THE DIRECT ACTION OF CARDIAC GLYCOSIDES ON THE KIDNEYS

(UDC 615.711.5-092 : 612.46 + 612.46-06 : 615.711.5)

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Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 60, No. 7,
Original article submitted March 2, 1964

In recent years data have been published which show the importance of the pathological role played by the kidneys, especially the glomerular apparatus, in the formation of edemas. In connection with this finding an increased interest has been taken in the role of the kidney factor in the mechanism of the action of anti-edema agents.

Cardiac glycosides exhibit a diuretic as well as a cardiotonic activity. The former is considered to be derived from the cardiotonic effect which brings about an improvement in hemodynamics and results in an increase in glomerula filtration and diuresis [1, 6, 10]. However, the data given by various authors are not in agreement with this idea. Thus, in heart- lung- kidney preparations, no relationship was apparent between the blood flow through the kidneys and the fluctuations in diuresis following the effects of cardiac glycosides [2, 7]. There are indications that, in the intact organism, the effect of cardiac glycosides on the secretion of urine is not accompanied by any essential change in the blood flow or filtration through the kidney [5]. This gives one grounds for assuming that cardiac glycosides exert a direct action on the kidneys. As is shown in chronic experiments on dogs [8], the injection of digoxin directly into the renal artery is attended by a rise in the excretion of water and sodium on the perfused side. However, under similar experimental conditions, Bartram [4] did not observe any diuretic effect from a preparation of digitalis.

The aim of our investigations was to study the direct action of strophanthin-K and convallatoxin on the activity of the kidney while paying particular attention to the role of filtration and reabsorption during the changes in diuresis.

EXPERIMENTAL METHODS

In acute and chronic experiments on 22 dogs studies were made on the kidney function when strophanthin-K and convallatoxin were directly injected in doses of 5-20 μg/kg on the weight of the animal. The acute experiments were carried out under hexanol narcosis. The abdominal cavity was opened by a small median incision, the bladder removed and catheters introduced into the ureter openings. The urine was collected every 10-20 minutes. Throughout the experiment a physiological solution was run into the tibial vein at a constant speed of 2.5-3 ml/min, as a result of which diuresis was maintained at a constant level. A cut was made along the left costal arch and a thin needle was introduced into the left renal artery and connected to a vessel containing 0.9% sodium chloride solution. During a control period of one to two hours, the physiological solution was run into the renal artery at a speed of 0.25-0.5-1 ml/min and was constant for each experiment. This solution was later changed for a solution of the compound under test. The speed of perfusion remained the same as before. After the preparation had been run in for 40-120 min the physiological solution was again substituted.

The chronic experiments, which had the advantage of eliminating the affects of narcosis, were carried out on dogs with separately investigated ureters. A few days prior to making the tests a thin rubber catheter had been introduced into the left renal artery on the side of the aorta [3, 9]. The remainder of the experimental procedure was the same as in the acute experiments.

The filtration-reabsorption function of the kidney was studied by Clarence's method, the creatine, sodium and potassium in the urine and in the blood stream by the flame photometer and the chlorine in the urine by Volgard's method.

