

## THE EFFECT OF ANGIOTENSIN II ON KIDNEY FUNCTION

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### Summary

The direct intra-renal effects of angiotensin II were investigated in isolated perfused rat kidneys. Angiotensin increased renal vascular resistance and decreased renal perfusate flow, while glomerular filtration rate was unchanged. In a perfusate concentration of 5ng/ml angiotensin had a natriuretic effect, but did not have any effect on renal handling of water.

### Introduction

Angiotensin II, in addition to its well known role in the regulation of aldosterone secretion and of peripheral vascular resistance, has been shown to have direct intra-renal effects. For instance, angiotensin II participates in the regulation of glomerular filtration [1], urinary electrolyte excretion [2] and renal water handling [3,4].

The direct intra-renal effects of angiotensin II have been studied in whole animal models, in which systemic effects could not be totally excluded, by the microperfusion technique, and in in vitro models. In the in vitro model angiotensin II effect was investigated on cortical slices or isolated tubules, so that the total effect of angiotensin II on a whole kidney could not be demonstrated. In the present study, the renal effects of angiotensin II were studied in an isolated perfused kidney.

### Material and methods

The study was performed on Wistar male rats, with a body weight of 280-350g, bred at the Beilinson Medical Center. After induction of anaesthesia with Nembutal in a dose of 0.5mg/kg given intraperitoneally, the left kidney was exposed, and the left ureter was catheterized. The inferior vena cava and aorta (and their collaterals) were ligated below the left renal pedicle and were cannulated. After

initiation of perfusion through the aortic cannula the aorta and inferior vena cava were ligated above the left renal pedicle, and the animal was sacrificed. The perfusion technique, using a modified perfusate composition (Krebs-Ringer saline with 3.6% Dextran (MW 70,000) equilibrated with 95% O<sub>2</sub>-5% CO<sub>2</sub>, and heated to 37°C) was as described by van Dongen [5].

The rats were allocated to two groups of 10: control group – the kidneys were perfused with the perfusate as described; angiotensin group – angiotensin II (Hypertensin, Ciba) was added to the perfusate at a concentration of 5ng/L.

The perfusion pressure was maintained constant at 120mmHg. After 10 minutes of perfusion (equilibration period) the following kidney functions were studied:

*Haemodynamics* Perfusate flow rate by timed collection of the effluent via the catheter in the inferior vena cava. Total renal resistance as calculated by the ratio between perfusion pressure and perfusate flow rate and expressed in mmHg/min/ml. Glomerular filtration rate as measured by creatinine clearance. Creatinine was added to perfusate at a concentration of 150mg/100ml.

*Urine electrolyte excretion* Expressed as total (UNaV, UKV) and fractional excretion of sodium and potassium (FENa and FEK), and as osmolar clearance (Cosm) using standard formulae.

*Renal handling of fluid* Urine volume as measured by timed collection of urine via the ureter catheter, free water clearance (CH<sub>2</sub>O), fractional excretion of water (FEH<sub>2</sub>O), and urine to plasma creatinine ratio, using standard formulae.

Perfusate and urine creatinine was measured using a Beckman creatinine analyser, sodium and potassium using a flame photometer and osmolality using an Osmette osmometer.

Significance of differences between the groups were calculated using the Student's 't' test.

## Results

### *Effects of angiotensin II on the kidney*

*Haemodynamic effects (Table I)* In the angiotensin group total renal resistance was significantly higher than that in the control group (17.6±5.7 versus 9.2±1.6mmHg/ml/min, p<0.001) and perfusate flow rate was significantly lower (7.4±2.2 versus 13.3±9.5ml/min, p<0.001). Creatinine clearance was similar in both groups while filtration fraction was significantly higher in the angiotensin group (3.8±1.31% versus 1.5±0.6%, p<0.001).

*Urine and electrolyte excretion (Table II)* Sodium excretion was significantly higher in the angiotensin II group as compared to the control group (UNaV 1.6±2.3 versus 3.6±1.4μEq/min, p<0.001). FENa (45.6±8.2% versus 13.9±7.4%, p<0.001), and osmolar clearance (140.1±56.5 versus 44.4±11.7μl/min, p<0.001), were both higher in the angiotensin II group than in the control group. UKV and FEK were no different in the two groups.

