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Short Communication

Hyperglycemic Response to Angiotensin II in Rabbits

(angiotensin II/glycogen phosphorylase/immunoreactive insulin)

SUMIO MASUMURA[a], MICHIO HASHIMOTO[a], and ISAMU TAKEDA[b]

[a]*Department of Physiology, Shimane Medical University, Izumo 693 and*
[b]*Department of Clinical Pathology, Shimane Prefectural Central Hospital, Izumo 693, Japan*

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We studied the effects of angiotensin II on the level of plasma insulin and on the activity of liver glycogen phosphorylase, during the hyperglycemic response to this polypeptide in rabbits.

The activity of liver glycogen phosphorylase increased during the initial stages of hyperglycemia and the peak was observed at 10 min after the injection of this polypeptide. However, with the elapse of time, the activity decreased and recovered to the control level. The level of plasma immunoreactive insulin (IRI) was unaffected by angiotensin II during the initial stages at 0–40 min and increased, when the level of blood glucose attained the maximum at 60 min. Moreover the elevated level continued for 20 min. Under such conditions, blood glucose appears to be gradually restored to the control level by the increase in IRI.

It has been reported that angiotensin II has a hyperglycemic action (1–3). In a previous study, we confirmed this finding in rabbits and observed the activation of liver glycogen phosphorylase (4). Our observations suggested that such a hyperglycemia would depend not only on the activation of liver glycogen phosphorylase but also on the reduction of insulin secretion. Thus, the question was raised as to whether or not this polypeptide actually impairs insulin secretion. We estimated this hormonal concentration in rabbit plasma together with the level of liver glycogen phosphorylase during the hyperglycemic reponse to this polypeptide.

Three groups of healthy, adult rabbits of both sexes were fasted for 12 hr before the experiments. Angiotensin II (50 μg/kg) was given i. v., and to the same number of controls, an isotonic solution (0.9 % NaCl) was injected.

In estimating the concentration of blood glucose, the first group of rabbits was not anesthetized. A blood sample (0.2 ml) was collected into heparinized syringes from a marginal vein of the ears at 0, 30, 60, 90 and 120 min after injecting angiotensin II. The concentration of blood glucose was estimated by the method of Somogyi (5).

To assay the level of liver glycogen phsophorylase (enzyme a), the second group was anesthetized by giving an i. p. injection of pentobarbital sodium (30 mg/kg) and segments of each liver were prepared. These (0.5–1.0 gm) segments were excised at 0 min, at 10 or 15 min and at 30, 60, 90 or 120

min after the intravenous administration. All blood vessels were clamped to prevent bleeding. The activity of liver glycogen phosphorylase was estimated by the method of Shimazu and Amakawa (6).

The third group was used for radioimmunoassay of plasma insulin, under unanesthetized conditions. A sample of plasma (0.1 ml) was obtained at intervals of 30 min, in the same manner as described above and the immunoreactive insulin was measured according to the method of Yalow and Berson (7). The kit used for the radioimmunoassay (Insulin Riakit) was purchased from Dainabot RI Institute (Tokyo, Japan).

The results are summarized in Figs. 1 and 2. Each value was compared with the initial value estimated just before the injection, in the same rabbit. Angiotensin II had a potent hyperglycemic action. In this process, the concentration of blood glucose increased moderately at 30 min and attained the maximum at 60 min after the intravenous administration (Fig. 1).

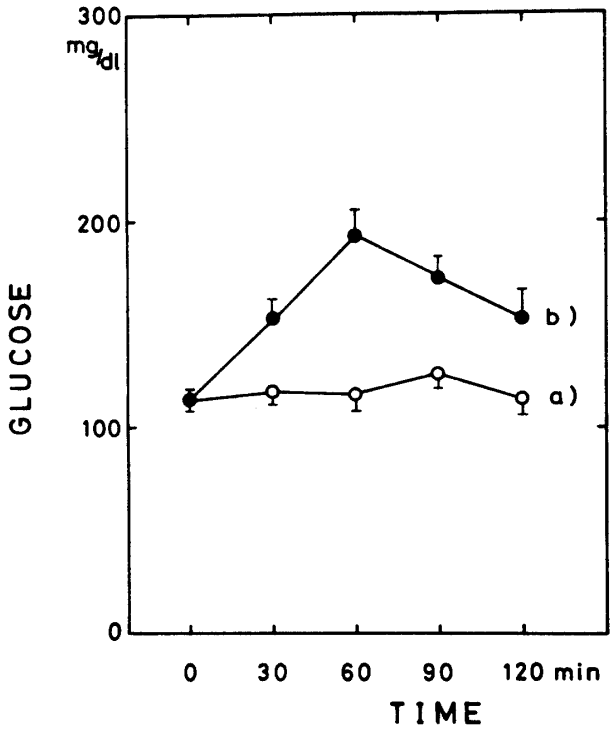

Fig. 1. The effect of angiotensin II on the blood glucose concentration. ○ : control. ● : intravenous injection of angiotensin II (50 μg/kg). Average of 6 tests. Vertical bars : ±standard error.

