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Effect of volume depletion on the afferent arterioles in the avian kidney*

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Summary. Nine white leghorn chickens were injected i.m. with furosemide (10 to 60 mg/kg body weight) twice daily for 18 days. The birds were then anesthetized with a combination of equithesin and diazepam and the kidneys perfused via the heart. Kidney tissue was sectioned serially and the granular epithelioid cells were counted in the juxtaglomerular apparatuses of the furosemide treated birds and in 3 normal chickens. Hyperplasia and hypergranulation of the epithelioid cells was found to occur in the juxtaglomerular apparatuses of both mammalian and reptilian type nephrons (with and without Henles loop) in the furosemide treated group. This finding was interpreted as an effect of hypovolaemia on the juxtaglomerular apparatuses. Furosemide caused an immediate stop in weight gain, an increase in the erythrocyte volume fraction and a sudden drop in blood pressure. The blood pressure later rose to subnormal levels. The heart rate was not altered. Plasma sodium and chloride fell significantly one day after furosemide administration and remained low throughout the experiment. Potassium fell during the second part of the experimental period. Captopril was injected after 18 days of furosemide treatment and lowered the blood pressure significantly. This was interpreted as indirect evidence for the presence of renin in the granular epithelioid cells and indicates the importance of the renin angiotensin system in maintaining the blood pressure in hypovolaemic conditions.

Key words: Juxtaglomerular apparatus – Renin-Angiotensin system – Hypotension – Furosemide – Chickens

* Dedicated to Prof. Dr. Dr. h.c. A. Bohle on his 65th Birthday

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Introduction

Furosemide is a potent loop diuretic that interferes with the macula densa feedback mechanism (Deetjen 1966; Thurau 1972; Burg et al. 1973; Wright and Schnermann 1974). Prolonged administration may cause sodium depletion, hypovolaemia and activation of the renin angiotensin system (RAS) (Vander 1967; Granger et al. 1972; Davis and Freeman 1976; Hollenberg et al. 1977). Numerous studies have shown hypergranulation and hyperplasia of the epithelioid cells in the afferent arterioles of the glomeruli following sodium depletion in mammalian species (Hartroft et al. 1953; Pitcock et al. 1959; Tobian 1967; Endes et al. 1963; Bohle and Sitte 1966). Taylor et al. (1970) and Siller (1971) found increased granulation and hyperplasia of the epithelioid cells in chickens on a low sodium diet, and after mercury diuretic. These studies however, did not differentiate between the mammalian and reptilian type nephrons.

The avian kidney has two types of nephrons, a mammalian type with Henle's loop lying in the renal medulla and a reptilian type without Henle's loop and without any relationship of the nephrons to the renal medullary tissue (Wideman et al. 1981; Morild et al. 1985). Both types of nephrons have a distinct macula densa in the distal tubule and a fully developed juxtaglomerular apparatus (JGA) (Christensen et al. 1982; Morild et al. 1985; Ogawa and Sokabe 1971). While furosemide is expected to have an effect only on the loop of Henle, the present study was undertaken to investigate if hyperplasia of the epithelioid cells also would occur in reptilian type JGAs belonging to a nephron system without the loop of Henle.

The importance of the RAS in maintaining blood pressure in sodium depleted chickens was

further studied by blocking the formation of angiotensin II with captopril. This angiotensin converting enzyme inhibitor has been used repeatedly to inhibit the formation of angiotensin II in humans (Gavras et al. 1978; Hollenberg et al. 1977; Hollenberg et al. 1981; Textor et al. 1981).

Materials and methods

Nine female white leghorn chickens, 15 weeks old, hatched at our department and fed on a standard diet with free access to tap water, were used for this study. The diet contained 0.19% NaCl, 1.20% Ca, 0.65% P and 29% protein.

