Glucose and Cyclic AMP as Stimulators of Somatostatin and Insulin Secretion From the Isolated, Perfused Rat Pancreas
A Quantitative Study

PIETRO P. G. GERBER, ELISABETH R. TRIMBLE, CLAES B. WOLLHEIM, ALBERT E. RENOLD, AND RALPH E. MILLER

SUMMARY

The secretory responses of beta and delta cells were compared in the isolated, perfused, rat pancreas. Insulin release was stimulated 50-fold and somatostatin (SRIF) secretion twofold when the glucose concentration was increased from 100 mg/dl to 300 mg/dl. When islet cyclic AMP (cAMP) was raised by 3-isobutyl-1-methylxanthine (IBMX), the secretion of SRIF was stimulated in a glucose-dependent manner (300 mg/dl > 100 mg/dl > 25 mg/dl). As expected, insulin release was also potentiated in a similar fashion. A difference in the glucose dependency of the cAMP effect was seen at 25 mg/dl glucose, where 0.25 mM IBMX enhanced the release of SRIF but not that of insulin. In contrast, at 300 mg/dl glucose, IBMX caused a greater potentiation of insulin release than of SRIF release. The release of insulin, when expressed in absolute terms, was stimulated more markedly than that of SRIF under most conditions tested. However, the expression of total hormone released during 30 min of stimulation as a percentage of tissue hormone content allowed a different interpretation of the results. For example, 2.1% and 1.8% of tissue insulin and SRIF contents, respectively, was released during exposure to 300 mg/dl glucose. Surprisingly, under basal conditions (100 mg/dl glucose), 1.0% of total SRIF content was released during 30 min compared with the release of only 0.04% of insulin. DIABETES *30*:40-44, January 1981.

The pancreatic islets exert a major regulatory function in the control of nutrient fluxes.[1] Since somatostatin inhibits insulin secretion, it is surprising that, with a few exceptions,[2] both insulin and pancreatic somatostatin release are stimulated by the same agents. However, beta and delta cells may have different sensitivities to certain stimuli in terms of threshold or magnitude of response. Therefore, we measured insulin and somatostatin release in response to two different stimuli, used at various concentrations either alone or in combination. In addition to the nutrient, glucose, the effects of raised cyclic AMP levels were tested by use of the phosphodiesterase inhibitor, 3-isobutyl-1-methylxanthine (IBMX). This agent raises pancreatic islet cyclic AMP levels under both basal and glucose-stimulated conditions.[3,4] The isolated, perfused rat pancreas was used, because this preparation preserves the microcirculation within the islet and, hence, the route by which stimuli normally reach the delta and beta cells.[5]

From the Institut de Biochimie Clinique, University of Geneva, Sentier de la Roseraie, 1211 Geneva 4, Switzerland.
Dr. Miller's present address is Albert Chandler Medical Center, College of Medicine, Department of Pharmacology, University of Kentucky, Lexington, KY 40536.
Address reprint requests to Dr. Elisabeth Trimble, Institut de Biochimie Clinique, Sentier de la Roseraie, 1211 Geneva 4, Switzerland.
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METHODS

Male Wistar rats, weighing 250-320 g, were fed normal laboratory rat chow. After overnight fasting, they were anesthetized with thiopental, 100 mg/kg i.p. The procedure used to isolate and perfuse the pancreas was that described by Penhos et al.[6] with minor modifications. The perfusions were carried out in a temperature-regulated chamber at 37°C. The pancreas was perfused with nonrecirculating medium at 4 ml per minute. The modified Krebs-Ringer bicarbonate buffer contained NaCl 121 mM, KCl 4.8 mM, $CaCl_2$ 1.0 mM, KH_2PO_4 1.2 mM, $MgSO_4$ 1.2 mM, $NaHCO_3$ 24.6 mM, dextran 4%, human serum albumin 0.2%, and aprotinin 400 KIU/ml. The basal perfusate contained, in addition, glucose 100 mg/dl or 25 mg/dl as indicated. The perfusing buffer was continuously gassed with a mixture of 95% O_2 and 5% CO_2; the partial pressure of oxygen in the buffer entering the pancreas was 450 mm Hg.

