The Effect of Secretin on Glucose-Stimulated Insulin Secretion in Man

KENJI SHIMA AND SEIICHIRO TARUI*

*Central Laboratory for Clinical Investigation and
The Second Department of Internal Medicine*,
Osaka University Medical School, Osaka*

Synopsis

The effect of physiological dose of purified secretin on glucose-stimulated insulin secretion was studied in healthy volunteers during a continuous infusion of glucose. The intravenous injection of ten unit of secretin during the infusion of glucose caused a greater rise in plasma insulin level and a more marked decrease in blood glucose concentration than either the infusion of glucose or secretin alone did, resulting in a significant increase in the insulinogenic index. One unit of secretin has no effect on plasma insulin and glucose concentrations in the fasting or hyperglycemic state.

The physiological role of secretin in regulating insulin secretion after ingestion of food was discussed.

The rise in plasma insulin that follows a glucose load is greater when glucose is administered orally than when it is administered intravenously (McIntyre *et al.*, 1965). The augmented release of insulin after oral glucose could be the result of the combined action of glucose and a hormone or hormones produced by the upper gastrointestinal tract (Unger *et al.*, 1967. Haddad and Owen, 1969.). It is possible that still unidentified substance(s) possessing an insulin-releasing capacity could be involved in this phenomenon. Several enteric hormones have been thought to be the attractive candidates for the insulin-releasing factors of the gastrointestinal origin because of their insulinogenic effect demonstrated *in vitro* and *in vivo* (Buchanan *et al.*, 1968; Duprè *et al.*, 1966; Lernmark *et al.*, 1969.). However, the facts that the doses of these hormones used for the experiments were of pharmacological orders and also the purity of the preparations was rather low, necessitate to reinvestigate the physiologic role of these

hormones in regulating insulin secretion using the pure preparations in physiologic doses.

The following studies were undertaken to reevaluate the effect of the physiologic dose of secretin on the glucose-induced release of insulin in man.

Materials and Methods

Four nonobese healthy male volunteers aged 18–22 served as subjects. After an overnight fast, the subjects were given an intravenous infusion of glucose at the rate of 6 mg/kg/min for 140 min by a constant infusion pump (Sharp mininjector TMP-50). Following a 80-min control period, one or ten unit purified secretin^Δ dissolved in 20 ml of isotonic saline was injected intravenously over two min. Venous blood samples were obtained *via* an indwelling needle inserted into the antecubital vein, at the times indicated in "Results" using the midpoint of injection of secretin as zero time for sampling thereafter. At an interval of several days, two kinds of control experiment were performed. Firstly, 20 ml of isotonic saline was injected during a continuous infusion of glucose in the same manner as the test experiment. Secondly, the subjects were given secretin alone.

Plasma glucose was measured by the Auto Analyzer modification of the Hoffman ferricyanide technique (Hoffman, 1937.), immunoreactive insulin (IRI) was determined using insulin assay kit (Phadebas).

Paired t test was employed to assess the statistical significance of the data.

Fig. 1. Plasma glucose and IRI responses to secretin during infusion of glucose in healthy subjects.

× $p < 0.05$, ×× $p < 0.025$,
vs the value at 0 time.

Results

In the fasting state, injection of 10 u secretin elicited a slight elevation of the insulin level ($7.4 \pm 1.4 \mu\text{u/ml}$ before injection, $10.7 \pm 1.3 \mu\text{u/ml}$ at 5 min.) and returned promptly to the control level within 10 min. Plasma glucose decreased to a small extent 10 ~ 20 min after the injection (Table 1, Fig. 1). No detectable changes in plasma glucose and IRI levels were observed after 1 u of secretin (Table 1).

During the first 30 min of the glucose infusion the mean plasma insulin level increased gradually from $9.3 \pm 2.1 \mu\text{u/ml}$ reaching a plateau of about $30 \mu\text{u/ml}$ in 45 min and kept the steady state until 80 min, at which time secretin was given. The injection of 10 u secretin during the infusion of glucose caused a greater increase in plasma insulin concentration comparing with that demonstrated after the injection of secretin without glucose. In the control experiment using isotonic saline no significant changes in plasma insulin level occurred during the corresponding period (Table 2, Fig. 1). The mean plasma glucose concentration also increased gradually reaching a plateau about 115 mg% 30 min after commencement of the glucose infusion.

Table 1. Plasma glucose and IRI responses to secretin in fasting healthy subjects

	after loading (min.)							
	0	2	5	10	20	30	45	60
Secretin 10 u	77.0*	77.0	74.3	72.8	70.3	70.3	71.5	70.8
BS mg%	± 5.0	± 3.7	± 4.2	4.4	± 2.9	± 5.3	± 5.4	± 5.9
p**				< 0.05	< 0.025			
IRI $\mu\text{u/ml}$	7.4	8.2	10.7	7.8	7.0	6.0	6.7	7.0
p	± 1.4	± 1.5	± 1.3	± 1.1	± 1.1	± 1.5	± 1.8	± 1.4
Secretin 1u	91.8	94.0	93.8	92.5	94.0	93.5	93.5	100.3
BS mg%	± 2.6	± 1.5	± 1.4	± 1.6	± 1.7	± 2.2	± 1.8	± 3.5
IRI $\mu\text{u/ml}$	8.3	8.2	9.5	8.5	9.2	9.1	7.9	8.1
	± 0.7	± 0.8	± 1.1	± 0.7	± 0.9	± 0.7	± 1.1	± 0.9

* Mean $\pm$ S.E.

