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EFFECTS OF 9-ALPHA-FLUOROHYDROCORTISONE ON BLOOD PRESSURE, PLASMA VOLUME, AND SODIUM, POTASSIUM AND WATER BALANCE IN RATS

By
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ABSTRACT

In normal rats on a standard sodium diet, the administration of 9-alpha-fluorohydrocortisone (9aFF) induced a rapid increase of blood pressure in parallel to an increase of plasma volume. Water and potassium balances became negative. Urinary sodium excretion remained unchanged or increased after high doses, whereas urinary sodium concentration and faecal sodium excretion were reduced. The diurnal rhythm of water and sodium excretion changed: during the night-period, renal water and sodium excretion were diminished, whereas during the day-period both were enhanced. Thus, some effects of 9aFF on electrolyte and water balance are similar to those of DOC, while other effects are similar to those of cortisone.

It is postulated that a shift of fluid from intracellular to extracellular compartments, which increases plasma volume, is of critical importance for the 9aFF-induced blood pressure elevation in rats.

The synthetic derivative of hydrocortisone, 9-alpha-fluorohydrocortisone (9aFF) increases blood pressure and improves the adaptive capacity of circulatory reflexes in patients who suffer from postural hypotension (Hickler et al. 1959; Schirger et al. 1962; Schirger & Molnar 1964; Legeler & Stoll 1971). It has been suggested that this beneficial effect is due to the sodium-retaining property of the steroid (Renold et al. 1955; Thorn et al. 1955; Mills 1962; Schirger & Molnar 1964).
In rats, 9αFF produces hypertension (Selye 1955; Knowlton et al. 1957; Hépp & Gross 1973). The increase in blood pressure is also found under conditions of sodium restriction, an effect which is similar to that observed with cortisone and in contrast to that observed with DOC (Knowlton et al. 1957; Gross 1957). Since 9αFF does not cause a significant reduction in urinary sodium excretion of rats (Lettenbauer & Nowak 1971), it may be assumed that the 9αFF-induced blood pressure elevation is mediated by mechanisms other than sodium retention.

The purpose of the present study was to investigate in rats the effects of 9αFF on blood pressure and plasma volume in correlation to its effects on electrolyte and water balance.

**Materials and Methods**

1. **Animals, diet and experimental schedule.** – Male Wistar rats (WU-strain, Ivanovas, Kisslegg/Allgäu) were placed into individual cages in a room with constant temperature (23 ± 1°C) and humidity (60 ± 3%) which was lighted automatically from 6.30 a.m. to 6.30 p.m. At 8 p.m., the rats were given 11.4 g of a synthetic diet containing 227.6 mEq/kg of sodium and 124 mEq/kg of potassium (Möhring & Möhring 1972b). In order to provide a vehicle for the oral application of 9αFF, the rats received an additional 0.7 g of the diet at 8 a.m., which in this case was electrolyte-free. The experimental schedule, which has been followed in all experiments described below, and which included daily handling procedures, feeding programme, adaptation period, etc., has been described in detail previously (Möhring & Möhring 1972b).

2. **Drug administration.** – 9-alpha-fluorohydrocortisone (9αFF) was administered as a 5% mixture with methyl-cellulose placed on the top of the diet at 8 p.m. and at 8 a.m. The rats thus ate the drug by their first bites. The standard dose of 9αFF administered was 0.5 mg per animal twice a day.

3. **Measurement of blood pressure and plasma volume.** – After the period of adaptation to the individual cages, the synthetic diet and the daily handling procedure, systolic blood pressure was measured in 40 rats (body weight 223 ± 11 g (sn)) by tail plethysmography in light ether anaesthesia (Byrom & Wilson 1938). Two days later, blood pressure was measured again. Subsequently, 0.5 mg 9αFF was given perorally twice a day to 17 rats for five consecutive days; the other 23 rats were taken as controls. On the second day at 5 p.m., blood pressure was measured again in all 40 rats. On the fifth experimental day, it was recorded in groups of 8 9αFF-treated and 11 control rats at 5 a.m. and in 9 treated and 12 control rats at 4 p.m.

