

{Chem. Pharm. Bull.
28(12)3693—3695(1980)}

Effects of Calcitonin and Epinephrine on Serum Glucose Concentration in Rats

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(Received June 25, 1980)

The effects of calcitonin (CT) and epinephrine on serum glucose concentration were investigated in fed rats. The administration of CT (80 MRC mU/100 g body weight) to adrenalectomized rats caused a significant increase in serum glucose. The simultaneous administration of CT (40 and 80 MRC mU/100 g) and epinephrine (7.5 and 15 μ g/100 g) produced a clear increase in comparison with that caused by epinephrine alone. On the other hand, CT did not change the glucose tolerance, while epinephrine markedly lowered it. The present results suggest that the hyperglycemic effect caused by CT is not mediated through the action of epinephrine from adrenal glands in rats.

Keywords—calcitonin; epinephrine; glucose; hyperglycemic effect by calcitonin; adrenalectomized rats

Introduction

It has recently been reported that calcitonin (CT) affects glucose metabolism. CT inhibits glucose uptake stimulated by insulin in the diaphragm muscle of rats.^{2,3)} CT also provokes a significant impairment of glucose assimilation and insulin output in man.⁴⁾

More recently, it was found that CT increases the serum glucose concentration in fed and fasted rats.^{5,6)} Thus, CT has a hyperglycemic effect in rats. However, it is uncertain whether this effect of CT is mediated through the action of epinephrine on serum glucose. The present study was therefore undertaken to examine the effects of CT and epinephrine on the serum glucose in rats.

Materials and Methods

Animals—Male Wistar rats, weighing about 100–120 g, were used. They were obtained commercially (Nippon Bio Supp. Center, Tokyo, Japan). The animals were fed commercial lab. chow containing 1.1% Ca, 1.1% P and 57.4% carbohydrate (Oriental Test Diet, Tokyo, Japan) and tap water freely.

Hormones and Drug—Calcitonin (lyophilized porcine calcitonin, 68 MRC U/mg protein, Armour Pharmaceutical Company, Kankakee Ill. U.S.A.) was dissolved in cold demineralized water. Calcitonin (CT; 40 and 80 MRC mU/100 g) was administered subcutaneously. Epinephrine (L-epinephrine bitartrate, Sigma Chemical Company, St. Louis, Mo., U.S.A.) was dissolved in cold demineralized water. Epinephrine (7.5 and 15 μ g/100 g) was administered subcutaneously. The demineralized water was injected as the control.

Glucose was dissolved in demineralized water. Glucose (0.1 g/100 g) was intraperitoneally administered to rats fasted for 24 hr. CT (80 MRC mU/100 g) and epinephrine (15 μ g/100 g) were administered immediately after the injection of glucose. The rats were bled at various times after the administration of the hormones.

Surgical Procedure—The adrenal glands were removed with fine forceps under light ether anesthesia. Twenty-four hours after the adrenalectomy, the rats were subcutaneously administered CT (80 MRC mU/

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100 g) and they were bled 60 min after the administration of CT. Control injections consisted of demineralized water.

Analytical Methods—The rats were bled by cardiac puncture under light ether anesthesia. Blood samples obtained by cardiac puncture were centrifuged 30 min after collection. The serum was separated and analyzed immediately. Glucose in the serum was determined with the Glytel *o*-toluidine reagent.⁷⁾

Statistical Methods—The significance of differences between the values was estimated by Student's *t* test. *p* values less than 0.05 were considered to indicate statistically significant differences.

Results

The effect of CT on serum glucose in adrenalectomized rats is shown in Fig. 1. The administration of CT (80 MRC mU/100 g) produced a significant increase of the serum glucose concentration in adrenalectomized rats as compared with the control rats.

The effects of CT and epinephrine on serum glucose were examined in fed rats (Table I). The administration of CT (40 and 80 MRC mU/100 g) or epinephrine (7.5 and 15 μ g/100 g) alone caused a significant increase in serum glucose. The simultaneous administration of CT (40 MRC mU/100 g) and epinephrine (7.5 μ g/100 g), or CT (80 MRC mU/100 g) and epinephrine (15 μ g/100 g) further enhanced the elevation of serum glucose caused by each hormone alone.

The differential effects of CT and epinephrine on an increase in serum glucose caused by a glucose load in fasted rats is shown in Fig. 2. The serum glucose was markedly increased by a glucose load (0.1 g/100 g). This increase was not altered by the administration of CT (80 MRC mU/100 g). On the other hand, the administration of epinephrine (15 μ g/100 g) markedly potentiated the augmentation of serum glucose produced by a glucose load. However, the simultaneous administration of CT and epinephrine to rats given a glucose load did not alter the elevation of serum glucose from that produced by epinephrine alone.

