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Research Article

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Uniphasic Insulin Responses to Secretin Stimulation in Man

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A B S T R A C T   Secretin-stimulated insulin release was studied in normal subjects. In response to rapid intravenous injections (pulses) of secretin, insulin levels reached a peak between 2 and 5 min and returned to basal levels with 15 min. In contrast to large glucose pulses, increasing secretin pulses did not elicit sustained or prolonged insulin responses. In addition, insulin responses to a pulse and infusion were essentially identical with that of a pulse alone. Increasing secretin pulses given in 1 day were associated with decreasing insulin responses but not when the same pulses of secretin were given over a 2 day period. When time was the sole variable, insulin responses progressively decreased after identical 15-U secretin pulses given every 30 min, but were unchanged when the interval was 105 min. These observations indicate that secretin in contrast to glucose stimulates insulin release which is uniphasic. They suggest that release occurs only from a stored, readily available pool. This insulin pool appears to be relatively small and can be discharged faster than it refills.

INTRODUCTION

Insulin secretion has been noted to be significantly increased after an oral glucose load compared with an identical amount of glucose given intravenously (1). Recent investigation has focused on gastrointestinal factors in an effort to explain this difference. Of the intestinal hormones studied, secretin has been found among the most potent insulin-stimulating substances (2). It has been shown to stimulate insulin release both in vitro and in vivo (3, 4), the accumulated data suggesting that biologically active insulin is released very rapidly following either intravenous secretin administration (2) or by substances known to stimulate endogenous secretin release (5).

In the past several years the concept of insulin release following glucose has been modified from an assumption of simple linearity to a more complex multiphasic secretory pattern (6, 7). We have recently proposed a two pool mechanism which attempts to resolve some of the ambiguities of glucose-stimulated insulin release in man (8, 9). The first of these pools is a small storage pool of readily available insulin which responds immediately to changes in the blood glucose level. The second pool responds more slowly to changes in glucose metabolism and its secetory pattern is manifested by the basal and steady-state insulin levels.

The similarity between our observations of acute insulin responses to glucose (8, 10) and the rapid secretin-stimulated responses reported by others (4, 5), prompted the further characterization of the pattern of insulin release following secretin administration.

METHODS

All subjects had no family history of diabetes, were less than 115% ideal body weight according to Metropolitan Life Insurance Company tables, and were studied at bed rest on the Clinical Research Center of the University Hospital after overnight (12 hr) fast. After placement of a butterfly needle in an antecubital vein and its patency maintained by a slow drip of 0.85% saline, four base line samples for glucose and immunoreactive insulin (IRI) were obtained during the following 60 min. Normal subjects were separated into five groups. The first group of five subjects received rapid intravenous injections (pulses) of secretin[1] every 75 min in the following doses: 10, 25, 75, 150, and 300 U. The second group of four subjects received secretin pulses over 2 days after a 60 min basal period on each day. The 1st day 10-U and 75-U pulses were administered; on the 2nd day a 300 U pulse of secretin was administered. A third group of four subjects were given a priming secretin dose of 15 U immediately followed by a 25 min infusion of 3 U/min for a total of 90 U. This method has been shown by Chisholm, Young, and Lazarus to achieve reasonably constant plasma secretin levels as measured by an immunoassay (5). A fourth group of six subjects received only 15-U pulses during the following time intervals: the first two pulses were separated by 105 min; the second, third, and fourth pulses were each sepa-
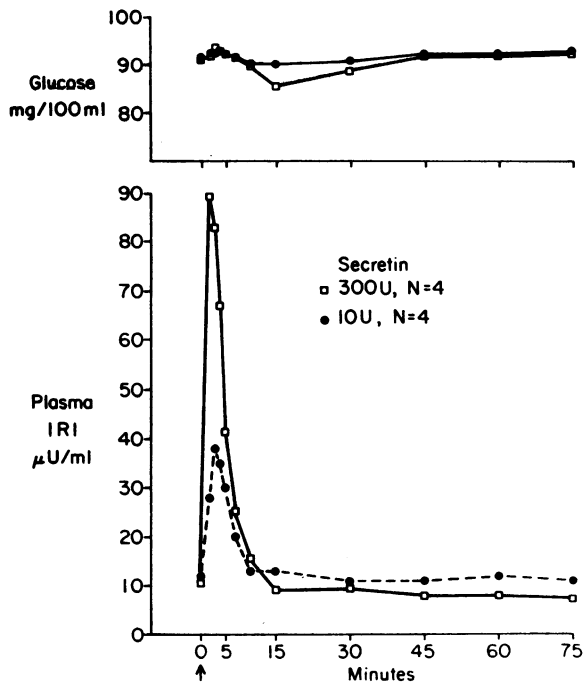
FIGURE 1 Mean glucose and insulin responses to small and large secretin pulses.
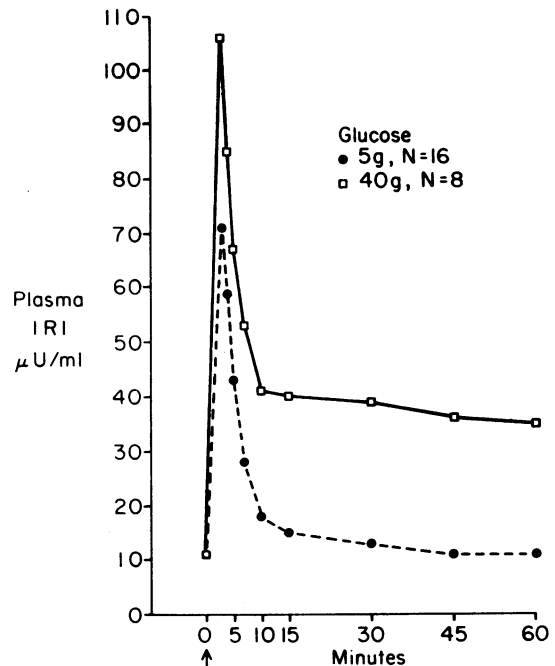

