MECHANISM OF THE INFLUENCE OF HEXAMETHONIUM ON SOME FUNCTIONS OF THE KIDNEY BEFORE AND AFTER ITS DENERVATION

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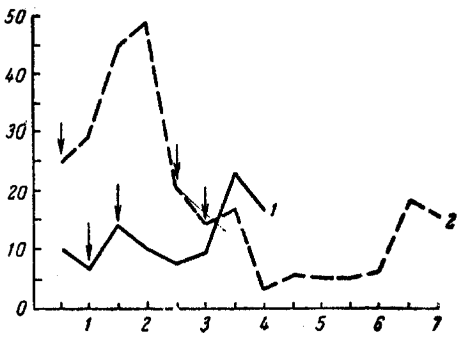
In earlier chronic experiments on dogs it was found [6] that ganglion-blocking agents – dicoline, hexamethonium, and pentamine (azamethonium bromide) – when administered to animals inhibited the secretion of urine whereas pachycarpine stimulated it.

To elucidate the mechanism of the inhibitory action of ganglion-blocking agents on diuresis, in the present investigation the influence of hexamethonium was investigated before and after denervation of the kidney.

The influence of denervation of the kidney on diuresis has been described by several authors, but the greatest interest is attached to the conclusive data obtained by A. G. Ginetsinskii and co-workers [3-5, 8]. While recognizing the trophic role of the nerves supplying the kidney, these workers stressed the foremost importance of humoral factors in the activity of the kidney, acquired in the process of evolution.

EXPERIMENTAL METHOD

Experiments were conduted on two dogs from which the urine was obtained by a simplified method, greatly facilitating care of the animals. Initially the right kidney was removed from the dogs. Later a fistula tube was introduced into the bladder. After a study of the function of the remaining left kidney, it was denervated. The kidney was freed from the surrounding tissues, the nerve twigs approaching the kidney were cut, the vessels were treated for a distance of 10-12 mm with 5% phenol solution – at first an aqueous solution, subsequently an alcoholic solution. The ureter was exposed at the point where it leaves the kidney, and it also was treated with phenol solution for, according to A. E. Smirnov [10], some nerve fibers reach the kidney via the ureters. In the experiment a water load was given, amounting to 15 ml/kg body weight, and milk (about 20%) was added to the water. The urine was collected every 15 or 30 min. Hexamethonium was injected subcutaneously in a dose of 3 mg/kg 30 min after the animals had received the water load.



Effect of hexamethonium on diuresis before (1) and after (2) denervation of the kidney. Along the axis of ordinates–volume of urine (in ml), along the axis of abscissas–time (in hours). In curve 1: first arrow–water load (15 ml/kg), second arrow–injection of hexamethonium (3 mg/kg); in curve 2: first arrow–water load (15 ml/kg), second arrow–water load (15 ml/kg), third arrow–injection of hexamethonium (3 mg/kg).

The kidney function was studied by the endogenous creatinine method. The creatinine in the urine and blood was determined by Folin's method based on the reaction with picric acid. The colorimetric estimations were made in the FEK-M photoelectric colorimeter using a green filter.

EXPERIMENTAL RESULTS

In the experiments carried out before denervation of the kidney, injection of hexamethonium caused delay in the excretion of urine, as the authors previously have shown [6]. The delay usually lasted for 45 min, and only occasionally for 75-90 min. As an example the results of an experiment when the delay was maximal are shown in the figure (curve 1). In the same experiment the kidney function was estimated by the endogenous creatinine method (Table 1).

The considerable increase observed in the creatinine concentration index after injection of hexamethonium demonstrates

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TABLE 1. Effect of Hexamethonium on Kidney Function in an Experiment before Denervation

	Creatinine concentration index	Volume of urine/min	Filtration/min	Reabsorption/min	Percent reabsorption/min
Before injection of hexamethonium.	73	0.47	34.31	33.84	98.63
After injection of hexamethonium:					
60 min.	125	0.27	33.75	33.48	99.20
120 min.	40	0.80	32.00	31.20	97.50

TABLE 2. Effect of Hexamethonium on Kidney Function on the 16th Day after Denervation

	Creatinine concentration index	Volume of urine/min	Filtration/min	Reabsorption/min	Percent reabsorption/min
Before injection of hexamethonium.	162	0.27	43.74	43.47	99.38
After injection of hexamethonium:					
60 min.	231	0.13	30.03	29.90	99.56
120 min.	287	0.18	51.66	51.48	99.65
210 min.	116	1.15	133.40	132.25	99.14

an increase in the reabsorption of water in the tubules. This is also clear from the increase in the percentage of reabsorption.

In the experiments after denervation of the kidney the inhibition of diuresis by hexamethonium was much stronger. The results of an experiment carried out on the 9th day after denervation are shown in the figure (curve 2). In this experiment two water loads were given in succession. After the first load the diuresis to a measure load was compared with the diuresis before denervation of the kidney. During the second load the effect of hexamethonium was studied.