After blood pressure measurement, 0.2 ml of a 0.5% solution of Evans blue in isotonic saline was injected into the left saphenous vein. Ten minutes later, 1 ml of blood was taken from the tail artery into a heparinized tube, and two glass capillaries were filled for the determination of haematocrit. After centrifugation of the blood, plasma concentrations of Evans blue were determined photometrically, and plasma volume was calculated. The mean difference between duplicate estimations was 0.7 ± 0.5% (sn, n = 20) for haematocrit and 0.3 ± 0.2% (n = 20) for plasma concentrations of Evans blue.
4. Balance studies. – In 12 rats, weighing 223 ± 10 g (sd), the effects of 2 × 0.5 mg 9aFF daily on 12-h and 24-h electrolyte and water balances were studied. Balance measurements were performed for three control days, during 5 days of steroid administration, and for additional 4 days after drug withdrawal.

In order to determine the dose-response relationship, the effects of three other doses were compared for the first 24-h period of drug application. Eight rats (body weight 230 ± 5 g) received 5 µg twice a day, 6 rats (body weight 254 ± 7 g) 25 µg twice a day, and 8 rats (body weight 247 ± 4 g) 100 µg twice a day.

Sodium and potassium balance data were expressed as fractional excretion rates in urine for 12-h and 24-h periods, and in faeces for 24-h periods. The values are given as percentages of the respective 24-h intakes. The validity and advantage of expressing balance data in rats by fractional excretion rates, and the accuracy of the balance method used have been demonstrated elsewhere (Möhring & Möhring 1972a,b).

5. Determination of haematocrit, serum osmolality, and serum sodium and potassium concentrations. – From groups of 9 rats each (body weight 217 ± 18 g), blood was collected at 5 a.m. and 4 p.m. on the first, second, third, and fifth day of 9aFF treatment (2 × 0.5 mg daily). In groups of 20 and 17 control rats, blood was taken on the last experimental day at 5 a.m. and 4 p.m., respectively. Blood was collected from a catheter placed into the superior vena cava via the left jugular vein. Two heparinized glass capillaries were filled for the determination of haematocrit. The collected blood was centrifuged immediately. Serum sodium and potassium concentrations were determined by flame photometry with a Zeiss M 4 Q II spectrometer and a FA II flame photometer; serum osmolality was determined by freezing point depression (osmometer Knauer). The mean difference between duplicate estimations was 1.2 ± 1.0 mEq/l (sd, n = 20) for serum sodium concentration, 0.06 ± 0.05 mEq/l (n = 20) for serum potassium concentration, and 0.9 ± 0.7 mOsml./kg for serum osmolality.

6. Statistics. – All values in the following text, Table 1 and Figs. 1–8 are means ± sem. Significances of differences between mean values were evaluated by Student’s t-test.

**RESULTS**

I. Effect of 9aFF (2 × 0.5 mg daily po) on blood pressure and plasma volume in rats

One and three days before start of 9aFF treatment, systolic blood pressure was similar in both the 23 control and 17 experimental rats (113 ± 1 mmHg). On day 2 of drug application, blood pressure had increased to 127 ± 1 mmHg (P < 0.01; n = 17), while it remained unchanged in the 23 controls (113 ± 1 mmHg). On day 5 of 9aFF treatment, blood pressure in the treated rats was 145 ± 2 mmHg (n = 8) at 5 a.m. and 140 ± 2 mmHg (n = 9) at 4 p.m. In the control animals, it was 115 ± 1 mm (n = 11) at 5 a.m. and 113 ± 1 mmHg (n = 12) at 4 p.m.

Plasma volume in groups of 11 and 12 control rats was similar at 5 a.m. and 4 p.m. (Fig. 1). Absolute plasma volumes were closely related to body weights in the 23 control animals (r = 0.92; y (plasma volume in ml) = –1.01 +
Plasma volume of rats after five days of 9aFF treatment (2 × 0.5 mg/day po). Values are means ± SEM. * indicates a difference of \( P < 0.01 \). The solid columns give the plasma volumes of normal control rats, the open columns the values of treated animals.

The upper part of the figure represents relative plasma volumes; the respective body weights were measured directly before plasma volume determinations (\( n = 11 \) for control and \( n = 8 \) for 9aFF-treated rats at 5 a.m.; \( n = 12 \) for control and \( n = 9 \) for 9aFF-treated rats at 4 p.m.). Absolute plasma volumes of control and treated rats of comparable body weights are given in the lower part of Fig. 1 (\( n = 16 \) for control and \( n = 8 \) for 9aFF-treated rats at 5 a.m.; \( n = 17 \) for control and \( n = 9 \) for 9aFF-treated rats at 4 p.m.). For further details see text.

