# IMPORTANCE OF DOSE AND HYPERTENSION IN THE MECHANISM OF THE RENAL EFFECTS OF ANGIOTENSIN

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Angiotensin was injected intravenously at the rate of 0.3-0.6 μg/min or 1.0-1.2 μg/min into dogs anesthetized with thiopental sodium. During the first 10 min of angiotensin injection the rate of glomerular filtration and the renal excretion of sodium, potassium, and water were all reduced. During the next 20 min, if a small dose of angiotensin was given, the renal excretion of electrolytes and water remained below its initial level, but if a large dose was given it rose sharply. Damping of the hypertensive changes by stabilization of the systemic arterial pressure by the pressure of a column of water caused no significant change in the character of the renal responses to injection of angiotensin, but the increase in sodium excretion was smaller than under ordinary conditions. It is concluded that the renal effects of angiotensin are more likely to be due to its direct intrarenal action than to changes in the systemic hemodynamics.

Interest of research workers in the study of angiotensin has recently increased, for much regarding the mechanism and even the effects of action of this substance remains unexplained or contradictory [2, 3, 6].

This investigation was undertaken to study the effect of different doses of angiotensin on the excretion of water and electrolytes by the kidneys and the role of the accompanying hypertension in the genesis of the changes observed.

## EXPERIMENTAL METHOD

Altogether 21 acute experiments were performed on noninbred dogs of both sexes under thiopental anesthesia (30-50 mg/kg). The experimental method was described earlier [1]. The minute volume of diuresis, the rate of glomerular filtration, and the excretion of sodium and potassium were determined. The arterial pressure was recorded by a mercury manometer. An intravenous infusion of angiotensin (Ciba) was given over a period of 20-30 min at the rate of 0.3-0.6 μg/kg per minute (small dose) or 1-1.2 μg/kg per minute (large dose). To damp the hypertension induced by angiotensin, a system of stabilizing the systemic arterial pressure by the weight of a column of water [1] was used. The statistical analysis of the results was carried out by the difference method, and for this reason arithmetical mean values (M) are shown in the table: changes in a particular index during injection of angiotensin can be judged from the mean value of the differences (ΔM with the appropriate sign), which is given with the mean error of the differences (±m).

## EXPERIMENTAL RESULTS

Preliminary experiments showed that either of the two doses of angiotensin used invariably induced a sharp decrease in the excretion of sodium, potassium, and water during the first 5-10 min, with characteristics indicating a decrease in the rate of glomerular filtration and in the filtration charge of the nephron.

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TABLE 1. Changes in Renal Function after Intravenous Injection of Small (0.3-0.6 μg/kg/min) and Large (1.0-1.2 μg/kg/min) Doses of Angiotensin in Acute Experiments on Dogs

| Index of kidney function | Small dose (7 expts.) | | | Large dose (12 expts.) | | |
|---|---|---|---|---|---|---|
| | M | Δ M±m | P | M | Δ M±m | P |
| Diuresis (ml/min) | 2,8 | −1±0,2 | <0,01 | 1,7 | +3,4±0,5 | <0,001 |
| Creatinine concentration index | 12,4 | +8,1±2,2 | <0,02 | 22 | −5,0±1,5 | <0,01 |
| Creatinine serum (ml/min) | 33,3 | −7,1±3,9 | >0,4 | 32 | +15±4 | <0,01 |
| Sodium excretion (meq/min) | 288 | −149±41 | <0,01 | 164 | +260±58 | <0,001 |
| Excretable sodium fraction (%) | 6,1 | −1,8±0,5 | <0,05 | 4,1 | +4,3±1,4 | <0,05 |
| Potassium excretion (meq/min) | 35,6 | −10,1±3,1 | <0,02 | 40 | +36±10 | <0,01 |
| Arterial pressure (mm Hg) | 127 | +26±4 | <0,01 | 125 | +28±3 | <0,001 |

