PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE 166, 35–38 (1981)

Effect of Captopril on the Blood Pressure Response to Angiotensin I in Turkeys (41020)[1]

MELVIN J. FREGLY, CHARLES F. SIMPSON, AND WILLIAM P. PALMORE

Department of Physiology, College of Medicine and Department of Preventive Medicine, College of Veterinary Medicine, University of Florida, Gainesville, Florida 32610

Abstract. These studies were designed to determine the presence of an angiotensin-converting enzyme in turkeys. Captopril, a converting enzyme inhibitor, prevented the elevation of diastolic, systolic, and mean blood pressures which occurs characteristically in response to administration of angiotensin I. However, the responsiveness of blood pressure to administration of angiotensin II and norepinephrine was maintained. Thus, the results suggest the presence of an angiotensin-converting enzyme in turkeys.

Little is known about the renin–angiotensin system of birds as illustrated by the number of reviews that fail to mention its presence in this species (1–6). However, Krista *et al.* (7) reported the measurement of plasma renin activity of the turkey by a commercial radioimmunoassay kit. The mean value was in the low range reported for normal humans (8). Using the same radioimmunoassay kit, we have been unable to detect plasma renin activity in our turkeys on three separate occasions.

Since the antibody used in this commercially available radioimmunoassay kit is raised in rabbits against angiotensin I coupled to rabbit serum albumin, it is possible that subtle differences in specificity may exist in the serum of the turkey which reduce the sensitivity of the assay. In addition, other factors affecting the sensitivity of the reaction, such as pH optimum, have not been established for the turkey. Hence, the studies described below were conducted to determine the effect of inhibition of the angiotensin-converting enzyme in turkeys on the responses of their blood pressure to administration of angiotensin I, angiotensin II, and norepinephrine.

Methods. Five broad-breasted white male turkeys, weighing from 3.4 to 8.6 kg were anesthetized with sodium pentobarbitol (35 mg/kg) which was supplemented as needed to maintain a stable systemic arterial pressure. One carotid artery was cannulated with PE-50 tubing and connected to a Narco Bio systems pressure transducer (P1000) which was coupled to a Narco Bio Systems polygraph. One wing vein was also cannulated with a 20-gauge indwelling catheter (Longdwel Catheter–Needle, Becton–Dickinson, Rutherford, N.J.) and used for injection of drugs.

The protocol for each bird varied, but in all cases the diastolic, systolic, and mean blood pressures in response to a pressor dose of angiotensin I[2] were measured before and after treatment with captopril[3] (30 mg/kg body wt, iv). The maximal pressures, measured within 3 min after drug treatment, were used to assess the results.

Results. Injection of either 6.0 or 12.0 μg of angiotensin I/kg, iv to turkey No. 1 resulted in similar increases in systolic, diastolic, and mean arterial pressures (Fig. 1A). Control blood pressures increased to 168/100 and 170/110 mm Hg following injection of 6.0 and 12.0 μg angiotensin I/kg respectively. After blood pressure was stabilized for 5 min following injection of angiotensin I, angiotensin II[2] (24.0 μg/kg) was administered. This compound increased blood pressure to even higher levels, but control pressures were also greater. Within 6 min

[1] Supported by Grants HL-14526-09 and HL-17909 from the National Heart, Lung, and Blood Institute.

[2] United States Biochemical Corp., Cleveland, Ohio.

[3] Captopril (D-3-mercapto-2-methylpropanoyl-L-proline) was kindly supplied by Dr. Zola P. Horovitz of the Squibb Institute for Research, Princeton, N.J.

