THE DIRECT EFFECT OF ACETYLCHOLINE ON KIDNEY FUNCTION

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Studies of the changes in the excretion of urine under the influence of acetylcholine [1-5, 8, 9] have revealed an inhibition of diuresis. During "spontaneous urinary excretion" the initial oliguria is replaced after a short time by an increase in diuresis [5]. In these investigations cited, the acetylcholine was injected into the general circulation of the animals. When the drug is injected in this manner, the secondary changes arising in various organs, notably the hypophysis, may mask the direct action of acetylcholine on the kidney tissue. One report [6] mentions an increase in urine secretion in both kidneys after injection of acetylcholine into the abdominal aorta, although in this case it is difficult to say whether the increase in diuresis is the result of the direct action of the drug on the kidney, or whether the acetylcholine, having entered the general circulation, produces a more general reaction with the inclusion of vascular reflexes or of other mechanisms.

The object of the present investigation was to study the action of acetylcholine on the diuresis after its injection into the renal artery, i.e., to study the direct action of this preparation on the glomerular and tubular apparatus of the kidney.

METHOD

Experiments were carried out on 30 dogs. Under hexobarbital or thiopental anesthesia a lateral incision was made and the left renal artery dissected. An isotonic solution of sodium chloride was then infused into the renal artery under constant pressure and at a rate of 1.0-1.5 ml/min; solutions of the preparations to be tested were also infused in this manner as required. The urine was collected every 5 min from each kidney separately. From determinations of the concentration of endogenous creatinine in the urine and blood, the changes in glomerular filtration and in the reabsorption of water in the renal tubules could be judged.

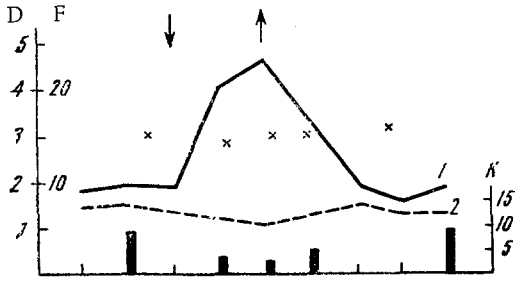

Fig. 1. Effect of acetylcholine (dose 40 μg/kg/min) on diuresis. Along the axis of abscissas—time (5 min intervals), along the axis of ordinates, on the left—diuresis (D) and filtration (F) (in ml/min), on the right—concentration ratio of creatinine (K); 1) diuresis of stimulated kidney; 2) diuresis of contralateral kidney, columns—concentration ratio, arrows—beginning and end of infusion of acetylcholine into renal artery.

RESULTS

Injection of acetylcholine into the renal artery in a dose of 8-40 μg/kg/min was accompanied in most cases by a sharp increase in the diuresis of the investigated kidney to 150-500% of its initial level; the diuresis of the contralateral kidney remained unchanged in these circumstances. The increase in diuresis began at once after the beginning of the infusion of acetylcholine; after the infusion had stopped the diuresis returned to its initial level within 5-10 min (Fig. 1). In certain experiments the increase in diuresis was more prolonged and continued for 20-30 min after the infusion had stopped. The increase in diuresis under the influence of acetylcholine was very

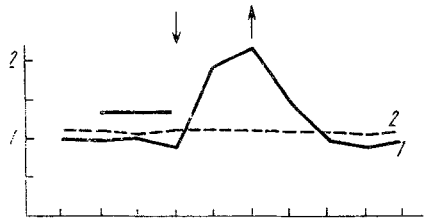

Fig. 2. Effect of acetylcholine (dose 20.5 μg/kg/min) of diuresis against the background of the action of azamethonium. Black rectangle—infusion of azamethonium (dose μg/kg/min) into renal artery. Remainder of legend as in Fig. 1.

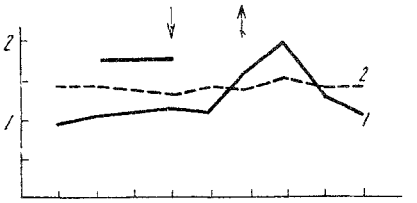

Fig. 3. Effect of acetylcholine (dose 27 μg/kg/min) on diuresis against the background of the action of atropine. Black rectangle—infusion of atropine (dose 26 μg/kg/min) into renal artery. Remainder of legend as in Fig. 1.

constant: in the course of one experiment acetylcholine could be injected several times, and every time a marked polyuria was observed. It was also found that following repreated injections of the preparation the polyuria was not diminished in degree by comparison than that following the first injection. This demonstrates that no adaptation to the action of adrenalin takes place.