** Compared with the value at 0 min.

Table 2 Plasma glucose and IRI responses to secretin during infusion of glucose in healthy subjects

		after loading (min)													
		-80	-65	-50	-35	-20	-10	0	2	5	10	20	30	45	60
secretin 0 u *	BS mg %	77.0** ±2.3	103.8 ±3.4	115.3 ±2.2	121.3 ±1.3	120.5 ±1.2	118.0 ±2.9	116.0 ±2.8	115.3 ±3.0	114.3 ±3.3	114.8 ±3.1	109.8 ±4.1	107.8 ±3.9	105.3 ±4.5	100.8 ±5.5
	IRI μ u/ml	8.3 ±1.3	19.0 ±4.7	23.3 ±5.6	25.2 ±4.1	30.3 ±5.5	31.8 ±6.2	30.9 ±6.1	29.6 ±5.1	28.3 ±5.1	34.9 ±5.2	32.8 ±7.6	34.0 ±6.0	32.3 ±4.6	29.4 ±2.5
secretin 10 u	BS mg %	83.5 ±3.6	107.8 ±8.5	115.8 ±7.5	117.0 ±6.2	115.3 ±5.0	115.8 ±5.2	113.3 ±7.3	113.8 ±8.0	113.0 ±8.1	112.3 ±7.8	99.5 ±6.3	93.3 ±6.9	90.0 ±7.1	88.0 ±6.1
	IRI μ u/ml	9.3 ±2.1	21.6 ±5.6	23.6 ±6.3	29.5 ±8.7	27.8 ±7.0	32.2 ±7.5	31.1 ±7.3	40.6 ±11.3	54.0 ±14.5	44.7 ±9.7	35.7 ±10.2	25.2 ±6.4	21.5 ±4.7	20.6 ±5.0
p***		<0.05 <0.025													
secretin 1 u	BS mg %	90.5 ±3.2	127.5 ±4.2	138.0 ±5.7	146.7 ±8.0	145.3 ±10.8	142.3 ±11.7	140.5 ±13.5	135.3 ±14.0	132.3 ±12.6	129.3 ±12.2	122.8 ±10.0	118.5 ±9.6	111.8 ±4.2	106.0 ±4.1
	IRI μ u/ml	8.8 ±0.6	22.9 ±3.3	25.4 ±4.1	27.1 ±4.1	31.5 ±5.3	33.9 ±5.2	33.3 ±5.6	31.6 ±4.9	33.6 ±4.2	34.0 ±5.5	39.4 ±5.9	36.9 ±5.9	34.8 ±5.0	29.4 ±2.8

* 20 ml of isotonic saline without secretin was employed as control.

** Mean $\pm$ S. E.

*** Compared with the value at 0 min.

Fig. 2. Effect of secretin injection on insulinogenic index.

× $p < 0.05$, ×× $p < 0.025$, vs the value at 0 time.

With injecting 10 u of secretin plasma glucose level tended to fall to a greater extent comparing with that observed in the control experiment during the corresponding period. As shown in Figure 2, the insulinogenic index, calculated by dividing the concentration of IRI by the glucose concentration at each sampling time, increased significantly at 5 and 10 min. after 10 u of secretin during the glucose infusion. When 1 u of secretin was injected during the infusion of glucose, no appreciable changes in plasma glucose and IRI levels were elicited.

Discussion

Stimulation of insulin secretion by the parenteral administration of secretin is now well established (Duprè, 1964; Unger *et al.*, 1966; Deckert, 1968.). It has been argued, however, that this is rather a pharmacologic effect of secretin and stimulated insulin secretion is not seen after the physiological release of secretin (Boyns *et al.*, 1967.). According to the report of Chisholm *et al.* (1969), the peak

value of serum secretin, determined by radio-immunoassay, after oral glucose or intraduodenal hydrochloric acid is about 10 mμg/ml, and those estimated by Kraegen *et al.* (1970) in two subjects during the infusion of 10 u secretin, the same amount as that employed as high dose in the present study, are 10 and 8 mμg/ml. These findings indicate that the doses of secretin used in our experiment are not pharmacological but physiological ones. Another argument is that agents contaminated in the secretin preparations, but not secretin per se, produce the stimulatory effect on insulin secretion (Rehfeld, 1972.). To eliminate this problem, the purest preparation of those available commercially for human use so far was employed in this study.