The preparative surgery required about 45 min, during which the rat breathed oxygen-enriched air. The time between ligation of the proximal aorta and the beginning of the arterial perfusion was a few seconds. The equilibration period, during which the pancreas was perfused with basal perfusate, was 30 min (−30 to 0 min). Baseline samples were taken at −2, −1, and 0 min. The stimulatory period lasted 30 min (0-30 min) and the poststimulatory period, 20

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min (30-50 min). Effluent samples were stored at −20°C until assayed for insulin and somatostatin (SRIF).

For the measurement of insulin and SRIF content, similarly treated rats were killed without pancreas perfusion. The pancreas and attached duodenum were removed and the tissue was extracted with acid ethanol by a modification of the Kenny technique[7] for insulin and SRIF content.

Insulin and SRIF were measured by radioimmunoassay using the charcoal separation technique.[8] Rat insulin and guinea-pig anti-pork insulin serum were used in the insulin assay.[9] In the SRIF assay, cyclic SRIF was used as standard, and N-tyrosylated SRIF, iodinated by the chloramine-T method,[10] was used as tracer after its purification with CM52 cellulose (column, 20 cm × 1 cm). The SRIF antiserum, raised in rabbits against SRIF conjugated to albumin by the glutaraldehyde method, showed no cross-reactivity with insulin, glucagon, pancreatic polypeptide, gastrin, motilin, secretin, or cholecystokinin-pancreozymin (the cross-reactivity studies were carried out by Dr. J. Ardill). SRIF standards were diluted in the same basal buffer as that used for the perfusion. The sensitivity of the assay was 15-20 pg/ml.

MATERIALS

Dextran T40 was obtained from Pharmacia Fine Chemicals AB, Uppsala, Sweden. Human serum albumin for perfusion was obtained from the Central Transfusion Laboratory, Swiss Red Cross, Bern, Switzerland. Aprotinin (Trasylol) was kindly provided by Prof. G. L. Haberland, Bayer A. G., Wuppertal, F. R. G. Three-isobutyl-1-methylxanthine (IBMX) was from Sigma Chemical Co., St. Louis, Mo. Rat insulin standard was obtained from Novo Research Institute, Bagsvaerd, Denmark; guinea-pig anti-pork insulin serum was a gift from Dr. H. H. Schöne, Farbwerke Hoechst, Frankfurt, F. R. G. Cyclic SRIF and N-tyrosylated SRIF were bought from Serono, Freiburg, F. R. G. SRIF antiserum was a generous gift from Dr. J. Ardill, Queen's University, Belfast, U. K.

Results were expressed as mean ± SEM of hormone output per minute or as integrated total areas and integrated incremental areas for the 30-min stimulation period.

The paired *t* test was used to evaluate the significance of stimulated secretion rates above basal rates.

RESULTS

Control experiments. When glucose concentrations were kept at 25 or 100 mg/dl throughout the entire perfusion, we found that stable values were reached at the −10 min sample, that is, 20 min after starting the perfusion (data not shown). Because of this, baseline samples were taken at −2, −1, and 0 min in subsequent experiments.

Effect of glucose on SRIF and insulin release. When the concentration of glucose in the perfusate was increased from 100 to 300 mg/dl, the rate of SRIF secretion increased by about 100% as early as 1 min after the change of the glucose concentration ($P < 0.02$). The rate of release reached a peak at 2 min and decreased slightly thereafter, but remained above baseline for the remainder of the stimulation period (Figures 1 and 2).

The stimulant effect of glucose on SRIF secretion was also significant when expressed as the integrated incremental area of SRIF release above baseline ($P < 0.02$; Table 1, line A). Figure 1 also shows that the rate of SRIF release returned to prestimulatory levels 2 min after the reintroduction of basal perfusate containing a glucose concentration of 100 mg/dl.

