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Metabolism of Aldosterone in Dogs with Renovascular Hypertension (38476)

J. ALAN JOHNSON, JAMES O. DAVIS, AND WILLIAM S. SPIELMAN

Department of Physiology School of Medicine, University of Missouri, Columbia, Missouri 65201

The secretion of aldosterone has been studied extensively (1) in dogs with experimental hypertension secondary to renal artery stenosis. In dogs with malignant hypertension,[1] the rate of secretion of aldosterone was increased, but in dogs with chronic renal hypertension aldosterone secretion was normal. In a recent study (2) in patients with essential hypertension, it was found that the elevated plasma aldosterone level resulted from a decrease in the metabolic clearance rate of aldosterone rather than from increased aldosterone secretion. The present study was designed to examine the rate of aldosterone metabolism in dogs with experimental renovascular hypertension. Hypertension was produced by renal artery construction and studies were made in both malignant renal hypertensive animals and in dogs with chronic renal hypertension.

Methods. Sixteen female mongrel dogs, weighing from 14.5 to 23.0 kg, were used in this study. The animals were fed a commercial diet which provided a daily intake of 65 mEq of sodium and 55 mEq of potassium; water was available *ad libitum*.

Arterial blood pressure was measured in all dogs at least three times each week. The conscious dog was placed in a supine position on a table and pressure was measured by direct femoral arterial puncture with a 22 gauge needle attached to a pressure transducer (Statham P-23Db); pressures were recorded on a Sanborn model 7700 recorder. Only those dogs which consistently showed control arterial pressures of under 130 mm Hg were used in the study. Renovascular hypertension was produced in nine dogs by removing the right kidney and approximately 10 days later constricting the left renal artery with a Goldblatt clamp. All surgical maneuvers were performed under pentobarbital anesthesia (35 mg/kg body wt) employing sterile surgical procedures. Five of the dogs developed malignant hypertension characterized by lethargy, vomiting, and a fall in body temperature; these animals also had elevated plasma renin activity, serum urea nitrogen, and plasma potassium concentration, and a decrease in the plasma concentration of sodium. Death occurred in these dogs within 2–4 days. The other four dogs developed chronic hypertension in which the only apparent abnormality was the elevation in arterial pressure. The seven normal dogs had no surgical procedures performed.

Tritiated aldosterone (from New England Nuclear Corporation), 1 mCi, with a specific activity of 52 Ci/m*M* and a radiochemical purity of 98%, was rechromatographed in a benzene:methanol:water system, eluted with ethanol, and stored in 1 ml aliquots of approximately 15 μCi in capped vials at $-15°$. On the day of the experiment a piece of polyethylene tubing (PE 50) was placed in the saphenous vein of the unanesthetized dog; this served as a route for injecting the tritiated aldosterone. Prior to injection into the dog, a 1 ml aliquot of tritiated aldosterone was diluted with isotonic saline to 25 ml in a volumetric flask. One-half ml of the diluted isotope was removed and was diluted further with saline to 50 ml in a volumetric flask. An aliquot of this was analyzed for labeled aldosterone concentration in order to determine the exact amount injected; the remaining 24½ ml was injected into the dog. After injecting the labeled steroid, 20 ml samples of blood were obtained from the jugular vein at 5, 10, 15, 20, 30, 45, 60, 75, and 90 min. These heparinized samples were centrifuged and the plasma samples were stored frozen until analyzed. Plasma concentrations of tritiated aldosterone were determined by the method described previously (3, 4).

Plasma renin activity was determined by

[1] The term malignant hypertension refers to the situation in which the animals developed a rapid fulminating type of experimental disease characterized by lethargy, vomiting, decreased body temperature, uremia, hyperkalemia and a marked elevation in plasma renin activity; death occurred within 2–4 days after the onset of these symptoms.

TABLE I. ALTERATIONS IN ARTERIAL PRESSURE AND PLASMA CONSTITUENTS IN EXPERIMENTAL RENAL HYPERTENSION.

