM glyceraldehyde. Mean results ± SEM of four perfusion experiments.

Thus, no increase in somatostatin secretion could be detected in response to 5 mM dihydroxyacetone (unpublished observations). The kinetics of the D-cell secretion were similar whether 11 or 22 mM dihydroxyacetone were infused (unpublished results).

Effect of mannoheptulose on glucose- and glyceraldehyde-induced hormone release. Figure 6 demonstrates the effect of 5 mM mannoheptulose on islet hormone release during perfusion with 8.3 mM glucose. The addition of mannoheptulose immediately suppressed both somatostatin and insulin secretion by 35% ± 10% ($2P < 0.05$) and 62% ± 3% ($2P < 0.001$), respectively, while glucagon release increased by 44% ± 11% ($2P < 0.05$). The secretory rates returned to their previous control levels after the removal of mannoheptulose.

The effects of 5 mM mannoheptulose on the glyceraldehyde-induced hormone release were investigated in four perfusion experiments (Figure 7). In the absence of glucose, the introduction of 5 mM glyceraldehyde caused an immediate, biphasic increase in somatostatin (by 100% ± 31%, $2P < 0.05$) and insulin release, and inhibition of the glucagon level (by 59% ± 8%, $2P < 0.01$) as expected. In contrast to the effects upon the glucose-mediated hormone release, mannoheptulose did not affect the triose-induced hormone release from the D-, B-, or A-cells (Figure 7).

Comparison of the effects of equimolar concentrations of fructose, galactose, ribose, and glucose. Basal somatostatin and insulin levels were low and basal glucagon was high during perfusion with a glucose-depleted medium as compared with the levels obtained in the presence of glucose (Table 2). When the non- or low-metabolized sugars fructose, galactose, or ribose were investigated at equimolar concentrations of 8.3 mM, somatostatin, insulin, and glucagon release remained unchanged. Neither did a doubling of the concentrations to 16.6 mM of the three substances alter the islet hormone release (unpublished observations). For comparison, the glucose-induced, clearcut increase in somatostatin (by 54% ± 8%, $2P < 0.01$) and insulin, and the concomitant suppression in glucagon output by 32% ± 2% ($2P < 0.001$), is also given in Table 2.

TABLE 2
Effects of equimolar concentrations (8.3 mM) of galactose, ribose, fructose, and glucose upon islet hormone release

		Galactose			Ribose			Fructose			Glucose		
	Exp.	A	B	Δ	A	B	Δ	A	B	Δ	A	B	Δ
Somatostatin (pg/ml)	1	26 ± 1	19 ± 1	9% ± 14%	21 ± 1	22 ± 1	2% ± 3%	25 ± 1	29 ± 1	11% ± 7%	45 ± 2	67 ± 2	54% ± 8%
	2	44 ± 2	39 ± 1	NS	34 ± 1	37 ± 1	NS	43 ± 1	39 ± 1	NS	50 ± 0	67 ± 3	2P < 0.01
	3	77 ± 2	91 ± 3		117 ± 2	118 ± 3		111 ± 3	124 ± 2		114 ± 3	187 ± 10	
	4	18 ± 1	26 ± 2		35 ± 1	33 ± 1		55 ± 2	69 ± 2		61 ± 2	104 ± 6	
Glucagon (pg/ml)	1	68 ± 3	55 ± 3	−2% ± 5%	53 ± 3	58 ± 2	3% ± 2%	83 ± 4	73 ± 3	−9% ± 4%	52 ± 3	35 ± 2	−32% ± 2%
	2	143 ± 6	131 ± 4	NS	152 ± 6	157 ± 6	NS	152 ± 13	154 ± 6	NS	130 ± 7	92 ± 6	2P < 0.001
	3	334 ± 4	375 ± 20		344 ± 6	335 ± 6		393 ± 17	334 ± 18		308 ± 11	216 ± 21	
	4	157 ± 2	158 ± 3		152 ± 6	157 ± 6		118 ± 8	105 ± 4		160 ± 11	103 ± 7	
Insulin (μU/ml)	1	5 ± 1	4 ± 1		3 ± 0	3 ± 1		5 ± 1	3 ± 0		5 ± 1	86 ± 22	
	2	1 ± 0	0 ± 1		1 ± 1	2 ± 0		0 ± 0	0 ± 0		5 ± 1	145 ± 26	
	3	0 ± 0	0 ± 0		1 ± 0	0 ± 0		0 ± 0	0 ± 0		1 ± 0	462 ± 90	
	4	2 ± 1	2 ± 0		0 ± 0	0 ± 0		0 ± 0	0 ± 0		4 ± 1	571 ± 104	

A represents the average value (± SEM) of the last five 1-min hormone values just before the addition of the sugar.
B represents the mean value (± SEM) of the ten 1-min hormone values obtained during the entire sugar infusion.
Δ indicates the percent change in hormone secretion in response to the sugar administration, i.e., $\left(\frac{B - A}{A} \times 100\%\right)$.

DISCUSSION

The main purpose of this study was to determine whether the D-cell recognition of glucose as a secretory stimulus involves the metabolism of the sugar.

