

A PHARMACOLOGICAL STUDY OF THE EFFECT OF ADRENALINE, NORADRENALINE AND ACETYLCHOLINE ON KIDNEYS

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Summary : The effects of different doses of adrenaline, noradrenaline and acetylcholine administered intravenous intrarenal and intra-cerebro-ventricular routes were studied on the urine out put in dogs. The findings are correlated with the known haemodynamic actions of these neurohumors as well as their direct actions on the reabsorptive mechanisms of the renal tubules. The effects of ICV administration are possibly due to the liberation of A.D.H. from posterior pituitary.

Key words: adrenaline noradrenaline acetylcholine kidney

INTRODUCTION

Contradictory reports are available regarding the effects of adrenaline (A) noradrenaline (NA) and acetylcholine (Ach) on renal functions. Thus A and NA have been reported to cause polyuria (3) as well as oliguria (1). Adrenaline infusion resulted in a decrease in G.F.R. and Na excretion (8) as well as an increase in G.F.R. (4). The effects of acetylcholine are also not very consistent.

These neurohumoral substances could be acting due to (a) their potent vascular action, (b) direct action on nephrons or (c) secondary to their action on A.D.H. release.

An attempt has been made in the present investigation to study the pharmacological actions of these neurohumours on urine output in dogs. The urine sodium (UNa) and urine potassium (UK) have also been measured.

MATERIALS AND METHODS

Dogs of either sex weighing 10 ± 2 kg anaesthetized with I.V. nembital (30-35 mg/kg body weight) were used. One femoral vein was cannulated and the B.P. recorded by cannulating the carotid artery. The trachea was cannulated and the animal was put on artificial respiration from the beginning. Abdomen was opened and both the ureters were cannulated up to the tip of renal pelvis by means of long polythene tubes which were collected in a measuring jar and the urinary out put measured every 10 min.

In some animals renal artery was cannulated for the administration of the drugs directly into the kidney. The abdominal cavity was opened and the kidney and the renal artery was

visualised. The renal artery arises directly from the aorta and before entering the kidney divides into two or more branches. One of the branches was cannulated by a fine polythene tube filled with normal saline and secured by ligatures. The cannula was clamped by means of artery forceps and was released for the drug administration. The renal flow was maintained by the other branches of renal artery. In studies with intrarenal drug administration the urine output from two kidneys was collected separately so that the other kidney served as control.

In some animals the lateral cerebral ventricle was cannulated by a polythene tube according to the technique of Bhargave and Tangri (5). Drugs were administered through the cannula at a constant volume of 0.5 ml (I.C.V.).

Spinal transection was done in some animals at the level of the atlanto-occipital joint.

Isolated kidney preparations :

This preparation was used to investigate the effects of the drugs on the renal vasculature. One kidney of the animal was isolated and perfused through the renal artery with aerated Locke's solution at 40°C. The renal vein was connected to a Palmer drop recording assembly which gave a measure of the drops coming out.

Urine sodium & potassium were estimated with the help of a Systronic flame photometer type 121 MK-1.

Design of the experiment :

After anaesthetizing the animal and completing the surgical procedures normal saline was infused intravenously into every animal at a constant rate of 20 drops per minute and this was continued throughout the experiment. In two initial experiments the effect of this infusion on urine volume UNa & UK in control animals was observed and it was found that the constant infusion caused a steady flow of urine after 60 min of starting the infusion.

The drugs were administered only after this steady flow was obtained.

Urine output was measured every 10 minutes.

RESULTS

Results are given in figures 1, 2 and 3.

Both A & NA (i.v.) caused a fall in urine volume in doses ranging from 0.1 to 5 µg/kg; however, an increase in the urine volume was observed by 0.1 µg/kg of A (Fig. 1 & 2). The UNa & UK did not change significantly. The fall in urine volume was observed even in doses which did not cause a rise in B.P. The effect of A was significantly decreased by prior administration of prisolone.

These drugs by intrarenal route caused a more marked decrease in urine output (Fig. 1&2) and there was a simultaneous significant decrease in UNa & UK as well. Even 0.1 µg/kg of A caused a fall in urine volume by intrarenal route. Prior intrarenal prisolone

not block the effects of A & NA. A rise in B.P. was observed by higher doses only; this was blocked by priscoline.

Adrenaline (ICV) showed a biphasic response. In doses of 0.1 to 0.5 $\mu\text{g}/\text{kg}$, it increased the urine output and in doses of 2.00 to 5.00 $\mu\text{g}/\text{kg}$, there was a significant decrease in urine output (Fig. 1). There was no effect on UNa & UK. After prior phenoxy benzamine all the doses

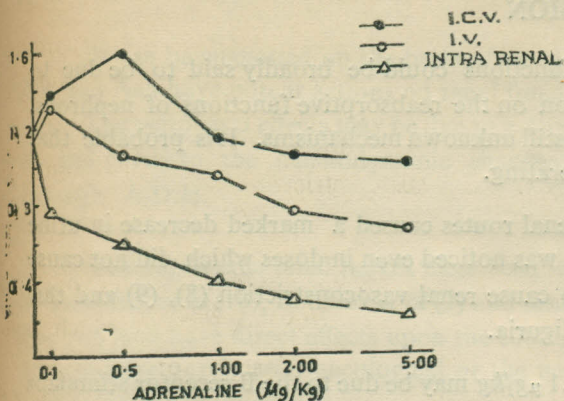


Fig 1 : Showing effect of different doses of adrenaline on urine volume in dogs

● I.C.V.
○ I.V.
△ Intrarenal

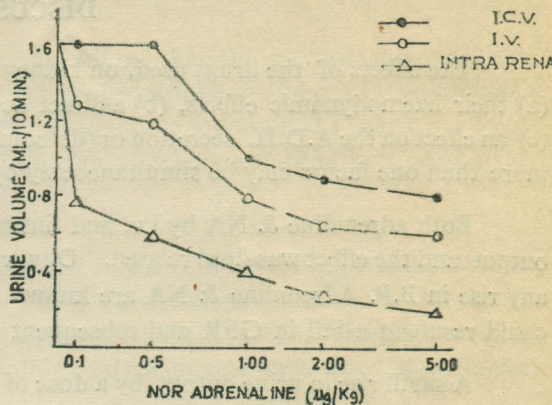


Fig. 2 : Showing effect of different doses of nor adrenaline on urine volume in dogs