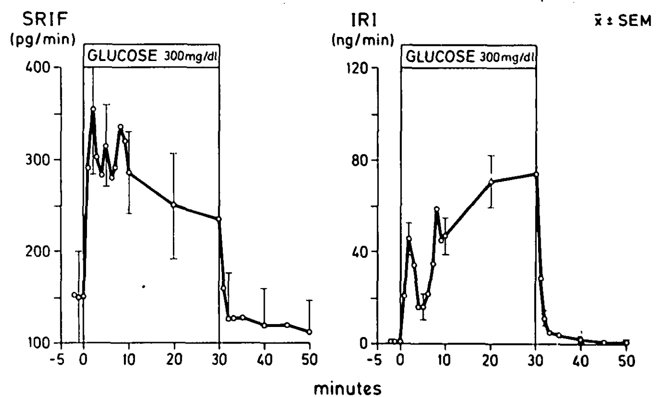

FIGURE 1. The effect of a change in the perfusing glucose concentration from 100 to 300 mg/dl on mean (± SEM) somatostatin and insulin secretion rates from the isolated, perfused, rat pancreas. At the high glucose concentration, somatostatin secretion rates were significantly greater than at the low glucose concentration ($P < 0.05$) at all times tested, except at 6, 8, and 30 min. Insulin secretion rates were also significantly greater during perfusion with 300 mg/dl than with 100 mg/dl glucose ($P < 0.05$), except at 5 min, the nadir between first and second phase secretion (N = 6).

Insulin release rose promptly after the increase in glucose concentration of the perfusate. The peak of the first phase occurred at 2 min, and a nadir at 4-5 min was followed by a secondary rise in secretion rate. When the glucose concentration was decreased to prestimulatory levels, there was a prompt fall in the insulin secretion rate within 1 min and basal release rates were approached 4 min later. There was a 57-fold increase in insulin secretion. Because of the low basal secretion rate, subtraction of basal secretion did not alter the total area of insulin secretion over 30 min (Table 1, line A).

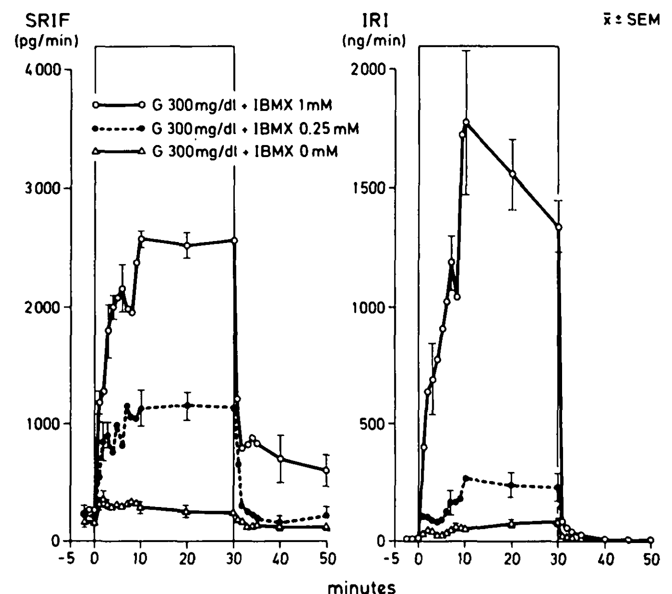

FIGURE 2. Somatostatin and insulin secretion from the isolated, perfused, rat pancreas in response to 300 mg/dl glucose and 3-isobutyl-1-methylxanthine (IBMX) (x̄ ± SEM). Basal perfusate contained 100 mg/dl glucose. During 0–30 min the perfusate contained either 300 mg/dl glucose plus 1 mM IBMX (N = 3), or 300 mg/dl glucose plus 0.25 mM IBMX (N = 5), or 300 mg/dl glucose alone (N = 6).

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TABLE 1
Integrated total and integrated incremental areas (0–30 min) and molar ratios for somatostatin and insulin release during stimulation with glucose alone or glucose and IBMX*

	Glucose (mg/dl)	IBMX (mM)	N	Somatostatin (ng/30 min) Total area (0–30 min)	Incremental area (0–30 min)	Total output† as % of tissue content	Insulin (μg/30 min) Total area (0–30 min)	Incremental area (0–30 min)	Total output‡ as % of tissue content	Somatostatin/ insulin§ (molar ratio)
A	300	—	6	8.1 ± 1.3	3.6 ± 1.0	1.8	1.6 ± 0.3	1.60 ± 0.2	2.1	0.019 ± 0.004
B	300	0.25	5	31.6 ± 4.1	25.2 ± 2.8	6.9	6.0 ± 1.3	6.0 ± 1.3	7.8	0.022 ± 0.005
C	300	1.0	3	69.0 ± 2.1	61.4 ± 1.9	15.1	40.4 ± 3.4	40.4 ± 3.4	52	0.007 ± 0.0005
D	100	0.25	3	34.2 ± 4.3	20.3 ± 6.5	7.5	4.13 ± 0.6	4.12 ± 0.8	5.3	0.033 ± 0.008
E	100	1.0	3	48.8 ± 7.0	38.9 ± 8.0	10.6	8.8 ± 1.7	8.7 ± 1.6	11.3	0.020 ± 0.002
F	25	0.25	4	12.6 ± 0.9	4.1 ± 0.6	2.8	0.06 ± 0.03	0.04 ± 0.04	0.08	0.787 ± 0.170
G	25	1.0	5	18.5 ± 3.6	7.4 ± 2.1	4.0	0.28 ± 0.09	0.28 ± 0.10	0.4	0.247 ± 0.057