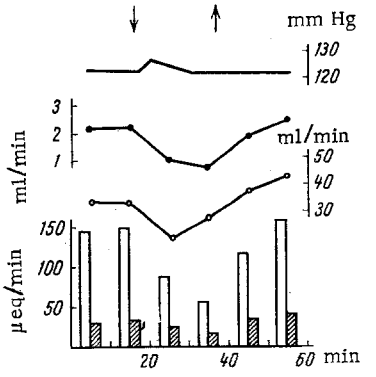


Fig. 1

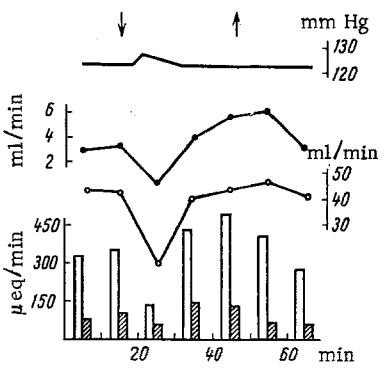


Fig. 2

Fig. 1. Changes in renal functions during intravenous injection of angiotensin (0.5 μg/kg/min) with arterial pressure stabilized. From top to bottom: arterial pressure, diuresis, rate of glomerular filtration. Unshaded columns denote sodium excretion, shaded columns – potassium excretion.

Fig. 2. Changes in renal functions during intravenous injection of angiotensin (1.2 μg/kg/min) with arterial pressure stabilized. Legend as in Fig. 1.

During the next 10-20 min of infusion the rate of glomerular filtration and also of excretion of electrolytes and water increased. However, during injection of the small dose of angiotensin the indices of renal function fell below the initial level, whereas during injection of the large dose they were considerably higher than initially. The results in Table 1 were obtained 10 min after the beginning of angiotensin injection. The disagreement between individual authors regarding the renal action of angiotensin are most probably attributable to differences in the doses used or in the periods of observation. Angiotensin also was shown to be unstable: if more than 20-30 min elapsed after its solution was made up, its renal effects were sharply reduced (the hypertensive activity persisted rather longer).

During injection of the small dose of angiotensin, superposed upon the very slight decrease in the rate of glomerular filtration a decrease in the excretion of sodium and water on account of their increased tubular reabsorption was observed. When the large dose was injected, after 10 min a well-marked increase in sodium and water excretion was observed; this took place on account of an increase in the rate of glomerular filtration and a decrease in tubular reabsorption (Fig. 1). The changes in potassium excretion were similar to those in sodium excretion. After the end of the infusion, irrespective of the dose of angiotensin all the indices of kidney function and arterial pressure returned to their initial level. Similar results were obtained by other workers [4, 5], and the inhibition of tubular sodium transport by large doses of angiotensin was attributed to changes in the intrarenal hemodynamics or an increase in pressure in the peritubular capillaries [7].

Stabilization of the arterial pressure in the present experiments introduced no essential changes in the renal effects of angiotensin. For instance, injection of the small dose of angiotensin with the pressure stabilized led to a decrease in the excretion of sodium, potassium, and water superposed upon a decrease in the rate of glomerular filtration; after the end of the angiotensin infusion the indices of renal function returned to their initial level (Fig. 1). Conversely, after injection of a large dose of angiotensin, the excretion of electrolytes and water increased, despite stabilization of the pressure, which was accompanied by some decrease in the circulating blood value in connection with the entry of some of the blood into the stabilization reservoir (Fig. 2). A statistical analysis of the results showed that after injection of the large dose of angiotensin, the increase in excretion of electrolytes and water was, nevertheless, rather smaller when the arterial pressure was stabilized than under ordinary conditions.

Analysis of these results suggests that the renal effects of angiotensin depend on the rate and duration of its injection and, in particular, they are connected with the direct effect of angiotensin on intrarenal filtration and reabsorption of the components of the blood and not with changes in the systemic hemodynamics.

## LITERATURE CITED


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