0.04 \times \) (body weight in g)). Haematocrit values were 47.7 ± 0.4 % (\( n = 11 \)) at 5 a.m. and 47.9 ± 0.4 % (\( n = 12 \)) at 4 p.m. After five days of 9aFF treatment, plasma volume per 100 g body weight was increased at 5 a.m. (Fig. 1, upper part), while haematocrit was reduced to 45.2 ± 0.4 % (\( P < 0.01 \), \( n = 8 \)). At 4 p.m., plasma volume (Fig. 1) and haematocrit (47.2 ± 0.6 %, \( n = 9 \)) were not significantly different from control values. Similar changes in haematocrit were observed in another experiment on the first, second and third day of 9aFF administration (Table 1).

Since there is a reduction in body weight gain or even weight loss during 9aFF treatment (see below), it seems likely that calculations of relative plasma volumes give falsely high values as compared with control rats. Therefore, absolute plasma volumes of 9aFF-treated rats were compared with control rats.
Table 1.
Haematocrit, serum sodium and potassium concentration, and serum osmolality in rats treated with 9-alpha-fluorohydrocortisone (0.5 mg twice a day po).

<table>
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<tr>
<th></th>
<th>Control</th>
<th>Day 1$</th>
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<td><strong>Haematocrit (%)</strong></td>
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<td>49.3</td>
<td>49.1</td>
<td>46.9**</td>
<td>49.5</td>
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<td><strong>Na$^+$ (mEq/l)</strong></td>
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<td>139.5</td>
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<td><strong>K$^+$ (mEq/l)</strong></td>
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<td>3.58</td>
<td>3.47</td>
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<td><strong>Osmolality (mOsm/kg)</strong></td>
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<td></td>
<td>296.8</td>
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<td>297.8</td>
<td>303.6**</td>
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<td>± 1.3</td>
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<td>± 1.4</td>
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Values are means ± SEM (n); *P < 0.05; **P < 0.02; ***P < 0.01; $ day of 9aFF treatment.
of comparable body weights at the start of the experiment (Fig. 1, lower part). Absolute plasma volume of control rats (body weight 210–235 g) was $8.38 \pm 0.09$ ml ($n = 16$) and of 9aFF-treated rats $8.82 \pm 0.15$ ml ($n = 8$) at 5 a.m. ($P < 0.01$). At 4 p.m., plasma volume was $7.92 \pm 0.16$ ml in the other 9 treated rats and $8.19 \pm 0.11$ ml in 17 control rats (body weight 205–230 g).

II. Effect of 9aFF (2 x 0.5 mg daily po) on electrolyte and water balance in rats

a. Diet intake. – During the first two days of drug administration, food intake remained unchanged. Then it decreased significantly ($P < 0.01$, paired

![Graphs showing food intake, body weight, and water intake and urine volume over days.](image)

**Fig. 2.** Effects of 9aFF (2 x 0.5 mg/day po) on food intake, body weight, water intake and urine volume. Values are means ± SEM ($n = 12$).
Effects of 9αFF (2 x 0.5 mg/day po) on 24-h sodium and potassium excretion in urine of rats. Values are means ± SEM (n = 12). Balance data are given as fractional excretion rates in urine according to the indicated formula.

data; Fig. 2). On the second day after cessation of drug application, food intake increased. At the end of the experiment, eight of the twelve rats consumed their daily portion of diet, while in the four other animals diet intake remained reduced by 0.5 to 1.5 g per day.

b. Body weight. – During the three control days, body weight gain was 1.9 ± 0.2 g. The same daily weight gain is observed in rats of the same strain, when living in colonies on a commercial diet and tap water ad libitum (personal observation). On the first day of 9αFF administration, body weight decreased by 3.3 ± 0.2 g (Fig. 2). During the subsequent four days, body weight remained nearly constant, although food intake began to decrease. On the day after cessation of drug administration, body weight increased by 4.7 ± 0.5 g. On the last days of the balance study, daily weight gain was similar to that of pre-treatment days, i.e. 1.9 ± 0.3 g.
c. Water turnover. – On the first day of 9αFF treatment, water intake decreased from 21.1 ± 2.2 ml to 18.7 ± 2.3 ml (P < 0.01, paired data), while urine volume increased from 14.8 ± 2.0 ml to 17.0 ± 0.5 ml (P < 0.01, paired data; Fig. 2). Accordingly, the difference between daily water intake and urine volume, which is a rough approximation of extrarenal water loss under steady state conditions, decreased from 6.3 ± 0.5 ml to 1.7 ± 0.5 ml (P < 0.01, paired data). Assuming that extrarenal water loss was not affected by 9αFF, this indicates a negative water balance of 4.6 ml. On the second and third days of 9αFF treatment, urine volume decreased, but the difference between water intake and urine volume was still diminished (P < 0.01).

