MECHANISM OF THE DIURETIC ACTION OF CHLORACIZINE*

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Chloracizine has a marked diuretic action and increases sodium excretion in rats although not by any direct action on the kidney. This effect is accompanied by an increase in the volume of intravascular fluid, a decrease in the total plasma protein concentration, and a decrease in the hematocrit index. A study of the endogenous creatinine clearance and transport of osmotically free water shows that the mechanism of the diuretic action of chloracizine is linked chiefly with an increase in the level of glomerular filtration and a decrease in the relative proximal reabsorption.

KEY WORDS: chloracizine*; excretory function of the kidneys.

The phenothiazine derivative chloracizine* was shown previously to have a marked effect on kidney function in rats [1].

It was decided to study the mechanism of the diuretic action of chloracizine and its action in stimulating sodium excretion and to determine as far as possible the localization of these actions in the nephron.

EXPERIMENTAL METHOD

The effect of chloracizine on the excretion and reabsorption of osmotically free water was studied in day-long experiments during ordinary diuresis and during the first 2 h after water loading (5% of body weight). Creatinine was determined by Folin's method in the urine and blood plasma and the osmotic pressure was measured by a thermoelectric method [2]. The sodium and potassium excretion also were determined by flame photometry and the filtration and transport of osmotically free water were calculated. The water spaces of the body were determined by the method described earlier [3]. The sodium-excretory and antidiuretic activity of the plasma were determined by a biological method in rats [7]. Chloracizine was injected subcutaneously (5 mg/kg) as a 0.1% solution. The direct effect of chloracizine on kidney function was studied in acute experiments on dogs with catheterization of both ureters. Chloracizine was injected into the left renal artery as a 0.1% solution at the rate of 100 μg/kg/min.

EXPERIMENTAL RESULTS AND DISCUSSION

As Table 1 shows, chloracizine considerably increased the 24-hourly diuresis of the rats and also the 2-hourly excretion of urine after water loading, and these effects were accompanied by an increase in the excretion of sodium and potassium and also by a marked increase in filtration. This effect evidently depended on certain extrarenal mechanisms, for no direct diuretic action of the drug on the kidney could be found (Fig. 1).

The redistribution of water in the body under the influence of chloracizine discovered previously [3] suggested a connection between its diuretic effect and the mechanisms of volume regulation. As Table 2

* 2-Chloro-10-(3-dimethylaminopropionyl)phenothiazine – Translator.

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TABLE 1. Effect of Chloracizine (5 mg/kg) on 24-h and 2-h Diuresis in Rats (M ± m)

Index studied	24-h Diuresis		Diuresis during 2 h after water loading	
	control ($n=15$)	expt. ($n=15$)	control ($n=15$)	expt. ($n=15$)
Diuresis (in ml)	6,8±0,42	18,4±0,96	7,7±0,35	11,9±0,52
Sodium (in μeq)	386±41,4	962±50,6	25±2,8	316±18,5
Potassium (in μeq)	408±36,0	868±64,4	51±4,2	135±8,2
Filtration (in ml)	630±28,2	874±38,6	64±1,1	83±2,4
Relative reabsorption (in %)	99±0,1	98±0,1	88±0,4	86±0,6

TABLE 2. Effect of Chloracizine (5 mg/kg) on Distribution of Water in Rats (in %)

Time of investigation	Total water	Intracellular water	Extracellular water	Intravascular water	Interstitial water
Control(15)	60,3±1,37	42,4±1,24	18,8±0,36	4,9±0,67	13,5±0,36
After injection of chloracizine					
4 h(8)	57,6±1,54	39,3±1,37	18,3±0,75	6,6±0,40 $P<0,001$	11,7±0,71 $P<0,05$
48 h(8)	58,9±0,62	40,5±0,92	18,4±0,62	6,1±0,33 $P<0,05$	12,3±0,40 $P<0,05$

Note. Number of observations shown in parentheses. Index of significance of indices shown only if differences between control and experiments are significant ($P<0.05$).