● I.C.V.
○ I.V.
△ Intrarenal

of A caused an increase in urine volume. NA (ICV) in doses of 0.5 to 5 $\mu\text{g}/\text{kg}$ decreased the urine volume (Fig.2) an effect which was completely abolished by prior phenoxybenzamine. There was no effect on UNa & UK.

Ach by I. V. and intrarenal routes caused a fall in urine volume (Fig.3) together with a fall in UNa & UK the maximum effect was observed by intrarenal route. The effects were

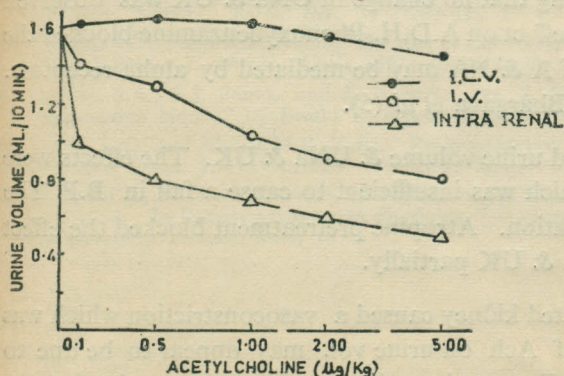


Fig 3 : Showing effect of different doses of acetylcholine on urine volume in dogs

● I.C.V.
○ I.V.
△ Intrarenal

significantly diminished by prior administration of atropine. Ach (ICV) was not very effective in decreasing the urine volume (Fig. 3). Effect of ICV administration of these drugs in spinal transected animals were exactly the same as in normal animals.

In isolated kidneys all the 3 agents caused a renal vasoconstriction.

DISCUSSION

The effects of the drugs used, on kidney functions could be broadly said to be due to (a) their haemodynamic effects, (b) a direct action on the reabsorptive functions of nephrons, (c) an effect on the A.D.H. secretion or (d) some still unknown mechanisms. It is probable that more than one factor may be simultaneously operating.

Both adrenaline & NA by i.v. and intrarenal routes caused a marked decrease in urine output and the effect was dose related. Oliguria was noticed even in doses which did not cause any rise in B.P. Adrenaline & NA are known to cause renal vasoconstriction (8), (9) and this could result in a fall in GFR and subsequent oliguria.

A small rise in urine output by a dose of $0.1 \mu\text{g}/\text{kg}$ may be due to the B receptor stimulant effect of small dose of A. Our findings are similar to those of Berne *et al.* (4) & Black (6).

Prior administration of an alpha blocker completely abolished the vasopressor response of the catecholamines but did not abolish the effect on urine volume and UNa & UK though they were decreased markedly.

The findings seem to suggest that A & NA affect the renal function by virtue of their renal vasoconstricting effect as well as a direct effect on the UNa reabsorption independently of their vasoconstricting effect. Similar possibilities have been put forward by Berne *et al.* (4) and Black (6).

ICV administration of A & NA resulted in a decrease in the urine output without any effect on UNa & UK. Small dose of A however gave a diuretic response. The effects were seen even in spinal animals. This fact and the finding that no change in UNa & UK was observed strongly indicative of this effect being due to an effect on A.D.H. Phenoxybenzamine blocked the effect suggesting that A.D.H. releasing effect of A & NA may be mediated by alpha receptors. The findings are in consonance with those of Bhargava *et al.* (5).

Ach by i.v. & intrarenal routes decreased urine volume & UNa & UK. The effects were observed even with a small dose of $1 \mu\text{g}/\text{kg}$ which was insufficient to cause a fall in B.P. The effect was more marked by intrarenal administration. Atropine pretreatment blocked the effect on B.P. completely and on urine volume, UNa & UK partially.

It is significant to note that Ach in isolated kidney caused a vasoconstriction which was partially blocked by atropine thus the effect of Ach on urine vol. may appear to be due to (a) renal vasoconstriction and/or (b) a direct effect on the sodium reabsorptive mechanisms.

The constriction of renal vessels may be due to the release of catecholamines from renal tissue a possibility supported by the work of Douglas and Rubin (7).

ICV Ach caused oliguria without any effect on UNa & UK. Same findings were obtained in spinal animals which could suggest that the effects of ICV Ach are due to the liberation of ADH, a finding well supported by the work of Bhargava *et al* (5).

It can be suggested on the basis of the present findings that the physiological agents A, NA and Ach have potent actions on renal functions both by peripheral and central administration. The peripheral effects may be due to a direct effect upon the sodium reabsorptive mechanisms and partly to the haemodynamic changes. The central effect are produced presumably through A.D.H.

The autonomic renal nerves have been implicated in the tubular reabsorption of sodium by Takenshi *et al* (10), Bonjour *et al* (2) and others and as a corollary it can safely be said that A, NA and Ach have direct effects upon the tubular reabsorptive mechanisms. Whether the effects observed are purely pharmacological or the neurohumoral substances have some physiological role is an open question.

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