After cessation of drug application, urine volume decreased further and water intake increased (Fig. 2). The difference between both was 10.1 ± 0.6 ml, indicating a positive water balance of 3.8 ml. On days 11 and 12 of the experiment, both urine volume and water intake had nearly returned to control values.
Effects of 9aFF (2 × 0.5 mg/day po) on 24-h sodium and potassium excretion in faeces of rats. Values are means ± SEM (n = 12). Fractional excretion rates were calculated according to the indicated formula.

d. Urinary sodium and potassium excretion. – Fractional excretion of sodium increased by 4.1% (P < 0.01, paired data) on the first day of 9aFF treatment (Fig. 3). On the subsequent days, it remained in the control range. However, total sodium excretion declined, reflecting the reduction in food intake. Fractional potassium excretion increased by 30% (P < 0.01) on the first day of drug administration (Fig. 3). On the next day, potassium excretion decreased, but in comparison with control values the balance was still negative (P < 0.01). On the following day, potassium excretion increased again.

After cessation of 9aFF administration, potassium retention was observed, while fractional sodium excretion did not change substantially (Fig. 3).

e. Urinary sodium and potassium concentration. – Twenty-four hour urinary sodium concentrations decreased on the first day of 9aFF treatment (P < 0.01,
paired data; Fig. 4). On the second and third day of 9aFF treatment, urinary sodium concentrations returned to control values. The changes in urinary potassium concentrations during drug application (Fig. 4) reflected the changes in fractional potassium excretion.

After withdrawal of 9aFF, urinary sodium concentrations increased, while potassium concentrations decreased ($P < 0.01$, paired data). On the last day of the balance study, both sodium and potassium concentrations were within the control range.

f. Faecal sodium and potassium excretion. – Faecal sodium excretion was reduced during the entire period of drug administration ($P < 0.01$, paired data; Fig. 5); potassium excretion was enhanced ($P < 0.01$). One and two days after drug withdrawal, sodium and potassium excretion returned to control values.

Fig. 6.

Effects of 9aFF (2 x 0.5 mg/day po) on 12-h sodium and potassium excretion in urine of rats. Values are means ± SEM (n = 12). 12-h excretion rates of sodium and potassium are given as percentages of the respective intakes. The upper part of Fig. 6 gives data for the night-period from 7 p.m. to 7 a.m., the lower part shows the values for the day-period from 7 a.m. to 7 p.m.
Effects of 9aFF (2 x 0.5 mg/day p.o.) on 12-h urine volumes of rats. Values are means ± SEM (n = 12). The solid parts of the columns represent the 12-h periods of the nights, the open parts of the columns the 12-h periods of the days. The solid horizontal lines give the mean values of the three control days.

g. Serum sodium and potassium concentrations and serum osmolality. – Serum sodium concentrations, which were measured in a separate experiment, showed a tendency to decrease during 9aFF treatment (Table 1). Serum potassium concentrations declined progressively during the period of 9aFF administration, except at 5 a.m. on day 2 of drug application. Serum osmolality was unchanged on the first day of treatment; then it increased (Table 1).

III. Effect of 9aFF (2 x 0.5 mg daily p.o.) on the diurnal rhythm of electrolyte and water excretion in rats

a. Sodium and potassium excretion. – During the three control days, fractional excretions of sodium and potassium (Fig. 6) were higher for the 7 p.m. to 7 a.m. period than for the 7 a.m. to 7 p.m. period (Möhring & Möhring 1972b). During the first 12 h of 9aFF treatment, i.e. from 7 p.m. to 7 a.m. (upper part of Fig. 5), sodium excretion decreased (P < 0.01, paired data). During the following days, sodium excretion declined further during the 7 p.m. to 7 a.m. period, while it remained elevated during the 7 a.m. to 7 p.m. period (P < 0.01).