FIGURE 2 Mean insulin responses to small and large glucose pulses.

rated by a 30 min interval. A fifth group of 16 normal subjects received 5-g glucose pulses. After the insulin and glucose levels had returned to essentially the prestimulated level, eight of these subjects received a 40 g glucose pulse.[2]

The injection time in all studies was within 15 sec except the 40 g glucose pulse which was administered in 30–40 sec. Samples were obtained at 2, 3, 4, 5, 7, 10, and 15 min and every 15 min thereafter, using the midpoint of injection as zero time for each pulse. Plasma glucose was measured by the AutoAnalyzer ferricyanide method and serum insulin, by a modification of a double antibody technique (11).

Calculations. Estimates of the acute insulin response were determined by the mean increment above basal from the 2 through 5 min insulin values (2–5' mean Δ IRI μU/ml).

RESULTS

I. General characteristics of the insulin response to secretin compared to that of glucose. Following a small (10 U) secretin pulse plasma IRI levels rose rapidly, and were detectable at 2 min with a peak within 5 min followed by a rapid return to basal levels by 15 min (Fig. 1). With a large (300 U) secretin pulse (Fig. 1), the plasma insulin response was greater but the timing was identical with that noted above. Although a similar early rapid insulin response was seen to a 5 g glucose pulse, the response to a 40 g glucose pulse (Fig. 2), in marked contrast, remained elevated much longer than the total 15 min secretin response, indicating a major dif-

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[2] Data in preparation.

ference in the later phases of the insulin response to large glucose pulses.

Although no change in plasma glucose was observed to the 10 U secretin pulse, the 300 U secretin pulse was associated with a decline in the plasma glucose level between 7 and 30 min, which was statistically significant ($P < 0.05$) at 15 min.

II. The acute insulin response to a pulse vs. a constant secretin stimulus. The rapid insulin output following a 15 U pulse in six normal subjects was compared with the insulin response subsequent to a 15 U secretin pulse
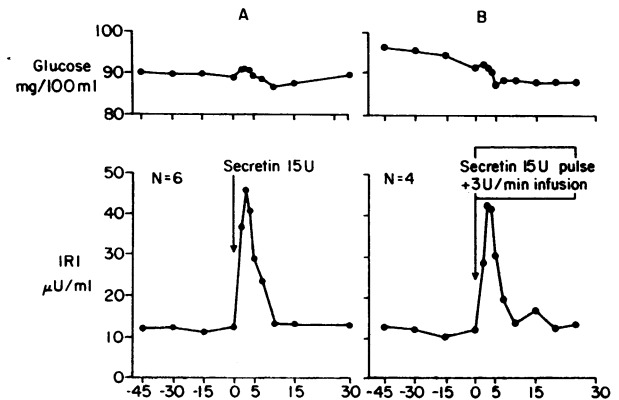