As shown in Fig. 2 (–●–), the activity of liver glycogen phosphorylase increased during the initial stages of hyperglycemia. Here, the peak of this activity was observed at 10 min after the injection. However, with the elapse of time, the activity decreased, finally to the control levels.

As is evident from Fig. 2 (–○–), there was no decrease in insulin secretion, as determined by radioimmunoassay. That is, plasma immunoreactive insulin (IRI) was unaffected by angiotensin II during 0—40 min. The level of IRI

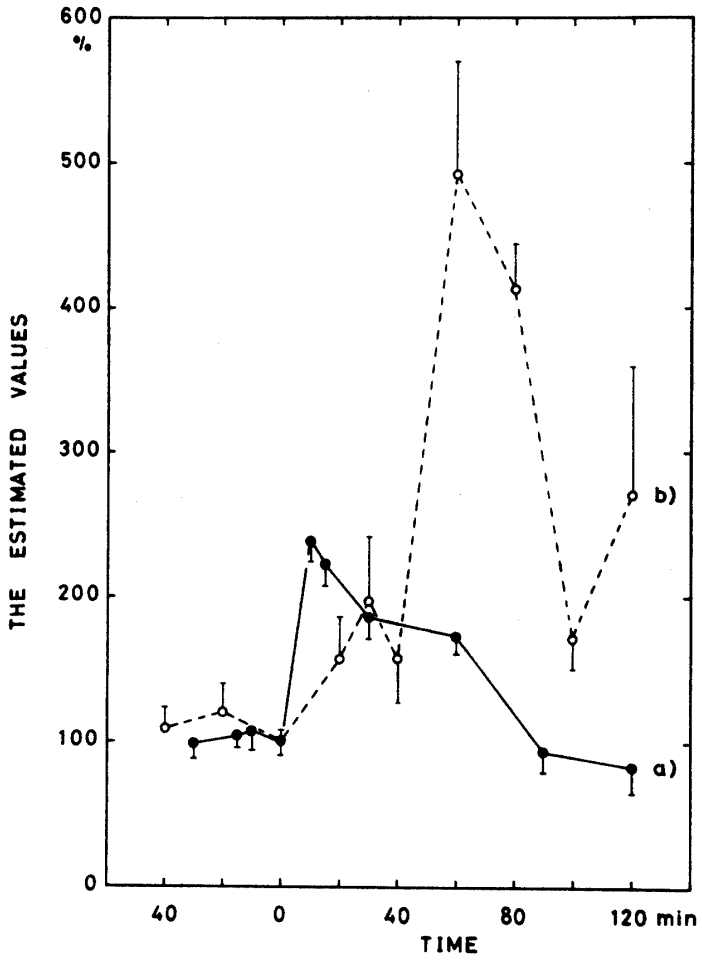

Fig. 2. The effects of angiotensin II on the liver glycogen phosphorylase activity and immunoreactive insulin level. The control values in these experiments were expressed in terms of 100 %. ● : the liver glycogen phosphorylase activity. ○ : the immunoreactive insulin level. Average of 6 tests. Vertical bars : ±standard error.

increased, when the level of blood glucose attained the maximum at 60 min. Moreover, the elevated level continued for 20 min. Under such conditions, blood glucose appears to be gradually restored to the control level by the increase in IRI.

These results suggest that the activation of glycogen phosphorylase was appreciably manifested, when the level of IRI was fairly constant, at the initial stages of hyperglycemia. During the first 0—40 min, glycogenolysis developed until the concentration of blood glucose rose to the peak level.

Other workers have analyzed the hyperglycemic action of this polypeptide in various species (1—3). Heidenreich *et al.* (1) found that this action was not abolished by adrenalectomy or by pancreatectomy. This would suggest that angiotensin II has a direct glycogenolytic effect. On the other hand, our present results indicate that this polypeptide causes a hyperglycemia through the activation of liver glycogen phosphorylase, but not through the impairment of insulin secretion. In this instance, catecholamines liberated by angiotensin II (8—10) probably contribute to activation of the enzymes.

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