The chickens weighed 1250±187 g before the experimental procedure started and were kept in individual cages. Blood pressure, serum electrolytes, uric acid, creatinine and erythrocyte volume fraction (EVF) were recorded twice before the injections with furosemide (Lasix Vet., Hoechst, FRG, 50 mg/ml) started on day 10. The blood pressure was measured with a non-invasive Doppler method. For this purpose a conical metal cuff, internally lined with an inflatable latex coat and connected to a sphygmomanometer, was placed on the leg after removal of the feathers. The Doppler ultrasound probe was positioned at the strongest signal point over the plantar arterial arch and the pulse rate registered as an acoustic signal from the Doppler device (Parks Medical Doppler model 822, Parks Medical Electronics, OR, USA). When the latex coat was inflated above the systolic pressure, the Doppler signal extinguished. On deflation, the systolic blood pressure could be read on the sphygmomanometer at the moment the Doppler signal again became audible. This procedure allows repeated recordings of blood pressure in conscious chickens. Each measurement was repeated 2–3 times. The recordings were made early in the afternoon.

Blood pressure was measured at day 1, 6, 11, 13, 15, 19, 21 and 27. The heart rate was recorded at the same time with the Doppler ultrasound device connected to a Hewlett Packard medium gain preamplifier (HP 8802A) and a Hewlett Packard thermic recorder.

The birds were weighed every morning and water intake recorded. Water consumption before the furosemide injections were started was 130±60 ml/day.

Furosemide was given as intramuscular injections twice daily from day 10 during the experimental period at 8.30 in the morning and at 3.30 in the afternoon. The birds were given 20 mg/kg in the morning and 10 mg/kg in the afternoon for the first three days (day 10 to day 12). They received 20 mg/kg twice daily for the next three days (day 13 to day 15). From day 16 the doses were individualized according to the condition and weight of each bird. The maximum dose given was 60 mg/kg per injection. Pilot experiments had shown that we could expect a mortality rate of about 60% if the birds received 20 mg/kg twice a day at the beginning of the experiment.

On day 27 the birds were given a single dose of captopril i.v. (25 mg/kg, Capoten, E.R. Squibb & Sons, NJ, USA). Repeated recordings of heart rate and blood pressure were made. In addition weight, EVF electrolytes, uric acid and creatinine was measured before and 12 h after captopril was given. The last EVF recording and blood sample collections were made a few minutes before the birds were anaesthetized for kidney perfusion.

An untreated control group of 4 birds was also given captopril at the same dose intravenously. Weight, blood pressure and pulse rate were measured as for the other birds.

Blood samples (3–4 ml) from the brachial vein were collected on day 1, 6, 11, 15, 21 and 27. The specimens were analyzed in an autoanalyzer (Technicon SMAC, Terrytown, N.Y., USA) and serum sodium, chloride, potassium, uric acid and creatinine were measured.

The kidneys were fixed by perfusion via the left ventricle of the heart with either 4% neutral formaldehyde or 2% glutaraldehyde in phosphate buffer (Kjærheim 1969). Prior to perfusion the birds were anaesthetised with equithesin (2.5 ml/kg i.m.) in combination with diazepam (5 mg/kg i.v.) given ten minutes later (Christensen et al., unpublished method). Kidney tissue from subcapsular and from deeper parts of the cortex was separately embedded in plexiglass. Semithin serial sections were cut on a Reichert Rotocut microtome and impregnated with silver (Movat 1961). With this procedure it was possible to distinguish between the larger mammalian type glomeruli lying near the renal medulla and the smaller reptilian type glomeruli lying in the subcapsular parts of the cortex (Morild et al. 1985).

The frequency of granular epithelioid cells in six reptilian type and six mammalian type JGAs from five randomly selected furosemide treated birds were examined. Thus there was a total of 30 JGAs of each type. The number of granular epithelioid cells in each JGA examined was recorded. We distinguished between granular cells of the afferent arterioles in preglomerular and intraglomerular position. The number of granular cells was very high in the furosemide treated birds and thus all granular cells in every section throughout each JGA were counted. In this way one granular cell was recorded several times. To find the number of granular epithelioid cells per JGA the sum of granular epithelioid cells counted in all sections from a certain JGA was divided by 5.375. This figure was the average number of sections in which one granular epithelioid cell was seen. To calculate this figure, 200 granular epithelioid cells were closely followed and measured. In three untreated birds, ten JGAs of each type were examined making a total of 30 JGAs of each type as the control material. In the untreated birds only a few granular epithelioid cells were found. Therefore they could easily be followed from section to section and the exact number recorded.