9aFF treatment always resulted in an increased fractional potassium excretion during the 7 a.m. to 7 p.m. periods (P < 0.01, paired data; Fig. 6, lower part). During the first 7 p.m. to 7 a.m. period of 9aFF administration
(upper part of Fig. 6), potassium excretion increased \((P < 0.01\), paired data). During the next night-period, it was in the control range; it increased again during the subsequent days. The net changes in the two 12-h periods combined have been shown in Fig. 3.

b. Urine volume. – During the first 24 h of 9αFF treatment, urine volume decreased during the night-period \((P < 0.01\), paired data; Fig. 7), while it in-
increased during the day-period (P < 0.01). The latter increase was greater than
the respective decrease during the preceding 12 h of the night. On the last day
of 9aFF treatment, urine volumes were the same during both 12-h periods.
However, the rhythm of 12-h water intake remained unchanged. Before 9aFF,
water intake was 19.7 ± 1.9 ml during the 7 p.m. to 7 a.m. period, and it was
1.5 ± 0.4 ml during the 7 a.m. to 7 p.m. period. On the last day of 9aFF
administration, water intakes were 17.7 ± 1.4 ml and 1.3 ± 0.3 ml, respectively.

IV. Dose-response relationship of 9aFF on sodium, potassium and
water balance in rats

The effects of four different doses of 9aFF were compared for the first 24-h
period of drug application (Fig. 8). Urinary sodium excretion was only affected
after administration of the highest dose of 9aFF (2 × 0.5 mg daily po), which
induced a small increase (P < 0.01, paired data). Fractional potassium ex¬
cretion was already enhanced by the smallest dose of 9aFF (2 × 0.005 mg daily)
and increased further in relation to the dose given. Weight gain was reduced
in a dose-dependent way, the highest dose inducing weight loss (Fig. 8). This
reduction in weight gain corresponded to the degree of negative water balance.
Food intake remained unchanged after all four doses investigated.

DISCUSSION

Blood pressure and plasma volume. – Systolic blood pressure was increased
on the second day of 9aFF treatment, and it reached levels of 140 to 150
mmHg within five days. Such a steroid-induced rapid increase in blood pres¬
sure is characteristic for cortisone and hydrocortisone, but not for DOC (Gross
1957; Knowlton et al. 1957).

In parallel to the rise in blood pressure, plasma volume increased. Although
this increase was found only at 5 a.m., while plasma volume was in the normal
range towards the end of a day at 4 p.m., the integral of the fluctuating plasma volume indicated an increase for any of the five days of 9aFF treat¬
ment. The increase in plasma volume might be critical for the 9aFF-induced
rise in blood pressure. This would be in accordance with the concept of the
pathogenesis of high blood pressure as outlined by Ledingham (1971a,b) and
by Guyton & Coleman (1969) and Guyton et al. (1972a,b). According to this
concept, an increase in blood volume and in extracellular fluid volume is the
trigger mechanism for blood pressure elevation. The increase in extracellular
fluid volume could be the consequence of (1) a reduction in renal salt and
water output or (2) an increase in salt and water intake (Guyton et al. 1972b).
Both conditions are not present in 9αFF-induced rise of plasma volume and blood pressure. Therefore, an increase in plasma volume and extracellular fluid volume via (3) a shift of fluid from intracellular compartments may be of importance for 9αFF-induced blood pressure elevation.

*Shift of fluid from intracellular compartments.* – Since 9αFF induced marked fluid and moderate salt loss on the first day of drug administration, the increase in plasma volume cannot be explained on the basis of salt and water retention. It may be deduced from the balance data presented that the increase in plasma volume and in extracellular fluid volume was due to a shift of fluid from intracellular to extracellular space. The total amount of sodium loss was 85 μEq. on the first day of 9αFF treatment; water loss was about 5 ml. Since serum sodium concentration and therefore sodium concentration of the extracellular fluid did not change, at least 4.4 ml of water must have been shifted into extracellular space in order to maintain the observed sodium concentration. Concomitantly, intracellular fluid volume must have decreased. An alternative explanation for the maintenance of serum sodium concentration would be that sodium had been shifted into intracellular compartments. This possibility is most unlikely in view of the increase in plasma volume. In addition, it is well documented that adrenal corticosteroids mobilize sodium from intracellular space (Levitt & Bader 1951; Luft & Sjögren 1952). Such a shift of water and salt from intracellular to extracellular compartments has been demonstrated to occur in dogs and rats after the administration of cortisone, corticosterone and related compounds, but not after DOC (Swingle et al. 1959a,b; Gotshall & LeBrie 1972). Thus, with regard to the shift of fluid, 9αFF has a cortisone-like effect in normal rats.