After the first load the diuresis differed very little, as also in the subsequent experiments, from the diuresis after loading before denervation of the kidney. This agreed with observations by other authors [2, 9]. In the second part of the figure it can be seen that after injection of hexamethonium, not only was inhibition of diuresis observed as before, but it lasted 3 h, and consequently twice as long as the longest inhibition of diuresis before denervation (see figure). It was also noted that the diuresis fell by a greater degree than in the experiments before denervation.

The results of one of the experiments in which the kidney function was determined by the endogenous creatinine method are given in Table 2. This experiment was carried out on the 16th day after denervation of the kidney. Inhibition of diuresis after injection of hexamethonium was observed for about 3 h.

It was noted that the concentration index, as in the other experiments, was higher than before denervation. It rose in the period of inhibition of diuresis, and at the same time the percentage reabsorption was increased. As a result of the considerable compensatory increase in diuresis after prolonged loading (up to 3 h) the indices of filtration and reabsorption were high.

Hence, the action of hexamethonium not only persisted after denervation of the kidney but was much stronger. Since the increase in the creatinine concentration index and the increase in the percentage reabsorption pointed to an increase in the reabsorption of water, some effect of hexamethonium on the output of antidiuretic hormone (ADH) may be suspected. However, there is no basis for this suggestion. According to A. A. Belous [1], acetylcholine and nicotine caused the release of ADH and delay of diuresis by their excitatory action on the cholinergic biochemical structures of the carotid bodies, or by their direct action on the posterior lobe of the pituitary. However, the substances used by the authors (hexamethonium in this investigation) do not excite but only block these biochemical structures. In addition, V. F. Vasil'eva [2] has shown that after denervation of the kidney the effect of administration of ADH are shown equally before and after denervation. Consequently, if the action of the ganglion-blocking agent in the present experiments were mediated through the release of ADH, the process of reabsorption would not have differed to such an extent before and after denervation of the kidney.

Nor can the suggestion be convincing that the changes in diuresis under the influence of injection of hexamethonium depend on a fall of the arterial pressure, for it would have to be assumed that the changes observed after denervation of the kidney took place because hexamethonium had begun to lower the blood pressure differently. It must be remembered also another ganglion-blocking agent (pachycarpine) in the author's experiments [6] did not inhibit diuresis but stimulated, although it was given in a dose of 10 mg/kg, causing a considerable fall in arterial pressure.

The same conclusion may be drawn as was expressed earlier [7], namely that hexamethonium affects certain elements of the nephron. After denervation of the kidney their sensitivity is increased, and this causes the great prolongation of the inhibition of diuresis by comparison with that observed when it acts on the normal kidney.

SUMMARY

In dogs overloaded with water diuresis decreases after subcutaneous injection of hexamethonium (C_6) prior to as well as after denervation of the kidney. Decrease of diuresis under the influence of C_6 lasts longer and is more marked after renal denervation. Counts after endogenic creatinine titration showed, that under the influence of C_6 the return absorption in the loops is increased. Analysis of data obtained suggests that C_6 acts directly on some elements of the nephron.

LITERATURE CITED

1. A. A. Belous, In the book: The Pharmacology of New Therapeutic Agents [in Russian], Leningrad (1953), p. 122.
2. V. F. Vasil'eva, The Influence of Efferent Nerves on Kidney Function, Candidate Dissertation, Novosibirsk (1953).
3. A. G. Ginetsinskii, I. I. Likhnitskaya, and E. P. Semenova, Byull. Éksp. Biol., Vol. 34, No. 8 (1952), p. 6.
4. A. G. Ginetsinskii, V. F. Vasil'eva, M. G. Zaks, et al., In the book: Problems in the Evolution of Physiological Functions [in Russian], Moscow—Leningrad (1958), p. 17.
5. A. G. Ginetsinskii, Physiological Mechanisms of Water and Salt Balance [in Russian], Moscow—Leningrad (1963).
6. V. É. Maevskii and P. I. Berenskii, Urologiya, No. 6 (1960), p. 5.
7. V. É. Maevskii and P. I. Berenskii, In the book: Abstracts of Proceedings of the 6th Congress of the Ukrainian Physiological Society [in Ukrainian], Kiev (1961), p. 284.
8. E. A. Nikolenko, In the book: Material on Evolutionary Physiology [in Russian], Vol. 2, Moscow—Leningrad (1957), p. 151.
9. A. A. Pavlovskaya, Byull. Éksp. Biol., No. 5 (1951), p. 305; No. 6 (1951), p. 395.
10. A. E. Smirnov, Anat. Anz., Vol. 30 (1951), p. 347.

All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of the first issue of this year.