Effect of Angiotensin 11 on Blood Glucose Level in the Dog.* (30285)

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It has long been known that a number of pressor agents have metabolic actions as well as their effects on the blood pressure. The most familiar example of this is the rise in blood glucose produced by epinephrine, norepinephrine and related substances(1). Although it has been suggested that angiotensin 11 can also raise the blood glucose level(2,3), experimental data have not been presented. Further, it has been suggested that angiotensin 11 may cause an increased endogenous production of catecholamines(4,5). Should this occur to any significant degree, these substances would be expected to raise the blood glucose, even if angiotensin 11 could not do so directly.

The purpose of this work was therefore to examine the effect of angiotensin 11 on the blood glucose level in the dog.

Methods. Sixteen experiments were performed on 7 trained, female dogs. No anesthetic was used and the dogs were fasting for 12 to 18 hours before the experiment. The dogs weighed 15 to 24 kg.

The experiments were divided into 3 groups: 1) control (5 experiments) 2) effect of angiotensin on venous blood glucose (6 experiments) and 3) effect of angiotensin on arterial blood glucose (5 experiments).

The procedure lasted 90 minutes. In the control group, N NaCl was infused at 0.191 ml/min throughout. In experiments in which angiotensin 11 was used, N NaCl was infused for 30 minutes at 0.191 ml/min, then angiotensin 11 at 0.100 μg/kg/min for 30 minutes, then a final 30 minutes of N NaCl at 0.191 ml/min. The angiotensin 11 was appropriately diluted so that it was delivered at the same speed as the saline. The synthetic octapeptide, asparginyl valine-5 angiotensin (HYPERTENSIN, CIBA) was used. A syringe pump was used for the infusions, which were intravenous in all cases.

Urine was collected at half-hourly intervals through an indwelling catheter. Blood samples (6 ml) were taken from a Cournand needle, in a forearm vein or in the femoral artery, at 15-minute intervals throughout the procedure, so that 2 estimations of blood glucose were performed in each of the 3 half-hour periods. Heparin was used as an anticoagulant.

In the experiments in which the arterial blood glucose was studied the mean blood pressure was measured by attaching a manometer to the arterial needle during the control and angiotensin periods.

Blood glucose was estimated immediately using the Nelson-Somogyi technique(6). The urine samples were tested for glucose qualitatively using glucose oxidase test paper.

Results. The results are summarized in Table I. Each figure given for blood glucose level is the mean of the 2 readings for that half-hour period. It can be seen that in many instances in both control and angiotensin studies there was a slight increment in blood glucose level in the second and third half-hour periods when compared with the values in the first half-hour. However, the mean increase in control and angiotensin experiments was very similar and quite small. It was not possible to show any differences statistically between the 3 groups of experiments.

Glycosuria did not occur in any experiment. The mean pressor response in experiments with an arterial needle in place was 48 mm Hg. The pressor response was evenly maintained throughout the 30-minute angiotensin infusion.

Discussion. The data indicate that this dose of angiotensin 11 has no influence on blood glucose over the time period studied in the fasting dog. The dose was selected as being one which produces a large pressor response, although it is unlikely that endoge-

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TABLE I. Effect of 0.100 μg/kg/min of Angiotensin 11 on Venous and Arterial Blood Glucose Levels in Dogs Compared to Controls in Which Only Saline Was Infused. Each reading is the mean of 2 measurements in each half-hour period.

Type of sample	Infusion	Time in min	Exp 1	Exp 2	Exp 3	Exp 4	Exp 5	Exp 6	Mean Δ
Venous	N NaCl	0-30 bl gluc mg%	91.7	77.5	89.6	78.8	88.3		
	"	30-60 Δ bl gluc*	+ .1	+10.1	+ 9.4	- 6.0	+8.1		+4.34
	"	60-90 Δ bl gluc*	- 2.5	+11.2	+10.4	+1.8	+9.0		+7.38
Venous	N NaCl	0-30 bl gluc mg%	106.5	100.5	77.2	88.7	94.5	94.5	
	Angio-tensin	30-60 Δ bl gluc*	+13.7	+ 5.0	+14.3	- 3.9	- 1.5	- 2.5	+4.18†
	N NaCl	60-90 Δ bl gluc*	+ 9.0	+ 7.0	+15.1	+1.5	- 4.1	- .5	+4.67†
Arterial	N NaCl	0-30 bl gluc mg%	81.0	97.0	96.1	99.6	73.9		
	Angio-tensin	30-60 Δ bl gluc*	+ 7.5	+ 4.6	+ 9.2	+8.3	+14.5		+8.82†
	N NaCl	60-90 Δ bl gluc*	+11.5	+ 2.5	+ 5.5	+6.9	+18.2		+8.92†

* Δ Bl gluc = change in blood glucose from mean control value in first 30 min (mg%).
† Not significantly different from the mean Δ in the experiments in which saline was infused throughout (top group).

nous angiotensin levels would reach this height under most physiological conditions.