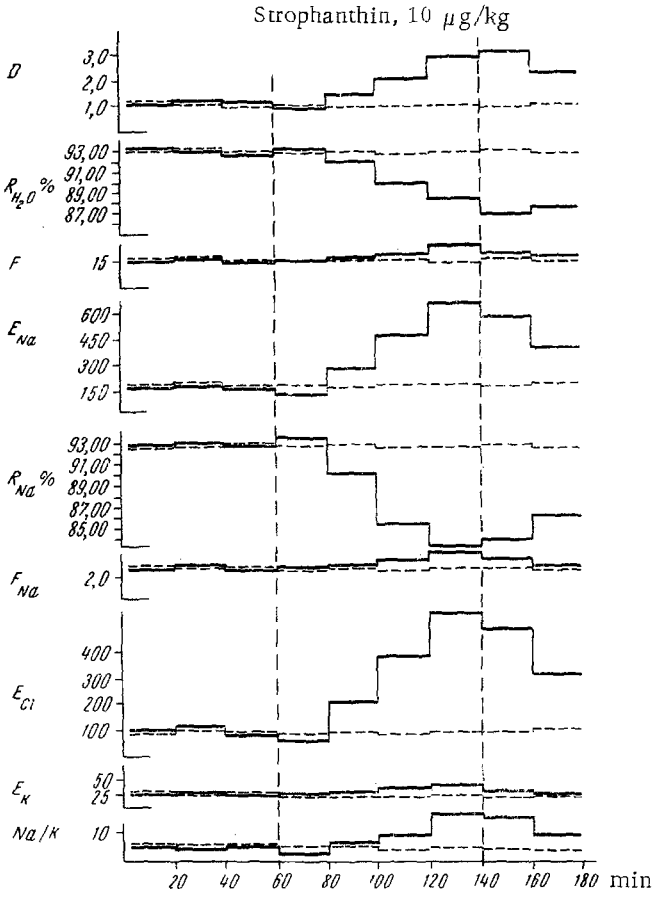

Fig. 1. Effect of small doses of strophanthin-K (10 g/kg) on kidney activity. Continuous line—left (perfused) kidney; Dotted line—right kidney; D) diuresis, ml/min; R_{H_2O}%) reabsorption of water by canals, % of filtrate; F) glomerular filtration, ml/min; E_{Na}) sodium excretion, microequiv/min; R_{Na}%) sodium reabsorption, %; F_{Na}) filtrated loading of sodium, microequiv/min; E_K) potassium excretion, microequiv/min; Na/K) ratio of sodium excretion to potassium excretion. The period of injection of strophanthin is given by the vertical dotted lines.

EXPERIMENTAL RESULTS

In the acute experiments, with the application of small doses (5-20 μg/kg) of the given preparations, an increase in diuresis was observed 20-40 min after the beginning of perfusion on the side into which the preparation had been injected; the excretion of urine from the right (control) kidney did not change during the experiment (Fig. 1, D). The polyuric effect was dependent on the existing depression of reabsorption; it dropped by 2-6% (Fig. 1, R_{H_2O}%). At first the speed of glomerular filtration either dropped or remained at the original level but, later, it rose slightly. These variations in filtration, naturally, did not affect diuresis to any great extent.

Together with polyuria, a sharp increase was observed in the excretion of sodium and chlorine which was the result of a depression in their reabsorption with the mild fluctuations in the filtrated loading of sodium (see Fig. 1).

The excretion of potassium by the perfused kidney did not change substantially (Fig. 1, E_K) and the sodium and potassium contents of the blood plasma remained as before.

Medium doses of strophanthin-K and convallatoxin (30-80 μg/kg) gave similar reactions but the variations were more marked. However, in the experiments of this series, a reduction in filtration during the first 20-60 min