FIGURE 3 Mean insulin responses to a secretin pulse (A) and pulse plus infusion (B).
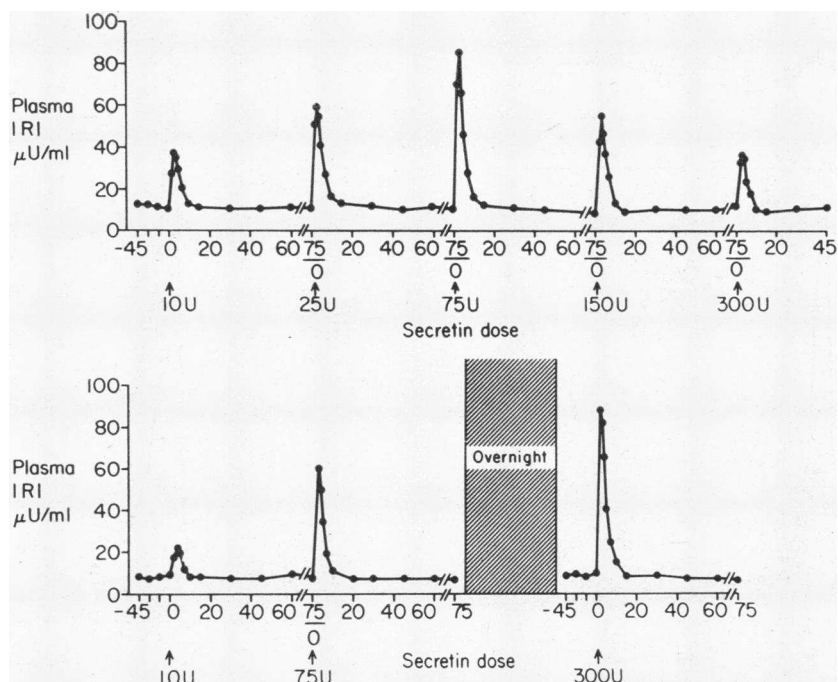
FIGURE 4 Mean insulin responses to graded secretin pulses given during a 1 day study (top) and during a 2 day study (bottom).

plus a 3 U/min infusion for 25 min in another group of four normal subjects (Fig. 3). The transient characteristic insulin response following a 15 U was unaltered despite continuously elevated secretin levels by a pulse plus infusion.

III. The effect of varying both time and secretin loads on the acute insulin response. When secretin was given at 75-min intervals in increasing amounts on 1 day, the acute insulin responses rose in parallel with the dose until the 75 U pulse was given. Beyond this level there was a uniform and significantly decreased insulin output to both the 150-U and 300-U secretin pulses (Fig. 4, top). When the same size pulses were given over a 2 day period to another group of four normal subjects (Fig. 4, bottom), the acute insulin responses increased with the increasing secretin stimuli. The insulin response to 300 U when given on the 2nd day of a 2 day study (Table I) was significantly ($P < 0.05$) increased, indicating that the time between injections was a critical variable in the magnitude of the insulin response.

IV. The effect of time on the insulin response to identical pulses of secretin. When 15-U secretin pulses were separated by 105 min the mean peak insulin responses in six normal subjects were identical. However, with subsequent repetitive administration of secretin pulses every 30 min there was a progressive fall in the acute insulin response which was statistically significant ($P < 0.05$) by the final (fourth) 15 U pulse (Fig. 5).

DISCUSSION

Minor decreases in the plasma glucose occur with secretin pulses; the nadir is usually seen between 7 and 30 min. The nadir always appears after the peak insulin response and with increasing secretin pulses and concomitant increased insulin output, the fall of the plasma glucose level tends to be greater. Simultaneous injections of glucose and secretin have been associated with an increased insulin response and a more rapid glucose disappearance (K_g) than with the same dose of glucose given alone (2), consistent with the concept that secretin is probably stimulating release of a biologically active insulin. In the present studies only a relatively minor fall in plasma glucose levels occurred at insulin levels comparable to those seen with 20 g of glucose. There are at least two possible explanations for the small decrease in plasma glucose: either these levels of insulin may not significantly enhance peripheral plasma glucose disposal as has been suggested by Meade, Kneubuhler, Barboriak, and Schulte, who infused small amounts of insulin into a peripheral or the portal vein of dogs (12); or secretin may stimulate both the release of insulin and the mobilization of hepatic glycogen stores, properties characteristic of glucagon. The latter possibility, although undocumented, is suggested by the fact that secretin and glucagon share common amino acid sequences, and are both lipolytic in vitro (13).

TABLE I

Mean 2-5' Δ IRI Response to Varying Doses of Secretin on 1 or 2 Days

One Day Study

Subject	Basal*	Secretin dose				
		10 U	25 U	75 U	150 U	300 U
	μU/ml			μU/ml		
D. J.	12.8	21.4	37.5	47.8	34	19.5
P. K.	11.2	33	66.5	80.5	50.5	22.3
J. H.	8.0	6.5	14.8	21.3	8.5	8
G. S.	16.3	21.2	44.3	75.5	47.3	21.5
Mean	12.0	20.5	40.8	56.3	35.1‡	17.8§
SEM	1.5	4.7	9.2	11.9	8.3	2.9

Two Day Study

Subject	1st day			2nd day	
	Basal*	Secretin dose		Basal*	Secretin dose
		10 U	75 U		300 U
	μU/ml	μU/ml			μU/ml
H. M.	8.5	24.5	62.5	9	99
T. C.	7.0	6.0	19.5	6.8	50.9
R. M.	6.0	8.3	37.8	8.0	54.8
D. T.	12.0	11.8	37.3	15.5	36.8
Mean	8.3	12.6	39.3	9.8	60.4‖
SEM	1.1	3.6	7.6	1.7	11.6

* Mean of four determinations.