* IBMX, 3-isobutyl-1-methylxanthine.
† Total tissue content of somatostatin: 457 ± 32 ng (N = 6).
‡ Total tissue content of insulin: 77.7 ± 7.0 μg (N = 6).
§ Somatostatin/insulin molar ratio under basal conditions—100 mg/dl glucose: 1.57 ± 0.47 (N = 20); 25 mg/dl glucose: 6.44 ± 2.38 (N = 9).

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EFFECT OF IBMX ON SRIF AND INSULIN RELEASE AT VARIOUS GLUCOSE CONCENTRATIONS

Glucose 300 mg/dl (Figure 2, Table 1). In these experiments, the concentration of glucose in the perfusate was raised from a basal of 100 mg/dl to 300 mg/dl, and IBMX, 0.25 mM or 1.0 mM, was added at the same time. [For comparison, data from Figure 1 (no IBMX) are plotted in Figure 2.] In the presence of 0.25 mM IBMX, there was a marked stimulation of SRIF secretion at 1 min, the rate of release increased gradually thereafter, and maximal rates, about four times basal, were attained by 10 min and remained unchanged until 30 min. A similar pattern of SRIF release was seen with 1 mM IBMX. Under these conditions the maximal rate was about nine times the basal.

To compare hormone release under different stimulatory conditions, we evaluated the incremental areas above baseline. When we compared the increases in SRIF secretion with the basal secretion, glucose 300 mg/dl alone caused a 0.8-fold (80%) increase in SRIF secretion (Table 1, line A). When IBMX, 0.25 mM or 1.0 mM, was added at the same time as 300 mg/dl glucose, there was a fourfold and eightfold increase in SRIF secretion, respectively, relative to the appropriate basal secretion (Table 1, lines B and C).

The combination of 0.25 mM IBMX and 300 mg/dl glucose caused insulin secretion to increase at as early as 1 min, with maximal secretion rates being achieved at 10 min. Thereafter, the secretion rate remained stable until the end of the stimulation. Similar, but more marked, changes in insulin secretion were found on addition of 1 mM IBMX.

When IBMX, 0.25 mM or 1.0 mM, was added together with 300 mg/dl glucose, there were 111-fold and 1122-fold increases in integrated insulin secretion, respectively, relative to the appropriate basal secretion (Table 1, lines B and C). It can also be seen in Figure 2 that there was an abrupt fall in the secretion rate of both insulin and SRIF when the basal perfusate was reintroduced.

Glucose 100 mg/dl (Figure 3, Table 1). The concentration of glucose in the perfusate was kept constant throughout the experiments, and IBMX, 0.25 mM or 1.0 mM, was added during the stimulation period. There was a prompt increase in the SRIF secretion rate at 1 min after introduction of IBMX, 0.25 mM or 1.0 mM, and a prompt decrease in the secretion rate when the basal perfusate was reintroduced. At the lower concentration of IBMX, the release pattern of SRIF was biphasic during the stimulation period.

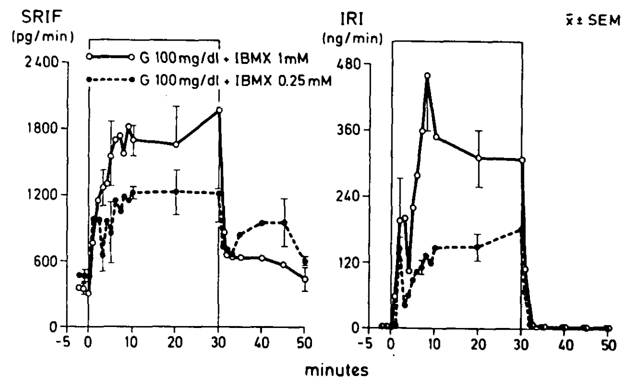

FIGURE 3. Somatostatin and insulin secretion from the isolated, perfused, rat pancreas in response to 100 mg/dl glucose and 3-isobutyl-1-methylxanthine (IBMX) (x̄ ± SEM). Perfusate contained 100 mg/dl glucose throughout. During 0–30 min, 1 mM IBMX (N = 3) or 0.25 mM IBMX (N = 3) was added.