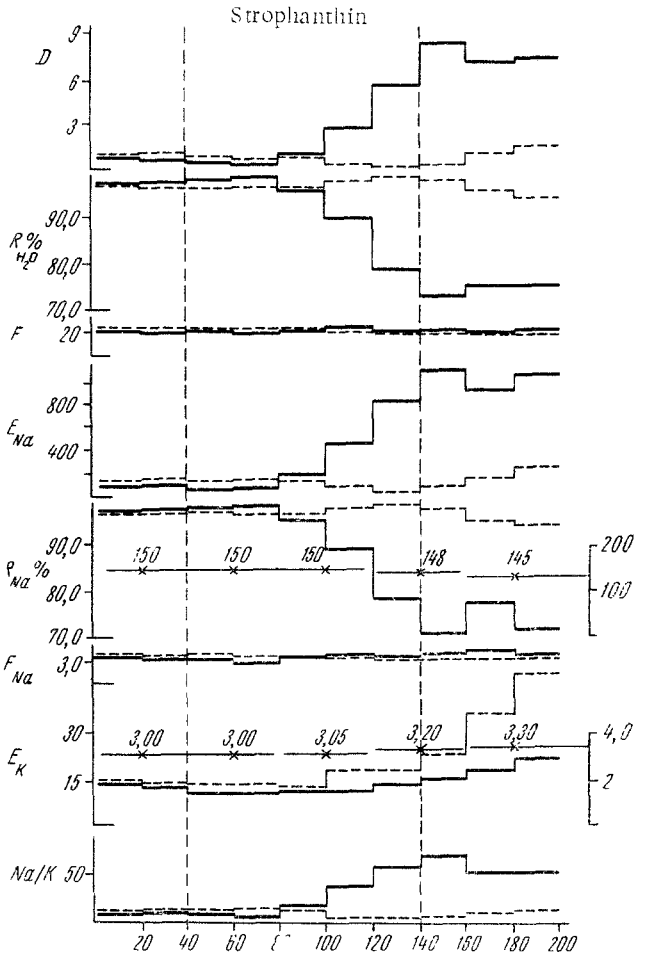

Fig. 2. Effect of large doses of strophanthin-K (100 μg/kg) on kidney activity. Symbols the same as for Fig. 1. Ordinates on the right—concentration of sodium (upper) and of potassium (lower) in the blood plasma. The curve for the excretion of chlorine is not drawn since it was almost identical with the curve for sodium excretion.

of perfusion was always present. In three experiments out of seven, during the period of maximum increase in diuresis or following it, a decrease in diuresis and saluresis developed in the contra-lateral kidney as the result of a rise in the reabsorption of water and sodium. The concentration of potassium in the urine from this kidney was slightly increased.

Strophanthin-K and convallatoxin in large doses (100-200 μg/kg) brought about, immediately or 10-20 min after the beginning of perfusion, a very sharp rise in diuresis and in the excretion of sodium and chlorine which was the result of a strong depression in reabsorption by the canals. In some experiments reabsorption dropped by more than 80% (Fig. 2). In this same series of experiments phase changes were observed in the control kidney. During the initial period of perfusion all the indices of its activity remained at a low level, but after that, when the maximun polyuria had developed on the perfused side, reabsorption of electrolytes and water by the control kidney increased and resulted in a drop in diuresis and in the excretion of sodium and chlorine. This phase was noted, as mentioned above, in a number of experiments in the preceding series and was, possibly, a compensating action. Afterwards, a phase set in which diuresis and the excretion of sodium and chlorine (decrease in their absorption) increased with a rise in the excretion of potassium.

In the corresponding chronic experiments which, judging from the literature, are conducted for the first time, we observed changes in kidney activity agreeing, in many ways, with those of the last series. It should be noted

that, under the conditions of the chronic experiments, the effect of corresponding doses of the preparations employed are considerably greater than those in the acute experiments. Thus, in order to bring about polyuria, which was obtained in acute experiments with doses of 50-100 μg/kg of strophanthin-K, it was sufficient in the chronic experiments to use the preparation at doses of 5-20 μg/kg.

The experiments described demonstrate the direct action of cardiac glycosides on the kidney as is shown very clearly by the use of small or medium doses when unilateral diuretic and saluretic effects are observed and the concentrations of sodium and potassium in the blood plasma do not change.

The decrease in diuresis and in the excretion of sodium and chlorine from the control kidney, observed in a number of experiments using medium doses of the preparations and in experiment 2 of the last series at the time of maximum effect on the perfused kidney, was possibly be compensatory—a response to a large loss of liquid and sodium—and dependent upon the mobilization of aldosterone and ADH. This seems probable because there is a rise in the reabsorption of sodium and water with some increase in the concentration of potassium in the urine. The phase in which and increase in diuresis and saluresis on the control side occurs, following on the perfused kidney, was observed only after the application of large doses of glycoside and, coinciding with changes in the concentration of sodium and potassium in the blood, was obviously connected with a spreading of the action of the cardiac glycosides to involve the control kidney in their sphere of action. This idea is upheld by the results of experiments on the intravenous injection of cardiac glycosides (these experiments will be the subject of a separate communication) in which a rise in the extraction of both sodium and chlorine and of potassium was recorded.

Throughout the experiments no differences could be found between the action of strophanthin-K and convallatoxin on kidney activity. It is obvious that the character of the glucon is of no great importance in the mechanism of the action of glycosides on the kidney.

The data obtained provide evidence for the direct action of strophanthin-K and convallatoxin on kidney activity. This action is directed in the first place and mainly on the function of the glomeruli; a depression of the reabsorption of water, sodium and chlorine by the canals was observed.

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