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The Glycogenolytic Action of Angiotensin II

(angiotensin II/hyperglycemia/phospho-phosphorylase)

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Angiotensin II has a glycogenolytic action in rabbit livers. Since this action can be blocked by propranolol, it appears that the glycogenolytic action of angiotensin II is mediated by a stimulation of the beta adrenergic receptors.

Heidenreich *et al.*(1—2) and Akinkugbe(3) have reported that angiotensin II (hypertensive polypeptide) has a hyperglycemic action in mammals. We ourselves have also confirmed this finding in rabbits. Since angiotensin II liberates catecholamines from the adrenal medulla(4—6), such a hyperglycemic action of this polypeptide can be anticipated. Since, when hyperglycemia develops, it is liver phospho-phosphorylase that usually plays the leading role, it is important to know whether or not this liver phospho-phosphorylase which prompts glycogenolysis is actually activated by this polypeptide. Therefore, the present study was undertaken for the purpose of clarifying the activation of this enzyme.

MATERIALS AND METHODS

Three groups of normal, adult rabbits of both sexes were used. The animals were fasted for 12 hr before the three experiments. Angiotensin II (50 μg/kg) was injected intravenously into the experimentals, while an isotonic solution (0.9 % NaCl) at the same dosage was similarly injected into the controls. Then, the following experiments were carried out :

1) To estimate the concentration of blood glucose, the first group of animals was used under unanesthetized condition. A blood sample (0.2 ml) was collected from a marginal vein of the ears at 0, 30, 90 and 120 min after injection. The concentration of blood glucose was estimated by the method of Somogyi(7).

2) To determine the activity of liver phospho-phosphorylase, the second group was anesthetized by an intraperitoneal injection of pentobarbital sodium (30 mg/kg) and then submitted to laparotomy to obtain three small segments of each liver. These segments (0.5—1.0 g) were exercised at 0 min ; at 10 or 15 min ; and at 30, 60, 90, or 120 min after the intravenous administration. On this occasion, forceps prevented the organ from bleeding.

3) The third group was available for intravenous infusion of propranolol (5 mg/kg) under anesthetized condition. This infusion extended over 30 min.

After the infusion, angiotensin II (50 μg/kg) was injected intravenously. Then, blood and liver samples were obtained by the same procedures described above. The activity of liver phospho-phosphorylase was determined by the method of Shimazu and Amakawa(8).

RESULTS AND DISCUSSION

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 animal. As shown in Fig. 1 (upper part), angiotensin II has a potent hyperglycemic action. In this process, the concentration of blood glucose increased moderately at 30 min and attained maximum at 60 min after the intravenous administration. The fact that hyperglycemia, which generally results from an excess production of glucose, chiefly by the liver, and from a decrease in its utilization by the various tissues, suggested that liver phospho-phosphorylase would be activated and involved in the glycogenolysis by this polypeptide, led us to turn our attention to the activity of this enzyme after intravenous injection of angiotensin II. The results are shown in Fig. 1 (lower part). The activity of liver phospho-phosphorylase increased during the early stages of the hyperglycemia. Here, the peak of this activity was observed at 10 min after injection. However, with the elapse of time, it decreased and recovered to the control level.

In our previous study(9), we could find no significant change in the enzymatic activity when animals were sacrificed at 30—120 min after an intravenous injection of angiotensin II. At that time, each activity obtained in the different rabbits was compared with one other. If speculation be permitted, changes in enzymatic activity could well have been masked by the individual variation of each control animal and this might be the reason why we failed to discover the enzymatic activation. Now, on the basis of the present study, it appears that the activity fairly increases during the early stages and thereafter decreases along a slope to the control level.

When animals had been previously treated with propranolol to block the beta adrenergic receptor of their livers, angiotensin II had hardly any effect on the concentration of blood glucose and on the activity of liver phospho-phosphorylase. These results are shown in Fig. 2. From all of these results, it is deduced that the glucose output caused by this polypeptide mainly depends upon the glycogenolytic enzyme whose activation is mediated by a stimulation of the beta receptor. Since angiotensin II liberates catecholamines from the adrenal medulla, the amines liberated would exert their action on the beta receptor.

