REVERSAL OF SOMATOSTATIN INHIBITION OF INSULIN SECRETION BY CALCIUM[1,2]

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SUMMARY: Somatostatin infusion inhibits insulin secretion by perfused rat pancreases. This inhibition is reversed by elevating Ca^{++} from its control 4.6 meq/l to 8 meq/l or 11 meq/l.

Somatostatin (1), the hypothalamic inhibitor of pituitary growth hormone, has been shown to inhibit the secretion of a number of other hormones as well. Among these are insulin (2, 3), glucagon (4), and TSH (5). Since the presence of Ca^{++} is essential for normal secretory processes of various hormones, including epinephrine (6), cortisone (7), and insulin (7, 8), it occurred to us that the diversity of hormonal secretions inhibited by somatostatin might involve antagonism or inactivation of Ca^{++} and that elevating the concentration of Ca^{++} above physiological limits might reverse

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the somatostatin inhibition of hormonal secretions. In this communication, we report the reversal of somatostatin inhibition of insulin secretion using the isolated perfused rat pancreas preparation.

EXPERIMENTAL

The preparation, perfusion medium, and insulin assay were those previously described (9). The perfusion medium contained 4.6 meq/l of Ca^{++}. The design of the experiment was as follows. After establishing perfusion through the preparation and allowing ten minutes for equilibration and temperature stabilization, the pancreas was stimulated by elevating the glucose concentration of the perfusate to 300 mg/100 ml. This was continued for 60 minutes. After 15 minutes of glucose stimulation, somatostatin was introduced to produce a somatostatin concentration of 50 ng/ml of perfusate, and this addition was continued for 30 minutes. After ten minutes of somatostatin infusion, additional Ca^{++} as $CaCl_2$ was introduced to produce total Ca^{++} concentration of 8 meq/l (2 experiments) or of 11 meq/l (2 experiments). Following ten minutes of elevated Ca^{++} concentration, it was dropped to the original level of 4.6 meq/l and infusions of somatostatin (50 ng/ml) and glucose (300 mg/100 ml) were continued for 10 minutes. Somatostatin was then stopped and glucose alone was continued for a final 15 minutes. Somatostatin was synthesized as previously described (10) and kindly put at our disposal by Dr. Choh Hao Li.

RESULTS AND DISCUSSION

Figure 1 shows the average results of the experiments in which Ca^{++} was elevated to 8 meq/l. The data from the two preparations were

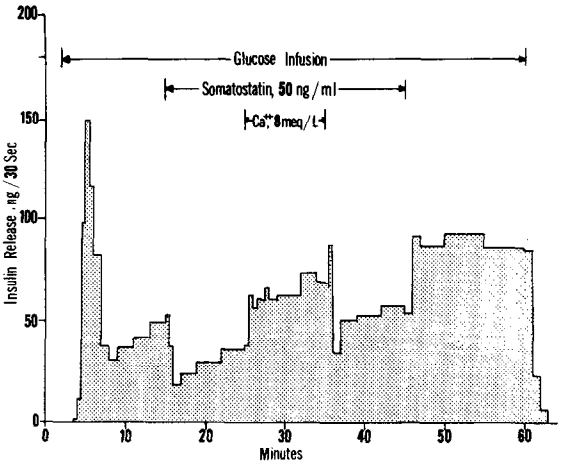

Figure 1: Time course of insulin secretions by two rat pancreas preparations in response to a constant glucose infusion (300 mg/100 ml). Ca^{++} elevated to 8 meq/l during the middle 10 minutes of a 30 minute period of somatostatin infusion (50 ng/ml).

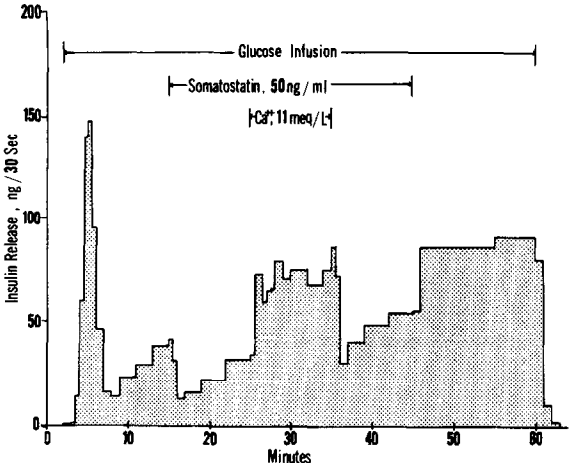

Figure 2: Time course of insulin secretions by two rat pancreas preparations in response to a constant glucose infusion (300 mg/100 ml). Ca^{++} elevated to 11 meq/l during the middle 10 minutes of a 30 minute period of somatostatin infusion (50 ng/ml).

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in close agreement and clearly showed a) the abrupt drop in secretory rate following introduction of somatostatin, b) the abrupt rise in secretory rate when Ca^{++} concentration was elevated and the abrupt fall when the original concentration of Ca^{++} at 4.6 meq/l was restored, and finally, c) the abrupt rise in secretory rate when somatostatin infusion was stopped,

quite comparable to our previous report (3). Figure 2 shows the average secretion of insulin in the two experiments in which Ca^{++} was elevated to 11 meq/l. Again the data from the two preparations were in close agreement and the greater amount of insulin was secreted during the period of the higher Ca^{++} concentration. During the 10 minute period when Ca^{++}concentration was 8 meq/l, the total amount of insulin secreted was 0.46 μg greater than the average of the proceeding and following 10 minute periods. When the Ca^{++}concentration was raised to 11 meq/l, the increase in total secretion was 0.75 μg for the 10 minute period. It is evident that the Ca^{++} effect is dose-dependent.

These results are in accord with our earlier reports that the amount of insulin secreted both in the initial rapid phase of secretion (8) and the total secreted during a 60 minute stimulus (9) are a function of perfusate Ca^{++}concentration (16 meq/l was the highest concentration used in these early experiments). Control experiments were carried out in which Ca^{++} was elevated to 11 meq/l for 10 minutes during a 60 minute stimulation by glucose at 300 mg/100 ml, but in the absence of somatostatin. This produced an increase in the rate of insulin secretion, confirming our prior results (8,9).

The data presented here show that increased Ca^{++} concentration is capable of potentiating glucose-induced insulin secretion, and furthermore, that such an increased Ca^{++}concentration reverses somatostatin inhibition of glucose-induced insulin secretion. These data strongly suggest that the mechanism of somatostatin inhibition of secretory processes may be involved with Ca^{++} inactivation or binding at some step of the secretory process.

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