The data was analysed statistically using a Minitab statistics program (Penn. State Univ., USA). A significance level of "p" less than 0.05 was accepted as statistically significant. The results in the text are given as means±SD.

The procedures described in this paper have been carried out in accordance with the ethical guidelines laid down by the National Commission on the Use of Laboratory Animals in Norway.

Results

Serial semithin section microscopy revealed a significant hyperplasia of granular epitheliod cells in the afferent arterioles of both mammalian and reptilian types of JGAs in furosemide treated birds compared to the JGAs of untreated chickens (Figs. 1, 2, Table 1). In the furosemide group, granular epithelioid cells were often found along the whole length of the afferent arteriole in the reptilian type JGA (Fig. 2). In the mammalian type, granular epthelioid cells were found mostly in the distal half on the arterioles. No granular epithelioid cells were found in the interlobular arteries and no evidence of mesangial cells transformed into granular epithelioid cells was seen. In

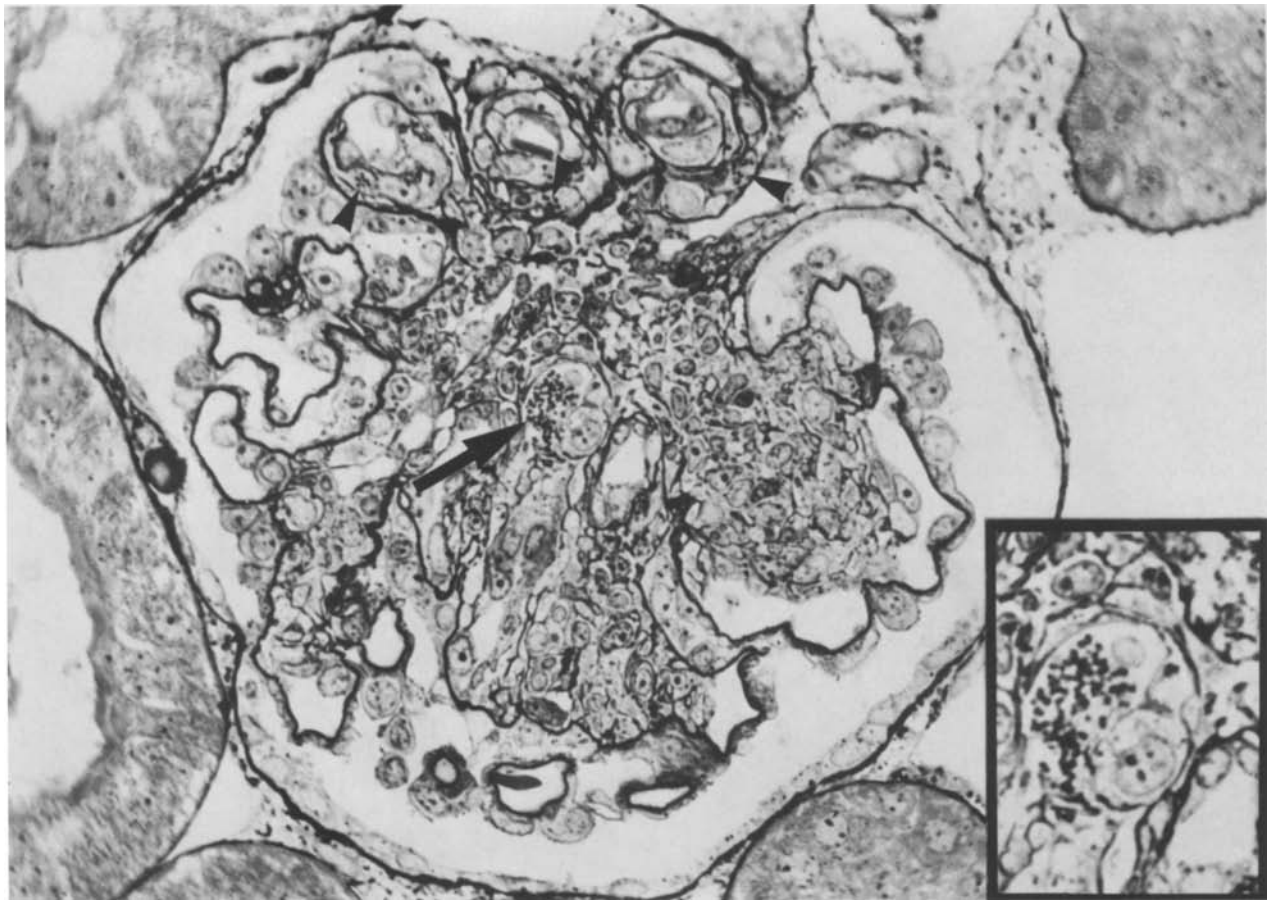

Fig. 1. Mammalian type glomerulus with granular epithelioid cells in the afferent arteriole (*arrowheads*). There are also granular cells in the intraglomerular part of the afferent arteriole (*arrow*). The inlet shows the intraglomerular part of the afferent arteriole with a granular cell at a higher magnification. Silver methenamine staining. Micrograph × 900

Table 1. Number of granular epithelioid cells per afferent arteriole in furosemide treated chickens and controls