Since epinephrine is capable of elevating the blood glucose well within an hour in the dog(7), one would have expected to see a rise in blood glucose in our data on this basis, if angiotensin 11 were a significant adrenal medullary stimulant. Reports suggesting the latter have involved complicated experimental procedures(4,5), which may have had some influence on catecholamine production. Also, such stimulation of the adrenal medulla has only followed injection of angiotensin into arteries leading to the adrenal glands. The normal release of angiotensin is into the renal vein, hence the physiological significance of such arterial injections is doubtful.

The duration of the study was, however, probably not sufficient to detect a rise in blood glucose on the basis of increased cortisol production. The latter has been shown to occur under some experimental conditions in response to angiotensin 11 infusion in dogs (8), although the physiological significance of this is not clear.

The suggestion that angiotensin 11 can cause glycosuria, either by raising the blood glucose(2,3) or by decreasing the renal tubular reabsorption of glucose(2) was not upheld in our results.

The small rises in blood glucose in all 3 groups of experiments in Table I were thought to be due to the stress of the procedure, which, although slight, may have resulted in a minimal endogenous release of catecholamines.

Summary. Angiotensin 11 given by intravenous infusion in a moderately large dose does not elevate either venous or arterial blood glucose levels within one hour in the conscious dog, nor does it produce glycosuria. This suggests that secondary release of catecholamines does not play a significant role in the physiological responses to angiotensin 11. The absence of glycosuria indicates that the renal tubular reabsorption of glucose was not affected by angiotensin 11 at this level of filtered load of glucose.

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Early Development in Monkeys of Cutaneous Resistance to Reinfection with *Rickettsia tsutsugamushi.* (30286)

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In the late 1940's the U. S. Army Scrub Typhus Research Unit in Malaya reported a striking difference in incidence of eschars in volunteers infected with scrub typhus who had received chloramphenicol prophylactically and in those who had not. In one experience, 4 subjects who did not receive chloramphenicol during a field trial developed eschars while an equal number of men who were given the drug during and after exposure failed to show such lesions. To explain the role of prophylaxis in eschar formation Smadel *et al* (1,2) postulated that during the suppression of growth of rickettsiae by the drug, sufficient local immunity developed in the skin to prevent subsequent development of an eschar. However, no experiments were performed by the group in Malaya to test the validity of the hypothesis. In 1951 studies were undertaken to elucidate this point by determining in monkeys the reactions to multiple intradermal inoculations of scrub typhus rickettsiae administered intermittently over periods of 1 and 2 weeks. The findings are presented now, even though the data are not extensive, in the hope that the observations will add information on the effects of the immune processes in development of skin lesions in scrub typhus.

Materials and methods. Nine young adult rhesus monkeys were inoculated into the anterior abdominal wall with 300 mouse ID_{50} of the Karp strain of *Rickettsia tsutsugamushi* contained in 0.2 ml of infected yolk sac suspension (63rd egg passage). Infectivity titrations were performed in mice each time an aliquot of infectious yolk sac pool was thawed for use. Group 1 monkeys received 3 inoculations at 3-day intervals; Group 2 monkeys received 4 inoculations, the second being given 6 days after the first and the third and fourth following at 3-day intervals thereafter; Group 3 monkeys also received 4 inoculations, the second being given 9 days after the first and the remaining 2 inoculations thereafter at 3-day intervals (Table I, column 3). The animals were examined each day for 17 days after the initial inoculation for developent of dermal lesions and for occurrence of fever. All monkeys were bled on days 0 and 31 for serum for use in serologic tests and a single monkey (Monkey 13) was bled on the second day of fever to obtain blood for rickettsial isolation.

Results. Development of specific skin lesions. Fig. 1 presents detailed results obtained in Monkey 12 and is illustrative of the dermal reactions obtained in the 3 animals in Group 1. On day 4 a lesion appeared at the site of the first injection and consisted of a small, slightly raised, erythematous area. By the sixth day the lesion had progressed to a necrotic eschar and scab. Healing began on the ninth day and on the seventeenth day, the scab had fallen off leaving a healed, slightly raised scar. A lesion at the site of the second injection was discernible 3 days after administration of the inoculum. It appeared overnight and on the first day of its appearance had reached its maximum size; this lesion did not progress to necrosis. It is seen in Fig. 1 that 6 days elapsed between inoculation and formation of a maximum-sized eschar at the site of the