0037-9727/81/010035-04$01.00/0

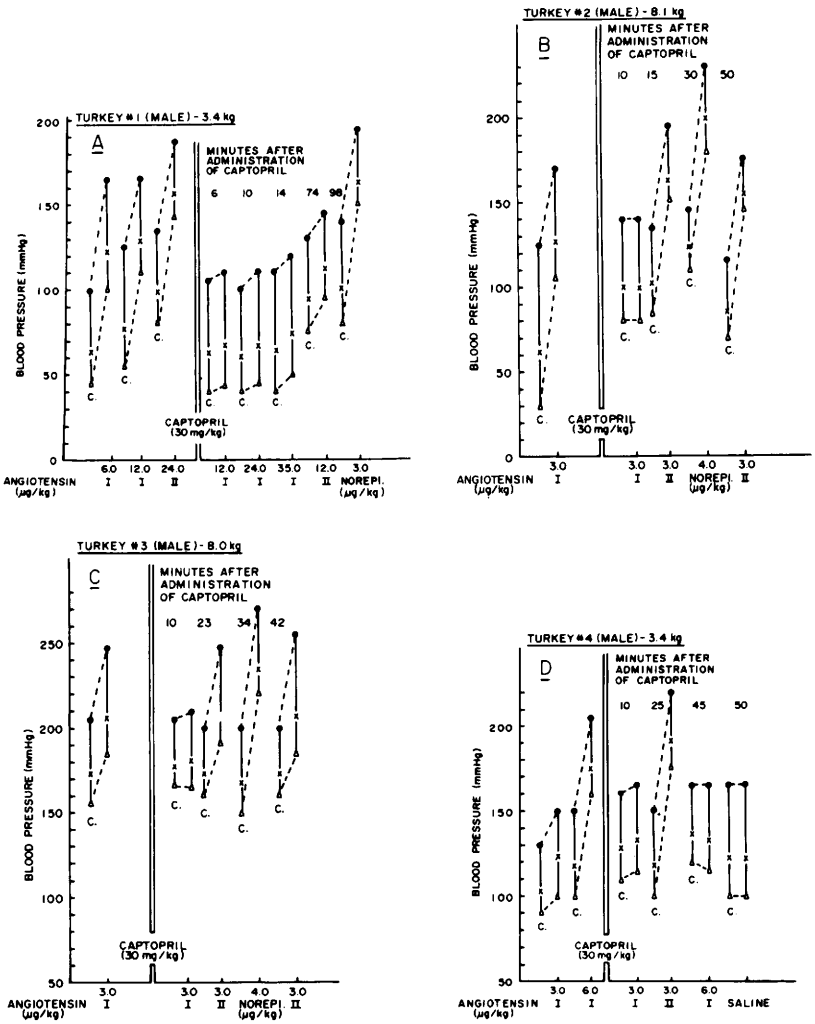

FIG. 1. The effect of captopril (30 mg/kg body wt, iv) on the response of blood pressure of male turkeys to administration of angiotensin I, angiotensin II, and norepinephrine is shown. The lowest pressure (triangle) is diastolic pressure while the highest (dot) is systolic pressure. Mean blood pressure is designated by x. Control pressure prior to administration of the pressor agents is designated as C. The results of studies in four turkeys are shown.

after blockade with captopril, injection of angiotensin I (12.0 μg/kg) had no effect on blood pressure. At 10 min after acute injection of captopril, 24.0 μg angiotensin I/kg also had no effect on blood pressure. A similar response ensued following injection of angiotensin I at 35.0 μg/kg. However, injection of either 12.0 μg angiotensin II/kg or 3.0 μg norepinephrine/kg at 74 and 98 min, respectively, after treatment with captopril induced a rise in blood pressure. (Fig. 1A).

Similar results were observed in turkey No. 2 (Fig. 1B). In the case of this bird, as with turkey No. 3 (Fig. 1C), 3 μg angiotensin I/kg increased blood pressure during the control period prior to injection of captopril (30 mg/kg, iv). In the case of turkey No. 2, the elevation of blood pressure was much greater than that observed in turkey No. 3 for the same dose of angiotensin I. Ten minutes after treatment with captopril, angiotensin I (3 μg/kg) had no effect on blood pressure. From 15 to 34 min after treatment

with captopril, injection of either angiotensin II (3.0 μg/kg) or norepinephrine (4.0 μg/kg) elevated blood pressure significantly. Injection of angiotensin II at 42 (turkey No. 3) and 50 (turkey No. 2) min after treatment with captopril again increased blood pressure (Figs. 1B and C).

In turkey No. 4, (Fig. 1D) injection of 3 and 6 μg angiotensin I/kg increased blood pressure in a graded fashion prior to blockade with captopril. After blockade with captopril, injection of either 3.0 or 6.0 μg angiotensin I/kg at 10 and 45 min, respectively, after treatment with captopril had no effect on blood pressure. However, injection of angiotensin II (3.0 μg/kg) elevated blood pressure. An iv injection of isotonic saline (0.1 ml/kg) was without effect (Fig. 1D).

In the case of turkey No. 5, injection of 3.5 μg angiotensin I/kg increased blood pressure prior to injection of captopril (Fig. 2). After treatment with captopril, the same dose of angiotensin I, administered at either 10 or 45 min after blockade, was without effect on blood pressure. Angiotensin II (3.5 μg/kg) and norepinephrine (5.0 μg/kg) increased blood pressure.

Injection of captopril had a negligible effect on blood pressure 10 to 20 min after treatment. One turkey (No. 1) had a marked fall in blood pressure; one had a large increase (No. 2), while the remaining three turkeys had slight to modest increases in pressure. Reasons for these differences are unknown.

These studies show that after administration of captopril to turkeys (30 mg/kg iv), a blockade of the effects of angiotensin I on blood pressure was observed within 6 min and persisted for at least 45 min.