When we expressed the results as integrated incremental release, IBMX 0.25 mM and 1 mM caused 1.5-fold and 4-fold increases, respectively, in SRIF secretion above the appropriate basal secretion rates (Table 1, lines D and E).

The insulin release profiles are shown in the right-hand panel of Figure 3. Under both conditions, insulin release was stimulated and the output with 1 mM IBMX was twice that seen with 0.25 mM (Table 1, lines D and E).

Glucose 25 mg/dl (Figure 4, Table 1). In this series of experiments the glucose concentration during the prestimulatory period was 25 mg/dl, and this concentration of glucose was maintained throughout the experiment. Under these conditions, IBMX both 0.25 mM and 1.0 mM caused small, but significant, increases in integrated incremental SRIF output ($P < 0.01$ and $P < 0.05$, respectively, over 30 min; Table 1, lines F and G).

Insulin release was not significantly stimulated by 0.25

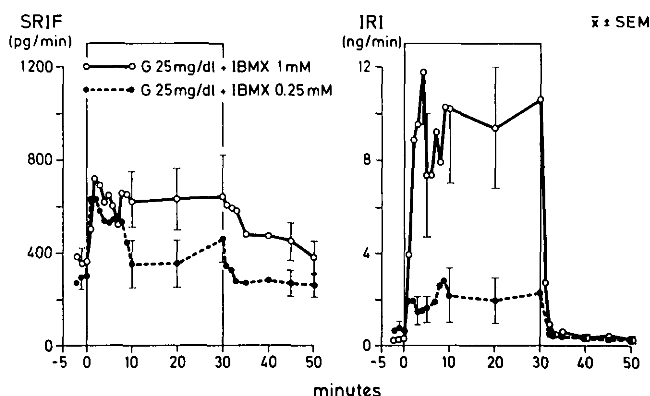

FIGURE 4. Somatostatin and insulin secretion from the isolated, perfused, rat pancreas in response to 25 mg/dl glucose and 3-isobutyl-1-methylxanthine (IBMX) ($\bar{x}$ ± SEM). Perfusate contained 25 mg/dl glucose throughout. During 0–30 min, 1 mM IBMX (N = 5) or 0.25 mM IBMX (N = 4) was added.

mM IBMX ($0.3 < P < 0.4$), while 1.0 mM IBMX did cause a significant increase in the integrated incremental secretion ($P < 0.05$).

INSULIN AND SRIF RELEASE EXPRESSED (A) IN MOLAR RATIOS AND (B) AS A PERCENTAGE OF THE TISSUE HORMONE CONTENT

In view of the marked differences in the magnitude of the secretory responses of insulin and SRIF to the various stimulatory conditions, we felt it important to express their release in molar ratios and as a percentage of tissue hormone content, as well as in absolute release rates.

Molar ratio of SRIF to insulin secreted (Table 1). At glucose 25 mg/dl and 100 mg/dl (in the absence of IBMX) the molar ratio of secreted SRIF to insulin was greater than 1. In the presence of either high glucose alone or IBMX at all glucose concentrations the SRIF to insulin ratio was less than 1. The lowest ratio was found under conditions of maximal stimulation, i.e., at 300 mg/dl glucose and 1 mM IBMX (see Table 1).

Hormone secretion as a percentage of tissue hormone content. In experiments in which we increased the glucose concentration from 100 to 300 mg/dl (Figure 1 and Table 1, line A), we calculated the basal hormone output over 30 min (i.e., the difference between total and incremental output expressed as a percentage of tissue hormonal content, also shown in Table 1). Under these conditions, basal SRIF output was 1.0% of total tissue content and basal insulin output was 0.04%. In contrast to these differences in basal output, the total output of SRIF and insulin, when stimulated with 300 mg/dl glucose, was similar (1.8% and 2.1%, respectively). The total outputs of SRIF and insulin were also similar when expressed as percentages of total tissue content during stimulation with IBMX 0.25 mM and 1 mM at glucose 100 mg/dl and also when stimulated with IBMX 0.25 mM at glucose 300 mg/dl. However, when stimulated with IBMX 1 mM and glucose 300 mg/dl, the insulin output was much greater than that of SRIF (52% and 15%, respectively). On the other hand, at glucose 25 mg/dl in the presence of both concentrations of IBMX, the somatostatin output was distinctly greater than that of insulin when expressed in this way (Table 1).

