EFFECT OF SOME PHENOTHIAZINE DERIVATIVES ON THE REGIONAL CIRCULATION OF THE KIDNEY

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Experiments on dogs showed that chlorpromazine and chloracyzine increase the renal blood flow, filtration remaining unchanged but reabsorption being increased. Diuresis is reduced by chlorpromazine, but increased in chronic experiments under the influence of chloracyzine.

Several investigators have stated that phenothiazine derivatives can modify the blood flow in the limbs [13, 16] and in the blood vessels of the heart [4-9,17]. With regard to the renal blood flow, the available information is fragmentary [12,14,16], but suggests an increase in the blood flow under the influence of chlorpromazine. The action of chloracyzine* on the renal blood flow has not been studied. The object of the present investigation was to study the effect of chlorpormazine and chloracyzine on the renal blood flow.

EXPERIMENTAL METHOD

Acute and chronic experiments were carried out. The acute experiments (42) were performed on dogs of different weights anesthetized with nembutal. The left kidney was exposed through a lateral incision and a thermoelectric pick-up introduced into the renal vein to record the renal blood flow. The volume velocity of the blood flow was determined by an instrument of the author's own design [11]. It is based on the fact that the movement of a warmed liquid is accompanied by the transmission of heat through the wall of the vessel along which the liquid flows and, consequently, between two points located at a given distance from each other a certain temperature difference will be found, depending on the velocity of movement of the fluid. The differential flow was recorded by a mirror galvanometer. Values of the blood flow (in ml/min) were found from the standard curve. The blood pressure was measured by a mercury manometer in the carotid artery. Urine was collected every 10 min by means of ureteric catheters. To maintain a sufficient level of diuresis, isotonic NaCl heated to body temperature was injected intravenously at a rate of 2 ml/min.

Chronic experiments were carried out on three dogs with exteriorized ureters. The experiments were carried out 14-16 h after feeding. To determine the renal blood flow, a constant intravenous infusion of 1% diodone solution was given at the rate of 1.5-2 ml/min. Diodone in the urine and blood was determined by the method of White and Rolfe as modified by Bac and co-workers [15].

The filtration-reabsorption function of the kidneys in both the acute and chronic experiments was estimated by recording the diuresis and by determining the creatinine concentration (after Folin) in the blood and urine. On the basis of these observations, the filtration and reabsorption values were calculated (using Rehberg's formulas).

Chlorpromazine (0.5-1 mg/kg) and chloracyzine (0.5-4 mg/kg) were injected intravenously.

EXPERIMENTAL RESULTS AND DISCUSSION

In the acute experiments, 30 min after its administration chlorpromazine caused a mean increase of 13-19% in the renal blood flow (Table 1), and after about 60 min the blood flow returned to its initial level. Immediately after injection of the drug the blood pressure fell by 20-30 mm Hg and remained at that level until the end of the experiments. The glomerular filtration during the first 20-30 min showed a tendency to diminish (not statistically significant), thereafter remaining essentially unchanged. The filtration fraction was reduced by 27-34% (Fig. 1). The diuresis fell significantly, because the tubular reabsorption showed a considerable increase.

*2-chloro-1-(3-dimethylaminopropionyl)phenothiazine.

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TABLE 1. Changes in Renal Blood Flow, Filtration, and Diuresis following Administration of Chlorpromazine (in % of initial level)

Index studied	Statistical index	In initial state	After injection of chlorpromazine					
			20 min	40 min	60 min	80 min	100 min	120 min
Renal blood flow (in ml/min	M	100	103,4	119,0	114,2	113,8	101,8	101,1
	$\pm m$	5,8	2,8	4,6	3,4	2,6	5,6	4,8
	P		<0,25	<0,01	<0,05	<0,05	>0,5	>0,5
Filtration (in ml/min)	M	100	92,4	100,9	100,7	95,1	103,0	111,0
	$\pm m$	6,8	4,8	7,1	3,9	8,3	15,6	9,1
	P		>0,25	>0,5	>0,5	>0,5	>0,5	>0,5
Diuresis (in ml/min)	M	100	63,0	40,4	41,1	34,2	30,8	30,3
	$\pm m$	3,6	6,4	6,5	7,1	5,9	7,2	6,7
	P		<0,001	<0,001	<0,001	<0,001	<0,001	<0,001

TABLE 2. Changes in Renal Blood Flow, Filtration, and Diuresis following Administration of Chloracyzine (in % of initial level)