‡ Significantly decreased, $P < 0.02$, compared with 75 U responses, paired t test.

§ Significantly decreased, $P < 0.05$, compared with 75 U responses, paired t test.

‖ Significantly increased, $P < 0.05$, compared with 300 U responses during the one day study by t test.

Confirming other studies (2, 4, 5), the present data clearly demonstraate that secretin, like glucose, stimulates rapid insulin release. The peak insulin response to a given pulse of secretin occurs within 5 min, usually at 2 or 3 min, similar to its responses to glucose. Allowing for a 2–3 min venous recirculation time the rapid insulin output to secretin would appear to be an almost instantaneous phenomenon at the islet cell. This would suggest that secretin is stimulating a storage pool of insulin which is available for immediate release, similar to the rapid insulin response to glucose.

With larger doses of glucose the insulin response after the immediate peak output continues for a considerable period of time (14). This continued insulin release may be either from further secretion from the storage pool or from another insulin pool as yet undefined. In contrast, the duration of insulin release to larger doses of
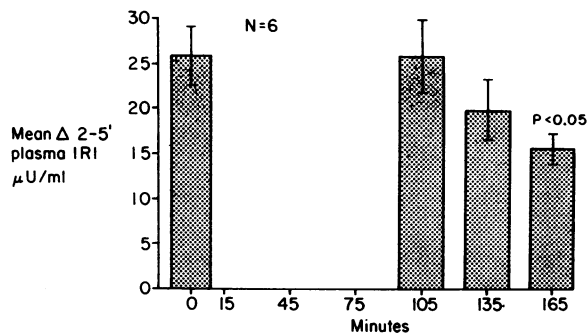

FIGURE 5 Mean incremental insulin responses to identical (15 U) secretin pulses given at two different time intervals.

secretin remains unaltered, implying that secretin stimulates release from only a small stored insulin pool. Moreover, this stimulation is not sustained in spite of large doses (300 U) of secretin, or continued secretin infusion which would maintain blood secretion levels for greater than 15 min (5). This characteristically uniphasic response also suggests that secretin stimulates insulin release only from a stored pool. The data from the results of the pulse infusion studies reported here are similar to those found by Boyns, Jarrett, and Keen (15) but different from the observations of Chisholm et al. (5), who reported pulse infusion studies in two subjects. The latter group found a continuous relatively unchanged insulin secretion in one subject and relatively steady insulin secretion which increased by the end of the infusion in another. The differences between the present data and that of Chisholm et al. are not readily apparent, except that the present study employed a total dose of 90 U, as opposed to 30 U by Chisholm et al. Since the insulin responses increase with increasing secretin pulses of 10, 25, and 75 U (Table I), and the sum of these pulses is greater than the total quantity of secretin given by the present pulse infusion study, the differences in total dose appear not to be a critical factor.

The fall in insulin responses to increasing secretin pulses during a 1 day study suggests that the pool of insulin available to secretin stimulation is limited, the effect of increasing secretin pulses being to diminish the response from this stored pool of insulin at a rate faster than required for refilling of this pool. That time may be critical is evident from the experiments in which the secretin doses are given over a 2 day period. Parallel increases of the acute insulin response to the 10-U and 75-U pulses are seen in both the 1 and 2 day study, but the responses to the 300 U pulse on the 2nd day of the 2 day study are greater than those to the identical pulse given during the 1 day study.

The effects of time were independently examined by administering identical (15 U) secretin pulses at two

different time intervals. Although the acute insulin re-
sponse was unchanged when pulses were separated by
105 min, it progressively decreased when one interval
was shortened to 30 min. These observations suggest
that the insulin responses are either derived from a small
storage pool which can be depleted faster than it refills
or that the sensitivity of the islet response to repetitive
secretin stimulation is altered. The net effect of either
possibility is a functionally depleted insulin pool.

The dose response curve for the 2 day study is curvi-
linear and appears remarkably similar to that seen when
the acute insulin response to glucose is plotted against the
glucose stimulus using 0.5- to 40-g pulses (10). This
curve is consistent with release of insulin from a small
storage pool with a dose response curve characteristic of
drug receptor interactions (16).

ACKNOWLEDGMENTS

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