Glucose stimulates somatostatin release;[1-5] the results reported here demonstrate a sigmoidal relationship between the extracellular glucose concentration and the increase in the output of somatostatin. The D-cell threshold for glucose is close to 5 mM and the steep portion of the dose-response curve occurs between 5 and 10 mM, indicating that the secretory response is most sensitive to changes in glucose concentrations within the physiologic range. Insulin is stimulated and glucagon is suppressed by glucose. A differential sensitivity to glucose, however, exists between the A-cell on one hand and the B- and D-cell on the other. Thus the glucagon release is reduced by even the lowest glucose dose of 1.25 mM while approximately 5 mM glucose is needed to elicit insulin or somatostatin responses.

Several lines of evidence seem to indicate that the somatostatin-stimulating action of glucose is dependent on its metabolism.

First, the two trioses glyceraldehyde (at concentrations between 1.25 and 5 mM) and dihydroxyacetone are stimulants of somatostatin secretion in the absence of glucose. Both these compounds, entering the glycolytic pathway at the triose phosphate level, are suitable fuels for islet metabolism.[13-15] Some controversy does, however, exist concerning the stimulatory effect of glyceraldehyde. Schauder et al.[19] recently reported that 3 as well as 10 mM glyceraldehyde inhibits somatostatin release from incubated rat islets. Our results obtained at the higher level of the dose-response curve at 10 and 20 mM glyceraldehyde tally with such an inhibitory effect. The reduced secretory rate of somatostatin observed at high concentrations of glyceraldehyde may be due to an inhibitory effect on some components of the secretory machinery other than the glucose recognition system, e.g., through lowering of the normal ATP content of the islets.[13] The ATP lowering effect may account for the inhibitory effect of large concentrations of glyceraldehyde observed here. In the present study, it is evident that glyceraldehyde is unable to induce a secretory response of the same magnitude as that induced by glucose. It is therefore possible that the isolated islet preparation of Schauder et al.[19] is insufficiently sensitive to pick up the comparatively weak stimulatory effect of glyceraldehyde.

Glyceraldehyde is more efficient than dihydroxyacetone in terms of the concentration needed to initiate an increase in somatostatin secretion. Since glyceraldehyde is more avidly metabolized by pancreatic islets than dihydroxyacetone,[14] this difference is also consistent with the idea that metabolism is important for the glucose recognition. Another dissimilarity between the actions of the two trioses is the difference in kinetics of the somatostatin secretion. When the perfused dog pancreas is exposed to low doses of glyceraldehyde, the ensuing secretory response of the D-cell is biphasic (Figure 7) followed by a short-lived off-response after its withdrawal. In comparison, dihydroxyacetone elicits a gradual increase in the rate of somatostatin release, which returns to the basal level without any rebound phenomenon (Figure 5). As regards insulin release, the present observations confirm previous findings: dihydroxyacetone and glyceraldehyde are powerful stimulants.[13-15,20] However, increasing the concentrations of the latter above 10 mM attenuates the insulin responses.[14,15,20] In addition, we found that both dihydroxyacetone and glyceraldehyde suppress the glucagon release (Table 1).

Second, in the present study, in accordance with the results of Schauder et al.,[21] it has been demonstrated that mannoheptulose, which inhibits glucose phosphorylation in islets, also inhibits the glucose-induced somatostatin release. Thus the decrease in the somatostatin release may be due to a decreased rate of glucose utilization of the islets. In contrast to its effect on glucose metabolism, mannoheptulose does not influence the metabolism of glyceraldehyde, because the triose enters the glycolysis below the metabolic block.[13,15] Accordingly, glyceraldehyde effects are not inhibited by mannoheptulose. The data obtained on B-cell function are similar to those on the D-cell and conform with previous reports:[12-15] mannoheptulose inhibits the glucose[11,12] but not the glyceraldehyde-stimulated insulin release.[13-15] Furthermore, this report demonstrates that mannoheptulose counteracts the glucose-induced inhibition of glucagon secretion, whereas it is unable to reverse the suppression induced by glyceraldehyde.

Third, it is also in agreement with the idea that metabolism is essential for the stimulus recognition in that the D-cell secretion is left unaffected by the poorly metabolized sugars galactose, ribose, and fructose. Likewise, Patel et al.[22] failed to detect any stimulatory effect of galactose. As regards insulin secretion, it is in good agreement with most of the available data that the three sugars, in the absence of glucose, have no influence on insulin release.[23] Neither was the glucagon secretion affected by these compounds.

The present study thus indicates that metabolism of glucose within the D-cell is fundamentally involved in the process of glucose recognition and thereby in initiating the somatostatin release. The findings are thus analogous to the results of Ashcroft on the B-cell.[24] As yet it is not possible to pinpoint which aspect of the glucose metabolism that is important for the somatostatin secretion, nor to say which metabolite(s) initiate the secretory process of the pancreatic D-cell. An indirect effect of glucose on the D-cell via alterations in glucagon and/or insulin seems unlikely since the glucose-induced suppression of glucagon would tend to lower the somatostatin secretion, and insulin apparently does not directly affect the D-cell function.[25-27]

In conclusion, although the role of the intact glucose molecule is not erased from the scenario, a considerable body of evidence indicates that the metabolism of the glucose molecule is required to elicit the whole physiologic endocrine response of the D- as well as the B- and A-cells.

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