Reports on the metabolic effect of angiotensin II are few. Several investigators have analyzed the hyperglycemic action of this polypeptide in various species(1—3). Heidenreich *et al.*(1) found that this action is not abolished by adrenalectomy or by pancreatectomy. They finally concluded that angiotensin II has a direct glycogenolytic effect. On the other hand, interpreting the present results, we may conclude that this polypeptide causes hyperglycemia through the activation of liver phospho-phosphorylase. Accordingly, catecholamines

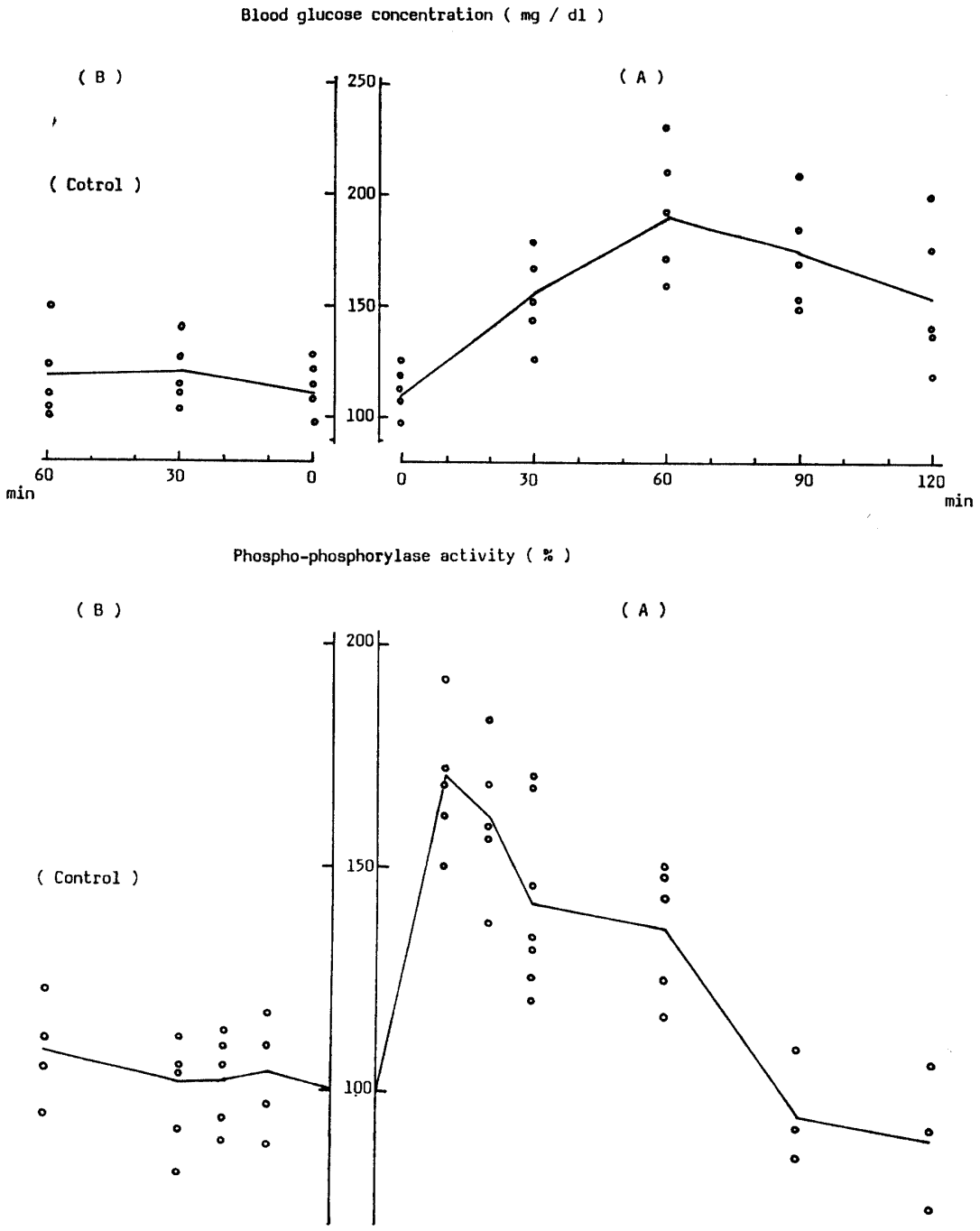

Fig. 1. Effect of angiotensin II on blood glucose concentration and phospho-phosphorylase activity. Upper part : time-response curve of blood glucose to this polypeptide. Ordinates : blood glucose concentration (mg/dl). Abscissae : time course(min). A : intravenous injection of angiotensin II (50 μg/kg). B : control. Lower part : time-response curve of phospho-phosphorylase to this polypeptide. Ordinates : phospho-phosphorylase activity (% of its initial value (0 min)). Abscissae : time course (min). A : intravenous injection of angiotensin II. B : control.