Ten unit of secretin had only a weak, if any, stimulating effect on the insulin secretion in the fasting man. However, the intravenous injection of the similar dose of secretin during the glucose infusion caused a greater rise in plasma IRI level than either the infusion of glucose or secretin alone and a significant increase in the insulinogenic index. More insulin was mobilized by secretin in the

hyperglycemic state than in the fasting even if the elevation of blood glucose level remains within the physiological range. The effect of secretin in this experiment can therefore be regarded as a potentiation of the secretion of IRI in response to hyperglycemia. The mechanism on which secretin enhances the IRI response to glucose is not necessarily clear. However, if a recent report that secretin activates adenylate cyclase in isolated islet from rat, resulting in elevated cellular cyclic AMP level (Kuo *et al.*, 1973.) is taken into consideration, it is likely to assume that secretin exerts the potentiating effect on insulin secretion through augmenting the cyclic AMP content in B-cell, which modulates glucose-induced release of insulin (Charles *et al.*, 1973.).

It remains to be settled whether the accelerated glucose disappearance noted after the administration of 10 u secretin during the glucose infusion, is attributed to the increased insulin secretion caused by secretin or to a direct action of secretin.

In any way, in the present study, an intravenous injection of small dose of secretin given to approximate serum secretin levels seen after physiological stimuli showed to be capable of augmenting the blood insulin response to hyperglycemia. These observations might suggest that secretin is one of the enteric factors responsible for the potentiation of insulin secretion which occurs after ingestion of food. The finding that stimulated secretion of endogenous secretin by the intraduodenal instillation of acid did not enhance the serum insulin response and the blood clearance of an intravenous glucose load in normal subjects (Boyns *et al.*, 1967) and patients with histamine-fast anacidity (Mahler and Weisberg, 1968), however, has casted a doubt about a physiological role of secretin in regulating insulin secretion after meals. Since fasting patients with portocaval shunts demonstrated a small rise in plasma insulin after intraduodenal instillation of HCl (Kaess *et al.*, 1970.), it might be reasonably

assumed that the magnitude of change of the insulin secretion rate following intraduodenal acidification is too small to be detected in the peripheral venous blood of the subjects without portocaval shunts due to the hepatic insulin clearance and the dilution of the hepatic vein blood. The similar conclusion was obtained from the experiment in which change in insulin levels of peripheral and portal vein blood was examined in dogs following the intraduodenal infusion of HCl (Boden *et al.*, 1973). Accordingly, the findings observed in the normal subjects and the anacid patients after intraduodenal HCl do not necessarily negate the idea that secretin is one of factors involved in "enteroinsular axis".

Although the preparation of secretin used in the present study is the purest of those available for human use, the purity is still not satisfactory. The results obtained here, therefore, have to be evaluated with due regard to this point.

Acknowledgement

We are indebted to Prof. Nishikawa for valuable advice and encouragement. The authors wish to appreciate Eisai Pharmaceutical Co. for supplying purified secretin.

Reference

- Boden, G., S. C. Gulati, N. Essa and O. E. Owen (1973). Proceedings of the Eighth Congress of the International Diabetes Federation, Brussels, 1973. *Excerpta Medica* Foundation, Amsterdam, p. 31-32.
- Boyns, D. R., R. J. Jarrett and H. Keen (1967). *Brit. Med. J.* **2**, 676.
- Buchanan, K. D., J. E. Vance and R. H. Williams (1968). *Amer. J. Physiol.* **215**, 1293.
- Charles, M. A., R. Fanska, F. G. Schmid, P. H. Forsham and G. M. Grodsky (1973). *Science*. **179**, 569.

- Chisholm, D. J., J. D. Young and L. Lazarus (1969). *J. Clin. Invest.* **48**, 1453.
- Deckert, T. (1968). *Acta Endocr.* **57**, 578.
- Duprè, J. (1964). *Lancet* **2**, 672.
- Duprè, J. and J. C. Beck (1966). *Diabetes.* **15**, 555.
- Haddad, J. G., Jr. and J. A. Owen, Jr. (1969). *Metabolism* **18**, 71.
- Hoffman, W. S. (1937). *J. Biol. Chem.* **120**, 51.
- Kaess, H., G. Schlierf and J. G. von Mikulicz-Radecki (1970). *Metabolism* **19**, 214.
- Kraegen, E. W., D. J. Chisholm, J. D. Young and L. Lazarus (1970). *J. Clin. Invest.* **49**, 524.
- Kuo, Wu-Nan, D. S. Hodgins and J. F. Kuo (1973). *J. Biol. Chem.* **248**, 2705.
- Lernmark, A., B. Hellman and H. G. Coore (1969). *J. Endocr.* **43**, 371.
- Mahler, R. J. and H. Weisberg. (1968). *Lancet* **1**, 448.
- McIntyre, N., C. D. Holdsworth and D. S. Turner (1965). *Lancet* **2**, 20.
- Rehfeld, J. F. (1972). *Scand. J. Gastroent.* **7**, 289.
- Unger, R. H., H. Ketterer, A. Eisentraut and J. Duprè (1966). *Lancet* **2**, 24.
- Unger, R. H., A. Ohneda, I. Valverde and A. M. Eisentraut (1967). *J. Clin. Invest.* **46**, 1125.