	Normal chickens	Furosemide group	Significance level
Preglom. reptilian type JGA	2±1.4	10± 4.6	$p<0.0001$
Intraglom. reptilian type JGA	2±0.9	6± 3.8	$p<0.0001$
Preglom. mammalian type JGA	1±0.8	13± 8.1	$p<0.0001$
Intraglom. mammalian type JGA	3±1.5	20±10.7	$p<0.0001$

3 out of 30 reptilian type JGAs in furosemide treated birds, granular epithelioid cells were found in the wall of the efferent arteriole. These cells were all found intraglomerularly. Granular epithelioid cells were not found in the efferent arterioles of the mammalian type JGAs in furosemide treated birds or in the efferent arterioles of any JGAs in the normal chickens. Mitotic figures were not found in any of the examined arterioles.

Significant changes in several variables were recorded the first day after furosemide administration had started. Body weight, which had been increasing continuously prior to the injections, fell significantly from the first day of furosemide to the next by 109±35 g. The range was between 60–165 g ($p<0.0001$). During the next 11 days weight loss continued, but was much less pronounced. Some birds started to gain weight on the third day after the furosemide injections had started (day 13) but a general weight gain for the group as a whole was not apparent at any time during the experimental period. All the animals drank normal amounts or more the first day on furosemide. The water intake varied considerably later on. Some birds drank increasing amounts of water, exceeding 900 ml per day. After 10 days on furosemide no bird was allowed to drink more than 400 ml/24 h.