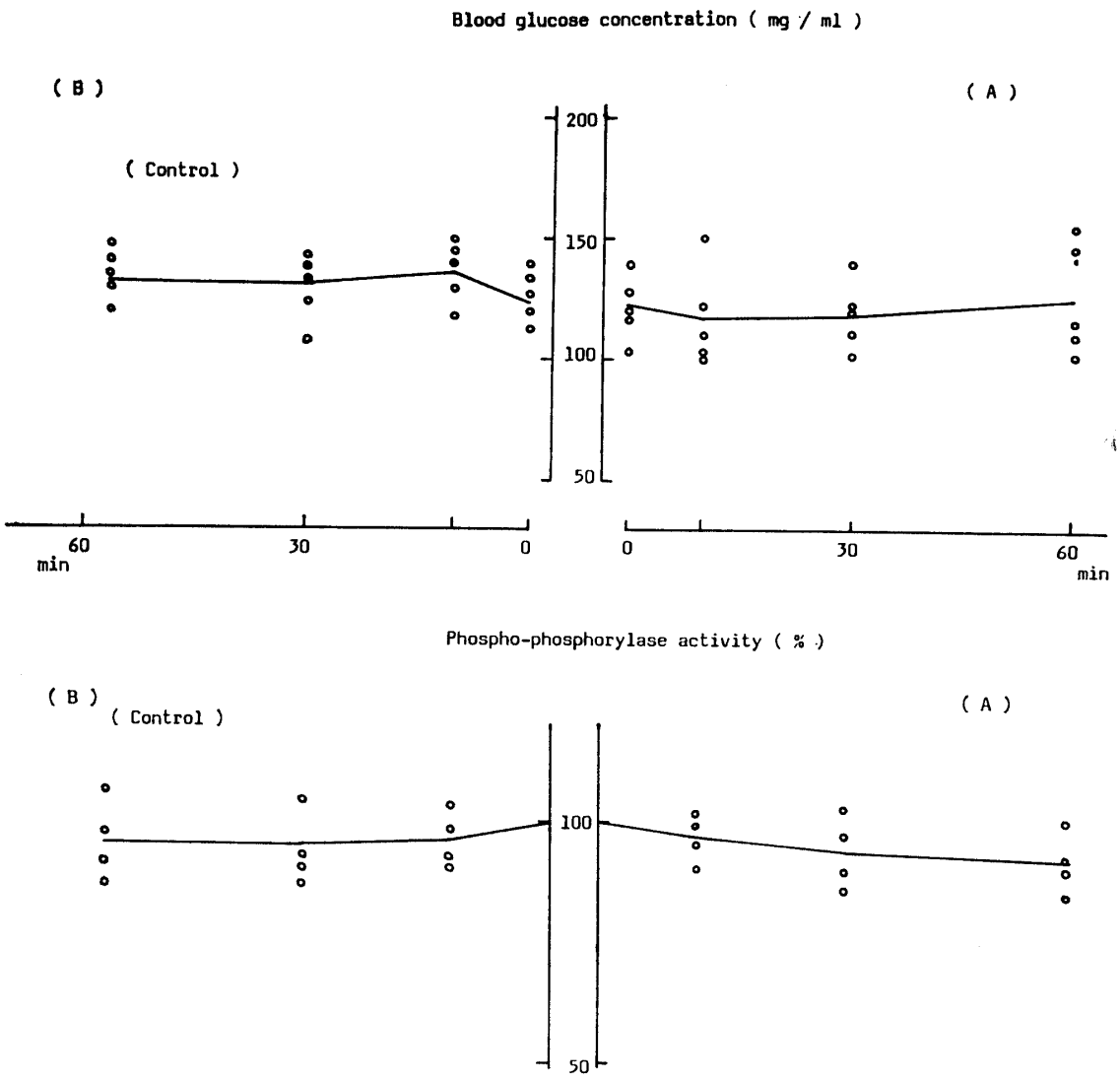

Fig. 2. Effect of angiotensin II on blood glucose concentration and phospho-phosphorylase activity after infusion of propranolol (5 mg/kg). Upper part : time-response curve of blood glucose to this polypeptide. Ordinates : blood glucose concentration (mg/dl). Abscissae : time course (min). A : intravenous injection of angiotensin II (50 μg/kg). B : control. Lower part : time-response curve of phospho-phosphorylase to this polypeptide. Ordinates : phospho-phosphorylase activity (% of its initial value (0 min)). Abscissae : time course (min). A : intravenous injection of angiotensin II. B : control.

may contribute to the enzymatic activation, but for the clarification of this mechanism, more adequate data will be required.

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