*Role of kidneys in blood pressure elevation.* – Since plasma volume increased despite a marked water and moderate salt loss, the “overriding dominance of the kidneys in hypertension” (Guyton et al. 1972a) may be questioned for 9αFF-induced blood pressure elevation. However, it might be argued that the shift of fluid and the corresponding increase in plasma volume during 9αFF administration were not compensated appropriately by renal salt and water excretion. This suggestion is supported by a study in man by Strauss & Earley (1959). When 9αFF was given to a man in whom extracellular fluid volume had been expanded by the infusion of saline (and not by a shift as in the present experiments), the sodium-retaining effect of 9αFF was no longer seen, whereas potassium excretion was enhanced. The infused salt and water were not excreted as in untreated subjects after saline infusion. We therefore suggest that, in rats, 9αFF induces an increase in plasma volume by its cortisone-like property via a shift of fluid and salt from intracellular to extracellular compartments. Because of its DOC-like effect, which will be discussed below, it retains the shifted water and salt in the extracellular space.

*Sodium, potassium and water balance.* – In normal rats on a standard diet,
9aFF failed to induce positive sodium balance, as is found in man and dogs (Renold et al. 1955; Thorn et al. 1955; Mills 1962; Schirger & Molnar 1964; Lynch et al. 1972). Furthermore, 9aFF induced water loss, whereas under DOCA treatment water and salt balances were positive (Möhring & Möhring 1972b). On the other hand, 9aFF reduced urinary sodium concentration and faecal sodium excretion. A marked potassium loss occurred, which was reflected in a progressive decrease of serum potassium concentration. These latter effects closely resemble those of aldosterone and DOCA (Thompson & Edmonds 1971; Haack et al. 1972; Möhring & Möhring 1972b). In this respect, it is of interest to note that in normal rats a high dosage of cortisone acetate failed to induce negative potassium balance on the first day of drug application, and a marked sodium and water loss occurred (Noble 1955; Haack et al. 1972). Thus, 9aFF has DOC-like effects on potassium balance and cortisone-like effects on water balance; its effects on sodium balance seem to be a summation of the actions of DOC and cortisone.

During 9aFF administration, urine volume and sodium excretion decreased during the night-period and increased during the day-period. Such changes in the diurnal rhythm of renal solute and water excretion have been amply demonstrated under treatment with cortisone-like steroids (Doe et al. 1960; Thomas et al. 1970). But the underlying mechanism remains unknown.

The alterations in the diurnal rhythm of water and salt excretion under the influence of 9aFF were reflected in changes of haematocrit and of plasma volume. Thus, at the end of the night-period, plasma volumes were elevated, while towards the end of the day-period, i.e. the period of enhanced salt and water excretion, they were within the control range. However, the diurnal fluctuations of plasma volume during 9aFF-induced blood pressure elevation were not accompanied by similar fluctuations in blood pressure. This indicates that, within the 24-h period of a day, additional factors might contribute to blood pressure elevation.

**Water and food intake.** – Although water balance became negative after the administration of 9aFF, water intake did not increase; it even decreased. Therefore, other factors must have counterbalanced the thirst-stimulating effect of a reduction in intracellular fluid volume (Fitzsimons 1972). Such factors could have been the increase in plasma volume observed during the night-period when 90 to 100 °/o of daily water were consumed, or a decrease in plasma angiotensin II concentration under the influence of 9aFF (Stricker 1966; Fitzsimons & Simons 1969; Fitzsimons 1972; Hepp & Gross 1973).

Food intake decreased on the third day of 9aFF treatment, an effect which has been observed under cortisone, but not under DOCA treatment (Knowlton et al. 1957; Möhring & Möhring 1972b). The suppression of the drive to eat might have been due to the increase in plasma osmolality (Kakolewski & Deaux 1970; Kakolewski 1972), which was observed under 9aFF treatment.
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