Discussion. The results of these studies suggest that an angiotensin-converting enzyme, inhibited by the angiotensin-converting enzyme inhibitor, captopril, is present in the broad-breasted white turkey. Thus, injection of angiotensin I prior to treatment with captopril elicited an elevation in both systolic and diastolic blood pressures, presumably as a result of its conversion to angiotensin II. However, after as long as 45 min following treatment with captopril, an elevation of blood pressure did not occur when angiotensin I was injected. Although the converting enzyme was inhibited, blood pressure of these birds was responsive to injection of either angiotensin II or norpinephrine. These results indicate both the presence of an angiotensin-converting enzyme in the turkey and its inhibition by the converting enzyme inhibitor, captopril.

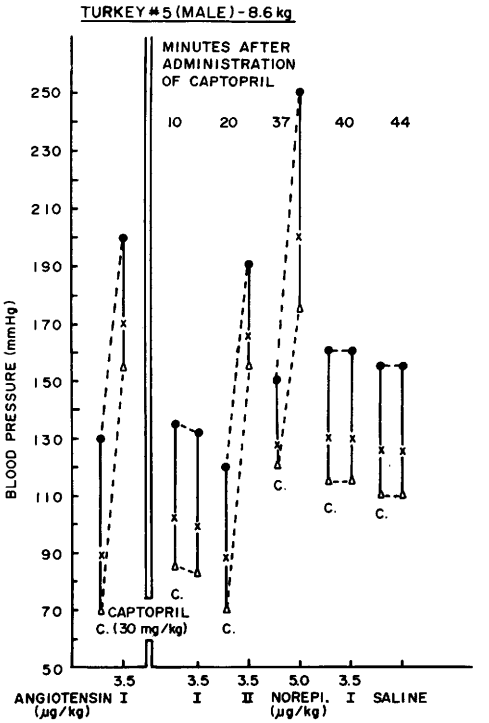

FIG. 2. The effect of captopril (30 mg/kg body wt iv) on the response of blood pressure of a male turkey to administration of angiotensin I, angiotensin II, and norepinephrine is shown. Designations in this figure are the same as those in Fig. 1.

The unanesthetized, broad-breasted turkey normally has a high systolic and diastolic blood pressure (180/140 mm Hg) (9, 10). Pentobarbital anesthesia lowered blood pressure in four of the five birds. Reasons for the failure to lower the blood pressure of turkey No. 3 are unknown, but may be related to the depth of anesthesia achieved in this bird (Fig. 1C). In spite of the initial level of blood pressure, captopril prevented an increase in blood pressure in response to administration of angiotensin I in all five birds.

The vertebrate class, Aves, has not previously been shown to have an angiotensin-converting enzyme. While these studies have not isolated the enzyme specifically, they suggest its presence on the basis of its inhibition by captopril. These studies also suggest that captopril does not affect the receptor for angiotensin II on vascular smooth muscle, since angiotensin II elevated both diastolic and systolic blood pressures in the presence of captopril. Inhibition of the angiotensin-converting enzyme also failed to affect vascular response to norepinephrine in the turkey. While these studies suggest the presence of a renin–angiotensin system in the turkey, its importance in the maintenance of blood pressure and its contribution to the high blood pressure normally observed in this species remain for further study.

We thank Mr. J. W. Carlisle for technical assistance and Mrs. C. Edelstein for the graphic illustrations.

1. Page, I. H., and McCubbin, J. W., "Renal Hypertension," p. 121, Year Book Med. Pub., Chicago (1968).
2. Davis, J. O., Amer. J. Med. **55**, 333 (1973).
3. Oparil, S., "Renin 1976," p. 94, Eden Press, Montreal (1976).
4. Davis, J. O., and Freeman, R. H., Physiol. Rev. **56**, 1 (1976).
5. Ganten, D., Hutchinson, J. S., Schelling, P., Ganten, U., and Fischer, H., Clin. Exp. Pharm. Physiol. **3**, 103, 1976.
6. Peach, M. J., Physiol. Rev. **57**, 313 (1977).
7. Krista, L. M., Nachreiner, R. F., and McDaniel, G. R., Poultry Sci. **57**, 553 (1977).
8. Laragh, J. H., Baer, L., Brunner, H. R., Buhler, F. R., Sealey, J. E., and Vaughn, E. D. *in* "Hypertension Manual, Mechanisms, Methods, Management," p. 313, Donnelley, New York, (1973).
9. Simpson, C. F., Fregly, M. J., and Neilson, J. T. M., Toxicol. Appl. Pharmacol. **48**, 67 (1979).
10. Simpson, C. F., and Fregly, M. J., Artery **4**, 453 (1978).

Received July 21, 1980. P.S.E.B.M. 1981, Vol. 166.