DIRECT INHIBITION OF INSULIN SECRETION BY SYNTHETIC SOMATOSTATIN

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SUMMARY: Synthetic somatostatin has been found to significantly inhibit glucose-induced insulin secretion by the perfused rat pancreas. This inhibition was observed to be rapidly reversible.

The existence of a hypothalamic factor capable of inhibiting growth hormone (somatotropin) secretion was reported by Krulich et al. (1). Subsequent investigations by Guillemin and co-workers resulted in the isolation of a polypeptide (somatostatin) from the ovine hypothalamus which possesses the ability to suppress the release of pituitary growth hormone (2, 3). Somatostatin has been synthesized by both the solid-phase (2, 4, 5) and the solution (6) methods.

Recent inquiries concerning the possible effects of somatostatin on other organ systems have been directed towards the pancreas. Alberti et al. (7) reported that somatostatin suppresses a glucose-induced rise of plasma insulin in humans and inhibits insulin secretion by perfused canine pancreases. We report herein a direct inhibiting effect of synthetic somatostatin on glucose-induced insulin secretion by the perfused rat pancreas.

RESULTS AND DISCUSSION

Figure 1 illustrates the time course of insulin secretion in response

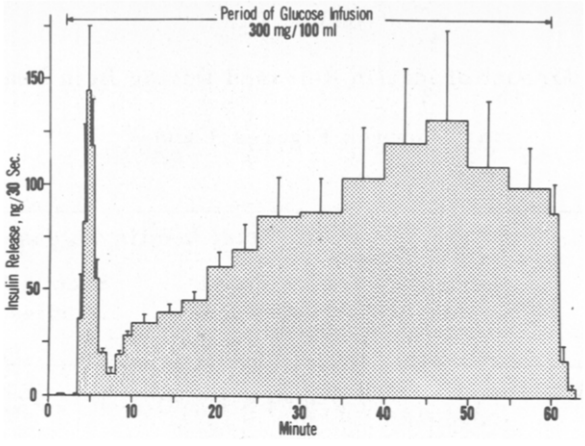

Figure 1: Time course of insulin secretion by 4 rat pancreas preparations in response to a constant glucose infusion (300 mg/100 ml) given from minutes 2 through 60. Mean insulin release is shown as ng/30 sec ± standard error.

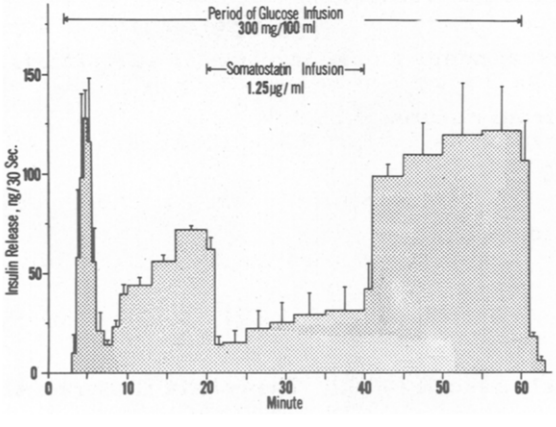

Figure 2: Time course of insulin secretion by 4 additional pancreas preparations in response to glucose (300 mg/100 ml) infused from minutes 2 through 60. Somatostatin was infused from minutes 20 through 40 at a rate to produce a concentration of 1.25 µg/ml. Mean insulin release is shown as ng/30 sec ± standard error.

to a constant glucose infusion of 300 mg/100 ml of perfusate, given from minutes 2 through 60. Insulin was determined by the radioimmunochemical method of Grodsky and Forsham (8), using the perfused rat pancreas

Table I

Total Amount of Insulin Released During Both Phases

as Shown in Figures 1 and 2

Condition	Dose μg/ml	Total Insulin Release [a] First Phase Minutes 2-8 μg	Second Phase Minutes 21-40 μg	p [d]
Glucose Stimulation [b]	0	0.50 ± 0.12 (4)	3.30 ± 0.65 (4)	
Glucose Stimulation [b] plus Somatostatin Infusion [c]	1.25	0.53 ± 0.06 (4)	0.94 ± 0.37 (4)	0.02
	0.25	0.67 ± 0.09 (3)	1.18 ± 0.61 (3)	0.05
	0.05	0.44 ± 0.04 (3)	1.50 ± 0.02 (3)	<0.05

[a] Mean ± standard error; number of pancreases in parenthesis.

[b] 300 mg per 100 ml from minutes 2-60.

[c] From minutes 21-40

[d] Compared with the control group.

preparation previously described (9). These data illustrate the typical biphasic pattern of insulin secretion characterized by an early transient release phase followed by a secondary rising phase of secretion as reported by Curry et al. (9).

Figure 2 shows mean insulin secretion (ng/30 sec ± SE) by four additional rat pancreas preparations which were stimulated by glucose in the same manner as those presented in Figure 1. In addition, synthetic somatostatin (4) was infused from minutes 20 through 40 at a constant rate with a perfusate concentration of 1.25 μg/ml. Within one minute following

somatostatin infusion, insulin secretion was suppressed dramatically by approximately 60 ng/30 sec, or about 80%. Although this depression continued throughout the entire period of somatostatin infusion, it is interesting to note that a moderate increase in secretory rate occurred. However, once the somatostatin infusion was stopped, insulin secretion rapidly increased by a factor of about 70 ng/30 sec. This reversal of inhibition occurred within approximately one minute.

The data are summarized in Table I. During the secretory phase when somatostatin was infused (minutes 21-40), insulin secretion was significantly depressed when compared to the control preparations. As little as 0.05 μg of somatostatin caused a decrease in insulin secretion from 3.3 to 1.5 μg in twenty minutes. In addition, the inhibiting effect of somatostatin is dose dependent. The data presented herein illustrate that somatostatin rapidly and directly inhibits insulin secretion in the rat and that this suppression is rapidly reversible.

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