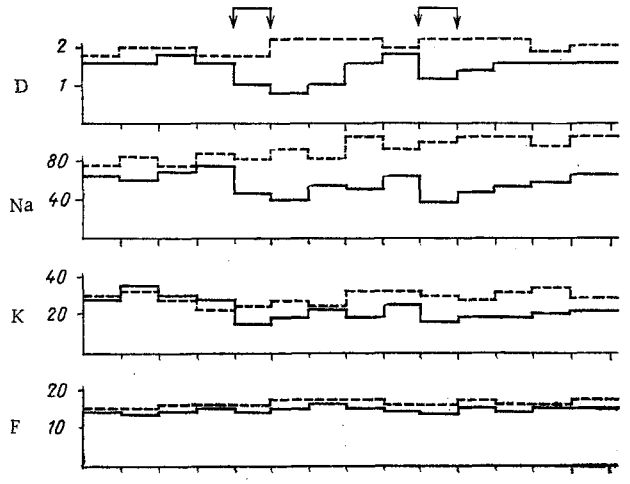

Fig. 1. Kidney function in dogs after injection of chloracizine into left renal artery (100 μg/kg/min). Abscissa, time intervals (10 min); ordinate, indices of kidney function. D) Diuresis (in ml/min); Na) excretion of sodium (in μeq/min); K) excretion of potassium (in μeq/min); F) filtration (in ml/min). Arrows indicate beginning and end of injection of chloracizine. Continuous line – left kidney, broken line – right kidney.

TABLE 3. Sodium-Excretory or Antidiuretic Activity of Plasma of Rats Receiving Chloracizine (5 mg/kg)

Animals	Sodium excretion (in % of initial value)	Diuresis (in % of initial value)
Control (10)	94,7±4,23	83,1±2,61
Receiving chloracizine (12)	98,5±7,42	95,8±3,13
	$P>0,5$	$P<0,05$

Note. Number of observations in parentheses.

TABLE 4. Effect of Chloracizine (5 mg/kg) on Total Plasma Protein Concentration and Hematocrit Index

Parameter studied	Before injection of chloracizine (n = 15)	4 h After injection (n = 15)	24 h After injection (n = 15)
Total plasma protein (in g%)	6,7±0,08	6,0±0,10	6,2±0,08
Hematocrit index (in %)	43,8±0,64	40,1±0,48	40,5±0,47

Note. In every case $P<0.05$.

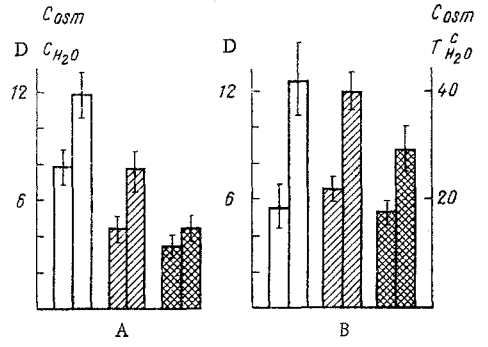

Fig. 2. Effect of chloracizine (5 mg/kg) on diluting and concentrating functions of the kidneys in rats: A) water diuresis in 2 h: unshaded columns – diuresis (D), obliquely shaded columns – C_{osm}, cross-hatched columns – C_{H_2O}. B) 24-h Diuresis: unshaded columns – diuresis (D), obliquely shaded columns – C_{osm}, cross-hatched columns – $T^C_{H_2O}$. First column of each pair is control, second after injection of chloracizine. Ordinate, parameters studied (all in ml).

shows, the increase in the intravascular volume was maintained for a long time, to correspond to the diuretic response of rats to a single injection of the drug, which continues for several days.

The increase in sodium excretion with an increase in the intravascular fluid volume has been associated with the appearance of a sodium-excretory factor in the blood [4, 6]. In the present experiments the sodium-excretory activity of the plasma of rats receiving chloracizine 4 or 24 h before the investigation (Table 3) was unchanged. Meanwhile the antidiuretic activity of the plasma was significantly lowered.

A definite role in the mechanism of the increased diuresis and sodium excretion could belong to dilution of the blood, as indicated by the lowered total plasma protein concentration and hematocrit index found in these experiments (Table 4). According to many workers, these factors play an important role in volume regulation. For instance, the decrease in the oncotic pressure in the capillaries of the renal glomeruli could lead to an increase in the filtration level, but a decrease in that pressure in the peritubular capillaries could lead to a decrease in reabsorption in the proximal tubules [5, 10]. Lowering of the hematocrit index, through a change in the viscosity of the blood, could cause a redistribution of the blood flow in the kidney, leading to an increase in the diuretic function [8, 9].

The reduction in the relative proximal reabsorption probably plays an important role in the diuretic action of chloracizine. This is because, during water loading, when the distal tubule is impermeable to water, the diuresis increases more than the filtration after injection of chloracizine. This view is confirmed by the increase in reabsorption and excretion of osmotically free water as a result of the action of chloracizine on animals with different degrees of hydration of the body (Fig. 2).

The increase in diuresis and sodium excretion under the influence of chloracizine is thus due chiefly to an increase in glomerular filtration and a decrease in relative proximal reabsorption, the causes of which include a redistribution of fluid in the body and a change in the physicochemical properties of the blood.

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