TABLE I. Haemodynamic effect of angiotensin II

	Flow rate ml/min	TRR mmHg ml/min	Creatinine clearance ml/min	FF %
Control	13.3±2.5	9.2±1.6	0.22±0.1	1.5±0.6
Angiotensin II	7.4±2.2	17.6±15.6	0.28±0.11	3.8±1.2
p	<0.001	<0.001	NS	<0.001

TRR: Total renal resistance

FF: Filtration fraction

TABLE II. Effect of angiotensin II on electrolyte excretion

	UNaV μEq/min	FENa %	Osm clear. μl/min	UKV μEq/min	FEK %
Control	3.6±1.4	13.9±7.3	44.4±11.7	0.99±0.4	123.5±33.5
Angiotensin II	17.5±7.3	45.6±8.7	140.7±56.5	1.3 ±0.4	124.5±29.9
p	<0.001	<0.001	<0.001	NS	NS

TABLE III. Effect of angiotensin II on renal handling of water

	Urine volume μl/min	U/P creatinine ratio	FE H <sub>2</sub> O %	CH <sub>2</sub> O μl/min
Control	40.7±11.7	5.6±1.8	19.4±6.8	-2.08±2.3
Angiotensin II	138.5±55.4	2.1±0.4	49.4±8.7	-1.9 ±3.2
p	<0.001	<0.001	<0.001	NS

*Renal handling of water (Table III)* In the angiotensin II group fluid excretion was higher than in the control group: urine volume was 138.5±55.4 versus 40.7±11.7 μl/min (p<0.001), FEH<sub>2</sub>O was 49.4±8.7% versus 19.4±6.8% (p<0.001). Urine to plasma creatinine ratio was lower in the angiotensin II group than in control group (2.1±0.4 versus 5.6±1.8, p<0.001). Free water clearance was similar in both groups.

## Discussion

Using a whole animal model Hall found that angiotensin II is essential for preservation of GFR in states of hypoperfusion [1]. It was assumed that the

constrictive action of angiotensin II is located in the efferent arteriole of the glomerular capillaries. Myers [6] in a micropuncture study performed on rat kidneys, found that the direct pharmacological effect of angiotensin II is limited to the efferent arteriole. However, in these animal studies systemic haemodynamic and hormonal effects of angiotensin II could not be absolutely excluded.

In the present study which used an isolated kidney model it is demonstrated that angiotensin II maintains GFR by means of a direct intra-renal action. In the angiotensin II group, renal perfusate flow was much lower than in the control group. This is a result of the potent vasoconstrictive activity of angiotensin II [7]. In spite of a 53 per cent lower renal flow in the angiotensin II group, GFR remained constant and filtration fraction rose from 1.5 per cent to 3.8 per cent, indicating that the constrictive action of angiotensin II is confined mainly to the glomerular efferent arteriole.

In the present study angiotensin II showed a marked natriuretic effect at a concentration of 5ng/L. In the angiotensin II group UNaV, FENa and osmolar clearance (another parameter of sodium excretion in this model) were 300 per cent higher when compared to the control group. There were no systemic effects of angiotensin II, and GFR and perfusion pressure were similar in both groups, hence natriuresis could not be accounted for by an increased filtered sodium load or by pressure natriuresis. Redistribution of renal flow which could also change sodium excretion was shown not to be influenced by angiotensin II [2]. Intra-renal vasoconstriction which can be caused by angiotensin II, cannot be implicated in producing the observed natriuresis, since it has been demonstrated that intra-renal vasodilation and not vasoconstriction cause natriuresis [8]. It can be concluded, therefore, that the natriuresis found in our study resulted from a direct effect of angiotensin II on tubular sodium transport.

In a few studies angiotensin II was reported to influence the rate of tubular fluid reabsorption in the proximal [2], as well as in the distal segments [4]. However, in a study using isolated perfused proximal tubule such an influence was not found [9].

In the present study urine volume and FEH<sub>2</sub>O were 300 per cent higher and urine to plasma creatinine ratio was 300 per cent lower in the angiotensin II group compared to the control group. This magnitude of increase in fluid excretion is very similar to the magnitude of increase in sodium excretion (300%). It may therefore be concluded that the increase in fluid excretion is secondary to the increase in sodium excretion, and not the consequence of a direct effect of angiotensin II on tubular fluid handling.

## References

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