EVF rose from 0.298±0.018 to 0.349±0.032

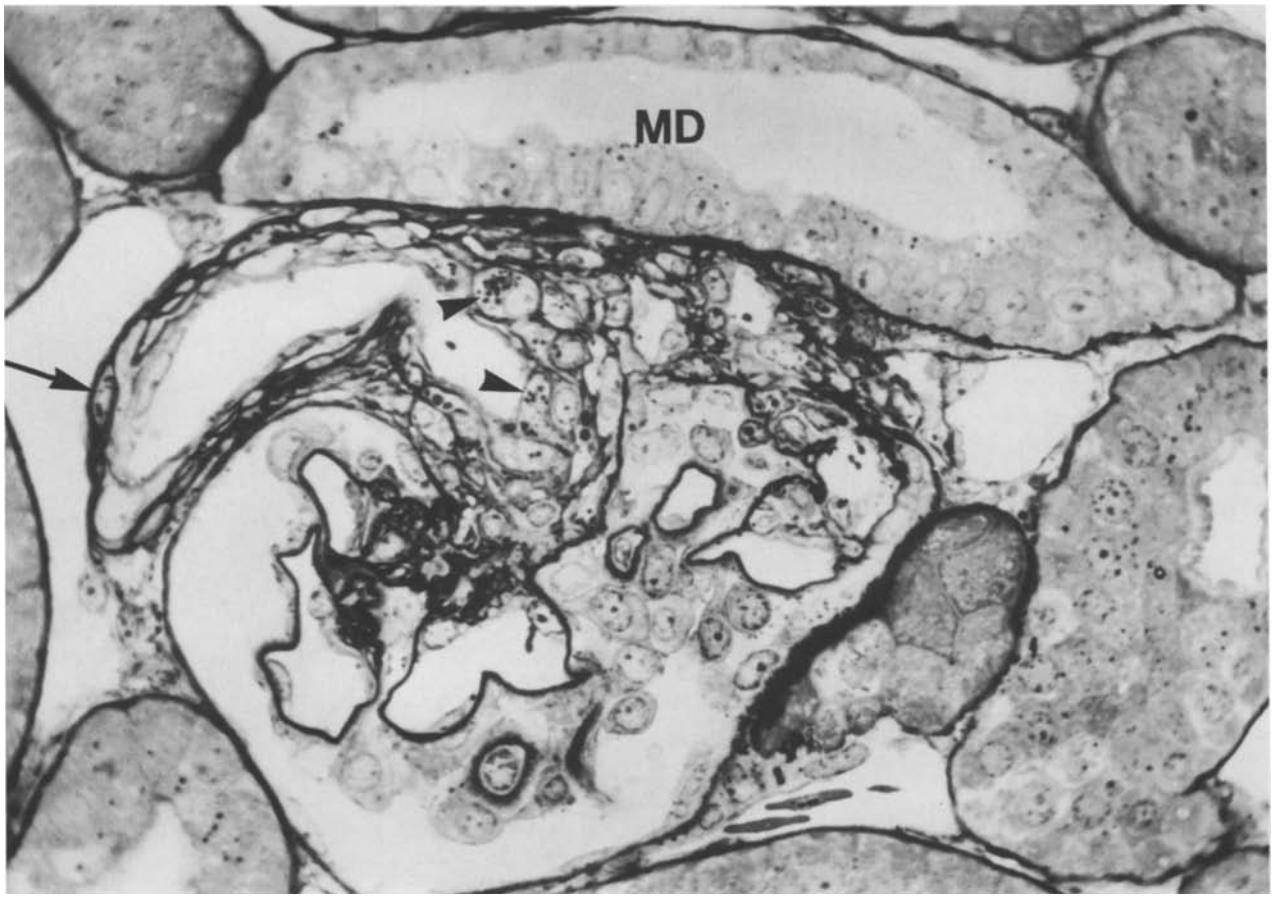

Fig. 2. Reptilian type glomerulus with JGA. Granular epithelioid cells are seen in the afferent arteriole (*arrowheads*). One granular cell in the preglomerular part of the afferent arteriole is marked with arrow. Macula densa (MD) is seen in the distal tubule. Between the tubule and the glomerulus Goormaghtigh cells. Silver methenamine staining. Micrograph × 900

after one day on furosemide ($p<0.0001$). After 6 days (on day 16) EVF was 0.400 ± 0.028 ($p<0.0001$).

The blood pressure fell significantly from 128 ± 12.9 mm Hg before furosemide to 116 ± 16.7 mm Hg one day after the first injection (day 11, $p=0.027$) and to 112 ± 22.5 mm Hg on day 15 ($p=0.0398$, Table 2). From day 15 no further significant reduction in blood pressure was observed (Table 2).

The heart rate was not significantly altered in any of the recordings, not even after pronounced hypotension following captopril administration.

The serum electrolytes showed acute and chronic changes. One day after starting furosemide injections, the concentrations of sodium and chloride ions were significantly lowered ($p<0.0001$, Table 2). During the days that followed, the plasma levels of these ions tended to increase, but remained significantly lowered. The potassium ion concentration fell significantly ($p<0.0001$) during the experiment although the fall was slower than for sodium and chloride. Uric acid increased significantly ($p<0.0001$), whereas creatinine showed no corresponding rise.