DISCUSSION

The present results show that an increase of glucose concentration from 100 mg/dl to 300 mg/dl caused a sustained stimulation of somatostatin release. The effect of glucose appears more unequivocal than that observed in other preparations of the perfused rat pancreas[11,12] and was similar to that reported for the perfused dog pancreas.[13] The timing of the onset of glucose-induced somatostatin release appeared similar to that for glucose-induced insulin release. However, while insulin was released according to the well-known biphasic pattern, with a gradually increasing second phase, the pattern of somatostatin release was not clearly biphasic.

The phosphodiesterase inhibitor, IBMX, which raises cellular cyclic AMP levels, caused somatostatin release at low, intermediate, and high glucose concentrations. Glucose and cyclic AMP acted synergistically on somatostatin as well as insulin release, e.g., 1 mM IBMX caused eight times more somatostatin release at 300 mg/dl glucose than at 25 mg/dl glucose. These results indicate a possible interplay between the nutrient, glucose, and the activation of the adenylate cyclase-cyclic AMP system. This may have physiologic importance, since activation of adenylate cyclase by β-adrenergic or glucagon stimulation is associated with increased somatostatin release.[14,15] Although the secretions of insulin and somatostatin in response to raised cyclic AMP levels depend on glucose, there may be a different glucose threshold for release of the two hormones. Thus, at 25 mg/dl glucose, 0.25 mM IBMX did not alter insulin secretion significantly, while the increment in somatostatin output was as great as that found with 300 mg/dl glucose alone. It is possible that IBMX increases the cAMP levels of beta and delta cells to different extents. Since at present the cAMP contents of beta and delta cells cannot be measured separately, the possibility cannot be excluded.

An apparent difference between delta and beta cell responses to IBMX stimulation was that, in the presence of glucose 100 mg/dl and 300 mg/dl, the induced fold increase in insulin secretion was much greater than that for somatostatin secretion. A different perspective of delta and beta cell secretory sensitivity was found by examining the molar ratios of somatostatin to insulin secreted under basal and stimulated conditions. At low and intermediate glucose concentrations in the absence of IBMX, the molar ratio of somatostatin to insulin secreted was greater than 1. By contrast, at high glucose concentrations, or in the presence of IBMX at all glucose concentrations, the somatostatin to insulin ratio was less than 1 (see Table 1). However, when we calculated hormone secretion as a percentage of tissue hormone content, we saw that, under many conditions of cellular stimulation, the beta and delta cells secreted similar percentages of their total hormone content (see Table 1, lines A, B, D, and E). In view of the vast differences in secretion rate when expressed in absolute terms, we were surprised to find that the stimulated release, expressed as a percentage of tissue content, was, under most conditions, similar for beta and delta cells. This might suggest that at the cellular level the stimulated secretory activity was similar for the two types of cell. By contrast, at a low glucose concentration, the delta cells secreted a greater percentage of their hormonal content than did beta cells. It is possible, therefore, that the conditions occurring at low glucose concentrations

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may be more conducive to somatostatin inhibition of insulin release than the conditions found at higher glucose concentrations. It has been shown by others using somatostatin antiserum that somatostatin may, indeed, inhibit insulin release at low and intermediate glucose concentrations.[16,17] Alternatively, it may well be that the relatively low rate of insulin release at low glucose concentrations may be more a reflection of the marked glucose sensitivity of the beta cell than a result of paracrine inhibition of insulin release by somatostatin.

In conclusion, the data presented here show clearly that the potentiating effect of cAMP on delta cells depends on the dose, as it does for beta cells. Whether this and the many other similarities between delta and beta cell responses to various stimuli are due to direct responses of these cells separately, or whether there are, in addition, local coupling devices[18,19] between the beta and delta cells which partially control their responses, cannot be decided on the results of these experiments.

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