	Arterial pressure (mm Hg)	Rectal temp. (deg C)	Plasma renin activity (ng AII/ml)	Serum urea nitrogen (mg %)	Plasma Na conc. (mEq/L)	Plasma K conc. (mEq/L)
Normal dogs (n = 6)	119 ± 2	101.6 ± 0.3	5.5 ± 0.7	14.2 ± 1.9	145 ± 0.5	4.7 ± 0.1
Chronic hypertensive dogs (n = 4)	183 ± 14	101.6 ± 0.3	6.0 ± 0.7	19.5 ± 1.5	142 ± 1.4	4.4 ± 0.1
P[a]	<0.01	NS	NS	NS	NS	NS
Malignant hypertensive dogs (n = 5)	186 ± 7	98.6 ± 0.5	55 ± 14	246 ± 23	134 ± 1.5	8.0 ± 0.6
P	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01

[a] Refers to changes from the normal dogs. The test statistic used was Student's t test for group comparisons. NS (not significant) = $P > 0.05$. Values are means ± S.E.M.

the method of Schneider *et al.* (5). Plasma concentrations of sodium and potassium were determined by flame photometry. Serum urea nitrogen determinations were performed by the clinical pathology laboratory of the University Hospital.

Results. As shown in Table I, the arterial pressures were greatly elevated ($P < 0.01$) in both groups of hypertensive dogs. The malignant hypertensive animals also had a decrease in rectal temperature, with increased levels of plasma renin activity, serum urea nitrogen and plasma potassium concentration, and a decrease in plasma sodium concentration. These functions were all normal in the chronic hypertensive dogs.

The data on the rate of removal of aldosterone from plasma for the normal dogs and for both groups of hypertensive dogs were analyzed in the same manner. The plasma concentrations of tritiated aldosterone, in percent of injected dose per liter, were averaged for each group at each time period. A semilogarithmic plot of these averages against time revealed a curve that could be defined by a multiple exponential equation. Because the curve appeared linear from the 30 min to the 90 min samples a regression line was determined for these values by the method of least squares (6). This line was extrapolated to zero time, and the extrapolated values at 5, 10, 15 and 20 min were subtracted from the experimentally determined values for these times. These differences also formed a straight line for which a regression line was calculated. Thus, it was apparent that the removal rates of aldosterone in normal dogs and in each group of hypertensive dogs could be defined adequately by a double exponential function (7) of the form

$$y_t = Ae^{-k_1 t} + Be^{-k_2 t}$$

where y_t is the plasma steroid concentration at time t, k_1 and k_2 are the decay constants for the fast and slow components respectively, and A and B are constants. The value for A was the ordinate intercept of the extrapolated regression line of the fast component, and the value for B was the ordinate intercept of the slow component; the slopes of the regression lines of the fast and slow components were the decay constants k_1 and k_2. This type of decay curve suggests that aldosterone distributes into two compartments, an inner compartment which includes the plasma and from which aldosterone is metabolized and an outer compartment into which aldosterone is reversibly transported from the inner compartment (8).

Figure 1 gives the plots of the calculated decay curves for aldosterone in seven normal dogs and in the four chronic hypertensive animals; Fig. 2 compares the calculated aldosterone decay curves in the five malignant hypertensive dogs with that of the normal dogs. The half-life ($T_{1/2}$) values for aldosterone were obtained by dividing 0.693 (the natural logarithm of 2) by the decay constants. The half-life of the slow component

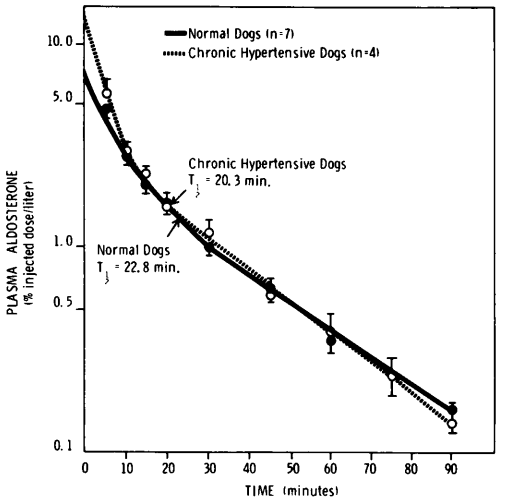

FIG. 1. Disappearance curves for aldosterone in normal dogs and in dogs with chronic renal hypertension.