After the birds had received captopril on day 27 the blood pressure fell significantly within 3 h ($p<0.0001$, Table 2, Fig. 3). Pilot studies had shown that the blood pressure started to fall after half on hour and that the fall reached its lowest point 3–4 h after the captopril injection. The serum concentrations of chloride and sodium ions both showed an acute significant fall following captopril injection ($p<0.0001$), whereas serum potassium remained unchanged ($p=0.064$, Table 2). Serum creatinine increased somewhat whereas uric acid rose to very high values. The increase however, was significant for both creatinine ($p=0.0355$) and uric acid ($p=0.0078$, Table 2).

In the control group not receiving furosemide 4 chickens were injected with the same amount of captopril. There was no fall in blood pressure and no changes in pulse rate or weight during the 5 h of repeated measurements that followed.

Table 2. Blood pressure and electrolyte measurements

Days	1	6	11	13	15	19	21	27a	27b	27c	27d
Blood pressure mm Hg	125 ±11.5	130 ±15.9	116 ±16.7	113 ±15.2	112 ±22.5	125 ±20.2	124 ±21.2	118 ±18.1	59 ±13.9	55 ±15.3	62 ±14.3
NA^+ mmol/l	158.8 ±2.2	160.2 ±4.1	145.1 ±5.5		153.1 ±4.3		153.7 ±4.1	151.8 ±4.1			147.4 ±3.0
K^+ mmol/l	4.4 ±0.7	4.2 ±0.6	4.1 ±0.8		3.1 ±0.3		3.0 ±0.6	3.3 ±0.5			4.0 ±0.8
CL^- mmol/l	117.8 ±2.1	121.2 ±2.7	93.3 ±4.0		103.3 ±4.5		106.6 ±4.1	103.9 ±4.3			101.0 ±3.7
Uric acid µmol/l	248.7 ±49.6	211.0 ±62.5			372.3 ±159.8		359.7 ±87.7	409.9 ±166.4			1618.1 ±1040.6
Creatinine µmol/l	55.7 ±4.0	54.8 ±3.5	52.0 ±7.5		49.8 ±7.4		45.0 ±7.0	49.8 ±9.7			71.2 ±25.3

Day 27a: Blood pressure before captopril; Day 27b: Blood pressure 3 h after captopril; Day 27c: Blood pressure 4 h after captopril; Day 27d: Blood pressure 8 h after captopril. All values are given as means ± SD

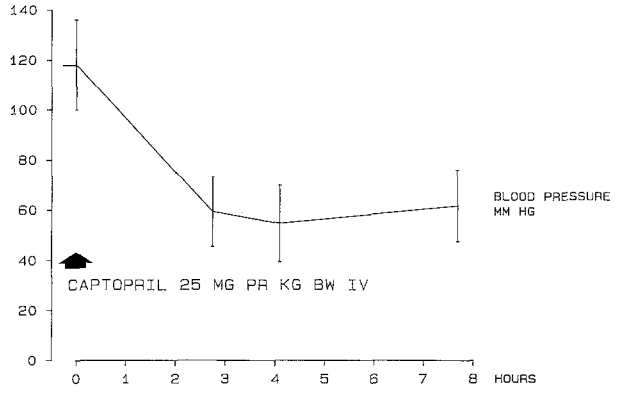

Fig. 3. Blood pressure measured about 3, 4 and 8 h after injection of one single dose captopril 25 mg/kg i.v. on day 27

Discussion

Acute experiments have shown increased kidney renin release in dogs receiving furosemide in doses as small as 0.5 and 2.5 mg/kg (Vander and Carlson 1869). In rabbits i.v. injections of furosemide (10 mg/kg) increased the plasma renin activity threefold after 7 min and caused a further increase after 45 min. There was a significant simultaneous fall in blood pressure (Meyer et al. 1968). Further the RAS has repeatedly been found to be stimulated and the blood volume reduced in animals and humans on a low salt diet (Brown et al. 1964; Brubacher and Vander 1968; Weinberger et al. 1968; Granger et al. 1972; Coleman et al. 1975; Hollenberg et al. 1977; Hollenberg et al. 1981; Fiselier et al. 1984). During the past decades there has however, been a considerable discussion whether the macula densa signal or the blood pressure is the appropriate stimulus for renin liberation (Thurau and Schnermann 1965; Tobian 1967).