The increase in diuresis caused by acetylcholine was accompanied by a marked decrease in the creatinine concentration ratio (Fig. 1). This shows that acetylcholine primarily has a marked action on the tubular apparatus of the kidney, inhibiting the reabsorption of water.

The magnitude of the glomerular filtration in most cases remained unchanged under the influence of acetylcholine (Fig. 1), and only in isolated experiments was a slight decrease found. However, the renal blood flow evidently rose, as indicated by the increase in the rate of infusion of the acetylcholine solution by 50-100% in the first 5 min (with a constant infusion pressure). When the acetylcholine was replaced by physiological saline, the rate of infusion rapidly returned to its initial level.

The action of acetylcholine on the diuresis in our experiments was effected through the direct action of the preparation on the structural elements of the kidney. Proof of this was given by the fact that the diuresis of the contralateral kidney was unchanged during and after the infusion of acetylcholine. Consequently, acetylcholine did not enter the general circulation or did so in negligible amount, having no detectable action on the organism. To obtain further confirmation of this, in some experiments acetylcholine was injected in the same or slightly larger doses intravenously. In these cases infusion of the drug was accompanied by a fall in diuresis, taking place equally in both kidneys. In these experimental conditions clearly the direct action of acetylcholine on the kidneys was not observed, but indirect effects, accompanied by inhibition of diuresis. Having demonstrated the character of the changes in diuresis under the influence of the direct action of acetylcholine on the kidney, we decided to study the mechanism of this action. In the first place it was necessary to discover whether the action of acetylcholine was associated with its action on nicotine-like or muscarine-like cholinergic systems.

Solutions of gangliolytics (hexamethonium or azamethonium) were fused into the renal artery over a period of 10-15 min in doses of 16-63 μg/kg/min, which had no significant effect on the diuresis (Fig. 2). Immediately or 5 min after this procedure, the infusion of acetylcholine into the renal artery began, as in the previous experiments; this was accompanied by an increase in diuresis as a result of a decrease in the tubular reabsorption of water. The simultaneous infusion of hexamethonium and acetylcholine likewise did not change the action of the latter on the diuresis. These facts demonstrate that the change in diuresis caused by the action of acetylcholine was not associated with its action on the autonomic ganglia.

Infusion of atropine sulfate in doses of 5-26 μg/kg/min into the renal artery was carried out during the period of 10-15 min immediately before infusion of acetylcholine, or the two substances were infused together. In these experimental conditions acetylcholine caused the same polyuria as before atropinization (Fig. 3). The only difference noted was that in some cases the polyuric effect of acetylcholine was observed 5 min after the beginning of its infusion into the renal artery, whereas in most control experiments the polyuria appeared more quickly. Hence, the change in diuresis brought about by acetylcholine was not associated with its action on the muscarine-like cholinergic systems in the kidney tissue, or alternatively these systems were very resistant to the action of atropine, for the doses which we used in the series of experiments were adequate to enter the general circulation and cause

changes in the activity of other organs (tachycardia, abolition of salivation, etc.). It is interesting to note that Granitsas [7] observed stimulation of the nitrogen-excreting function of the kidneys as a result of the action of very small doses of acetylcholine not affecting the blood pressure. This effect of acetylcholine like-wise was not blocked by administration of atropine.

In conclusion it should be noted that acetylcholine, in doses of 8-40 μg/kg/min, when injected into the renal artery caused a sharp rise in diuresis by inhibiting the reabsorption of water in the renal tubules. This action of acetylcholine on diuresis differs from that observed after injection of the drug into the general circulation. In the latter case it was evidently not the direct action of acetylcholine on the kidney that was observed, but its indirect effects: with larger doses an increased secretion of antidiuretic hormone was observed, either by a reflex mechanism or by the direct action of the drug on the hypophysis [1, 2], while with smaller doses the action of acetylcholine on the vessels was responsible [4]. These indirect effects masked the direct action of acetylcholine on the kidney tissue.

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