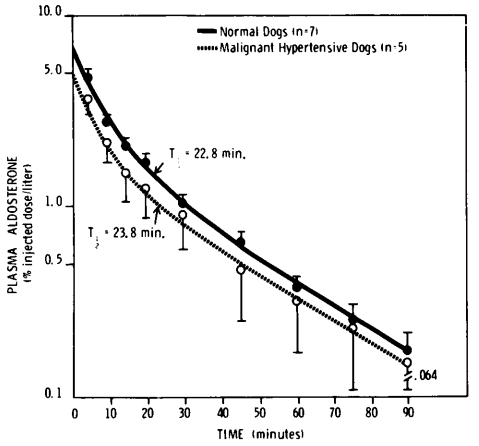

FIG. 2. Disappearance curves for aldosterone in normal dogs and in dogs with malignant renal hypertension.

averaged 22.8 ± 1.5 (SEM) min for the normal dogs; the half-life averages for the chronic and the malignant hypertensive dogs were 20.3 ± 0.7 and 23.8 ± 4.8 min respectively. The slopes of the slow components for the normal dogs were compared statistically to those of the chronic hypertensive dogs and to those of the malignant hypertensive dogs by an analysis of covariance (6); no significant differences were seen between the normal dogs and either of the two groups of hypertensive dogs.

Discussion. The plasma level of aldosterone is a function of both the secretion rate of aldosterone and its metabolic clearance rate. Under steady state conditions, the plasma level is equal to the secretion rate divided by the metabolic clearance rate; consequently, a decrease in the metabolic clearance rate results in a higher plasma level of aldosterone. Studies have indicated that the liver is the organ principally responsible for the removal of aldosterone from the plasma, although there is some extrahepatic removal (3, 9).

There have been variable reports on the question of whether or not aldosterone metabolism is altered in patients with various forms of hypertension. Vecsei *et al.* (10) determined the rate of aldosterone secretion and the metabolic clearance rate of aldosterone in patients with a variety of conditions; their data indicated that in patients with renal artery stenosis and hypertension the aldosterone secretion rate was increased, but the metabolic clearance rate of aldosterone was unaltered. Similar findings were reported by Lommer *et al.* (11) for hypertensive patients with renal artery stenosis. These workers (11) also found no change in the metabolic clearance rate of aldosterone in patients with mild or severe essential hypertension; it is noteworthy, however, that the patients with severe essential hypertension did have an increase in aldosterone secretion. In contrast, Nowaczynski *et al.* (2) found the rate of aldosterone secretion to be within normal limits in their patients with benign essential hypertension, but observed an increase in plasma aldosterone concentration which was the result of a decrease in the metabolic clearance rate of aldosterone. These workers have continued to study this problem over several years and have accumulated an increasing amount of data to support their thesis that aldosterone metabolism is decreased in patients with benign essential hypertension (12).

In the present study, dogs with chronic hypertension or with malignant hypertension had essentially the same plasma aldosterone half-life as did the normotensive dogs, and as indicated in Fig. 1 the plasma aldosterone decay curves for the chronic hypertensive

dogs and the normal dogs were very similar. Therefore, these data suggest that no major alterations in plasma aldosterone removal occurred in experimental renovascular hypertension. Because the secretion rate of aldosterone is not increased in dogs with chronic renovascular hypertension (1), these findings suggest that the plasma level of aldosterone is within normal limits in this experimental hypertensive model. Although experimental hypertension in the dog may not be entirely analogous to the hypertensive syndromes observed clinically in the human, the present study does suggest that at least in the dog the chronic maintenance of an elevated arterial pressure is not dependent on an elevation in plasma aldosterone concentration.

Summary. The rate of metabolism of aldosterone was measured in seven normal dogs, 4 dogs with chronic renal hypertension and five dogs with malignant renal hypertension. Tritiated aldosterone was injected intravenously and the rate of disappearance of authentic aldosterone was determined. The disappearance curves were resolved into two exponential components and the plasma half-life was measured from the slow component which reflects the rate of metabolism of aldosterone. The half-life of aldosterone was essentially the same for the three groups of dogs. It is concluded, therefore, that the rate of aldosterone metabolism is normal in dogs with experimental renal hypertension.

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