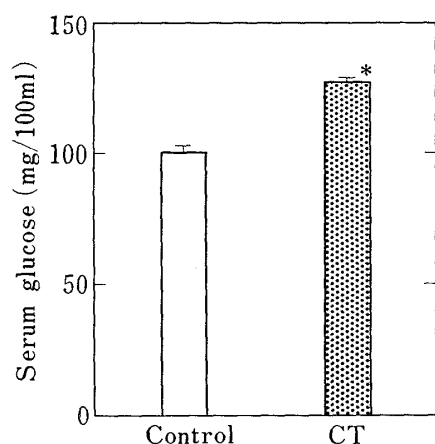


Fig. 1. Effect of Calcitonin (CT) on the Serum Glucose Concentration in Adrenalectomized Rats

The rats were adrenalectomized 24 hr prior to the subcutaneous administration of CT (80 MRC mU/100 g), and they were bled 60 min after the administration of CT. Each bar represents the mean of 5 animals. Vertical lines represent the SE. *, $p < 0.01$ as compared with the control. □; Control, ▨; CT.

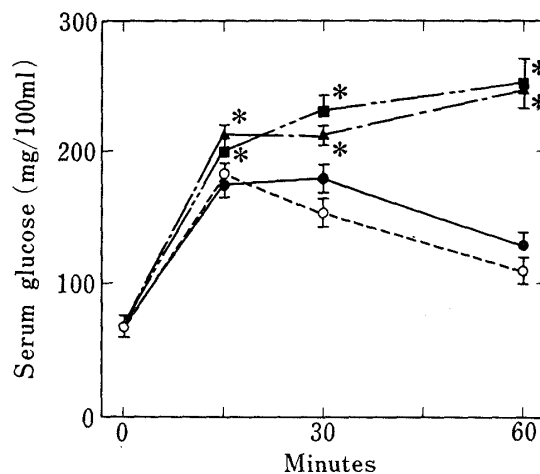


Fig. 2. Differential Effects of Calcitonin (CT) and Epinephrine on an Increase in Serum Glucose Concentration caused by a Glucose Load in Rats

Glucose (0.1 g/100 g) was intraperitoneally injected immediately after the subcutaneous administration of CT (80 MRC mU/100 g) or epinephrine (15 μ g/100 g). Each point represents the mean of 5 animals. Vertical lines represent the SE. *, $p < 0.01$ as compared with the control (○). --○--; glucose, --●--; CT+glucose, ---▲---; epinephrine+glucose, ----■----; CT+epinephrine+glucose.

TABLE I. Effects of Calcitonin (CT) and Epinephrine on the Serum Glucose Concentration in Rats

Treatment ^{a)}	Serum glucose ^{b)} (mg/100 ml)
Control	117.2 ± 4.1
CT (40 MRC mU/100 g)	148.1 ± 5.0 ^{c)}
CT (80 MRC mU/100 g)	162.0 ± 4.2 ^{c)}
Epinephrine (7.5 µg/100 g)	213.9 ± 8.6 ^{c)}
Epinephrine (15 µg/100 g)	230.2 ± 5.8 ^{c)}
CT (40 MRC mU/100 g) + epinephrine (7.5 µg/100 g)	256.8 ± 5.9 ^{c,d)}
CT (80 MRC mU/100 g) + epinephrine (15 µg/100 g)	279.1 ± 7.1 ^{c,e)}

a) CT or epinephrine was administered subcutaneously. The rats were bled 60 min after the administration of the hormones.

b) Values are mean ± SE.

c) $p < 0.01$ as compared with the control.

d) $p < 0.01$ as compared with epinephrine (7.5 µg/100 g).

e) $p < 0.01$ as compared with epinephrine (15 µg/100 g).

Discussion

It is known that calcitonin (CT) has a hyperglycemic effect not mediated through hypocalcemia caused by the hormone.^{5,6)} From the previous study with glucagon, which induces hyperglycemia in rats, an entirely different pattern of increase in serum glucose was observed compared with that of CT-treated rats.⁵⁾ Thus, it was suggested that the mechanism responsible for hyperglycemia caused by CT may not be related to glucagon release.⁵⁾

In the present study, CT caused a significant increase in the serum glucose in adrenalectomized rats, indicating that the hyperglycemic effect of CT is not mediated through the secretion of epinephrine from the adrenal glands. CT further enhanced the elevation of serum glucose after the administration of epinephrine. In addition, CT did not prevent glucose tolerance, while epinephrine inhibited it markedly. Judging from these results, authors consider that CT causes an increase in serum glucose concentration that is not mediated through the action of epinephrine.

On the other hand, the mechanism by which CT increases the serum glucose level has not been fully resolved. The hyperglycemic effect of CT is clearly exhibited in both fed rats and starved rats.^{5,6)} CT is capable of stimulating an increase in phosphorylase and glucose-6-phosphatase activities, and a decrease in glycogen level in the liver of rats.⁵⁾ CT may stimulate the production of glucose in the liver of rats. However, the mode of action of CT remains to be elucidated.