Siller (1971) and Taylor et al. (1970) reported hyperplasia and hypergranulation of granular epithelioid cells in chickens kept on low sodium diet and after the administration of a mercury diuretic. However, in these studies no attempt was made to differentiate between mammalian and reptilian type nephrons. In the present experiment this differentiation was of major importance because furosemide acts on the loop of Henle and thus only exhibits its action on the mammalian type nephrons since they alone possess a loop of Henle. A direct effect of furosemide on the proximal tubule has not been demonstrated conclusively (Deetjen 1966; Thurau 1972; Burg et al. 1973; Wright and Schnermann 1974). The lowered blood pressure must therefore have been caused by the effect of furosemide on the mammalian type nephrons. The reptilian type JGAs were passively exposed to the lowered blood pressure induced by furosemide. The results show that hypotension may be an appropriate stimulus for hyperplasia of granular epithelioid cells. There is no reason to believe that the filtrate should be handled differently in the reptilian type nephrons during the experiment than under normal conditions. In the mammalian type JGAs the increased sodium load in the distal tubule could have been a stimulus for hyperplasia of the granular epithelioid cells via the macula densa, but there is experimental evidence that furosemide inhibits the macula densa signal (Thurau 1972; Wright and Schnermann 1974). This blockade will also probably be operative in the reptilian type nephrons. Therefore, the

decreased blood pressure in all probability was the stimulus in both types of nephrons. This interpretation supports the baroreceptor theory, originally proposed by Tobian (1967), as a potent mechanism leading to renin liberation.

We also observed granular epithelioid cells in the reptilian type JGAs in untreated, normal birds. This finding is of particular interest as granular epithelioid cells have not previously been encountered in the afferent arterioles of reptilian type glomeruli in the normal chickens (Wideman et al. 1981).

The major finding of the present study, that the avian kidney reacts as a mammalian kidney with hypergranulation and hyperplasia of the granular epithelioid cells after receiving diuretics, confirms the findings of Taylor et al. (1970). We were however, not able to find transformation of mesangial cells into granular epithelioid cells as reported by Siller (1971). This may be due to the fact that we used semithin serial sections, while Siller (1971) used conventional sections from paraffin embedded tissue. Differentiation between epithelioid cells in the intraglomerular parts of the arterioles and mesangial cells is difficult, and in our opinion is only possible on semithin serial sections. The extremely high number of granular epithelioid cells found after furosemide treatment showed that smooth muscle cells must have been transformed into renin-producing cells during the experiment. As we were unable to find mitotic figures the transformation probably reflects a metaplasia. This has previously been shown in the rat (Cantin et al. 1977).

Despite substantial weight loss and blood volume reduction, the decrease in blood pressure was relatively small and probably reflects the stimulation and effectivity of the RAS. Due to the stimulation of the RAS the birds were able to adjust their blood pressure during the experimental period despite prolonged furosemide administration. The ability and importance of the RAS in maintaining blood pressure was evident after admistration of captopril which caused a pronounced fall in blood pressure (Table 2). Results obtained with a specific renin antibody in dogs are also in favour of this mechanism. The blood pressure fell significantly in sodium depleted and remained unaltered in sodium replete dogs (Stephens et al. 1976; Kimbrough et al. 1977; Dzau et al. 1980).

A small reduction in blood pressure is usually recorded following captopril administration to normal rats and humans (Coleman et al. 1975; Hollenberg et al. 1977; Hollenberg et al. 1981; Hollenberg and Passan 1982). This was not observed in the present experiments on chickens and may indicate that the RAS participates less in maintaining blood pressure in normal chickens than in mammalian species. The antidiuretic hormone arginine-vasotensin may play a greater role than the RAS in normal birds (Braun 1982).

When the birds received captopril they all developed an acute renal failure. This was evident by a rapid rise in serum uric acid. Serum creatinine did not show a similar concomitant rise, since nitrogen metabolism in birds primarily involves formation of uric acid (Folk 1969; Lonsdale and Sutor 1971). The birds had free access to drinking water during the test period with captopril and the body weight remained stable. This, together with the acute renal failure may have caused the observed fall in EVF from 0.390 ± 0.027 in the morning to 0.360 ± 0.015 in the evening (Table 2).

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