Index studied	Statistical index	In initial state	After injection of chloracyzine					
			20min	40 min	60 min	80 min	100 min	120 min
Chloracyzine (2 mg/kg)								
Renal blood flow (in ml/min)	M	100	117,0	127,1	125,7	109,6	96,5	93,4
	$\pm m$	5,5	3,3	4,7	7,1	3,7	1,9	2,2
	P		<0,05	<0,01	<0,02	<0,25	<0,25	<0,25
Filtration (in ml/min)	M	100	91,0	90,6	81,0	90,0	79,0	75,8
	$\pm m$	8,4	9,7	9,5	5,2	10,3	7,9	9,4
	P		>0,5	>0,5	>0,25	>0,5	>0,1	>0,1
Diuresis (in ml/min)	M	100	69,7	73,5	70,4	58,7	53,0	71,6
	$\pm m$	5,9	8,7	9,2	13,0	9,4	5,9	11,9
	P		<0,02	<0,05	<0,05	<0,01	<0,001	<0,05
Chloracyne (4 mg/kg)								
Renal blood flow (in ml/min)	M	100	125,3	145,0	145,3	125,2	113,5	96,5
	$\pm m$	6,6	3,1	12,6	11,9	4,6	8,9	0,06
	P		<0,01	<0,02	<0,01	<0,02	<0,25	<0,25
Filtration (in ml/min)	M	100	94,7	80,0	113,3	84,0	86,5	98,0
	$\pm m$	9,4	4,9	16,0	6,4	11,0	15,0	10,2
	P		>0,5	>0,25	>0,25	>0,5	>0,5	>0,5
Diuresis (in ml/min)	M	100	40,8	41,3	37,5	35,3	50,8	59,0
	$\pm m$	4,9	15,0	16,7	16,3	13,8	9,3	11,0
	P	—	<0,002	<0,05	<0,02	<0,02	<0,01	<0,05

Chloracyzine in a dose of 0.5 mg/kg increased the renal blood flow for 30 min, and in doses of 2-4 mg/kg for 60-70 min (Table 2). The blood pressure was essentially unchanged. The glomerular filtration remained at the same level, but diuresis was considerably reduced because of an increase in reabsorption. The filtration fraction was reduced, suggesting greater dilatation of the efferent vessels.

In the chronic experiments, during the first 40-60 min after injection of chlorpromazine and chloracyzine an increase in the renal blood flow averaging 25-47% was observed (Fig. 2). During the second hour of observation the blood flow frequently fell below its initial level. The glomerular filtration in the first period increased slightly, while the filtration fraction showed a tendency to decrease. Under the influence of chloracyzine, after some increase in the first period the diuresis returned to its original level, but in some cases it remained high until the end of the experiment. In these experiments, chlorpromazine caused a decrease in diuresis.

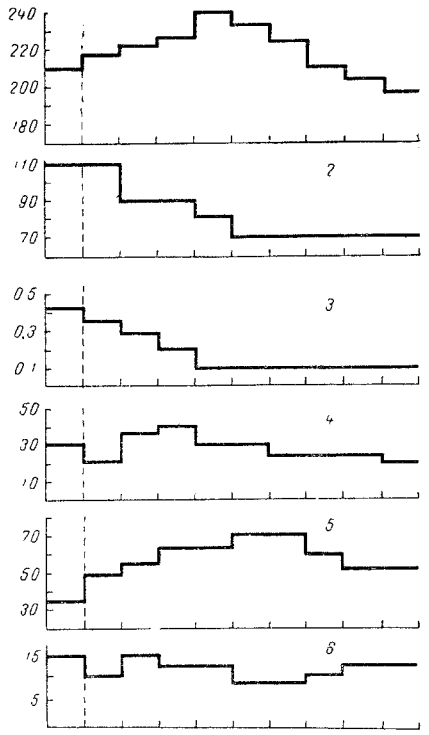

Fig. 1

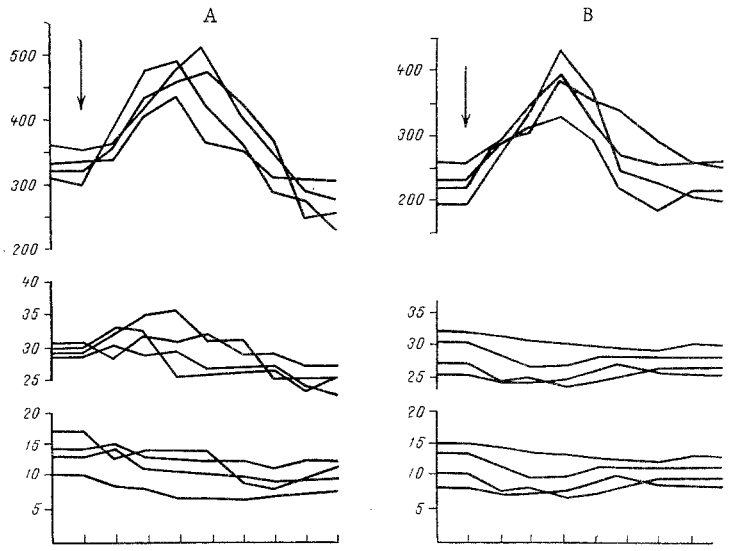

Fig. 2

Fig. 1. Effect of chlorpromazine in renal function (dog Ezop, weight 18.5 kg, experiment on October 24, 1966). 1) Renal blood flow (in ml/min); 2) blood pressure (in mm Hg); 3) diuresis (in ml/min); 4) glomerular filtration (in ml/min); 5) creatinine concentration index; 6) filtration fraction. Broken line denotes time of injection of chlorpromazine in dose of 0.5 mg/kg. Abscissa: time marker, 10 min.

Fig. 2. Effect of 0.5 mg/kg chlorpromazine (A) and 2 mg/kg chloracyzine (B) on renal blood flow (in ml/min), glomerular filtration (in ml/min), and filtration fraction. From top to bottom: renal blood flow, glomerular filtration, filtration fraction. Abscissa: time marker, 15 min. Arrow indicates time of injection of drug.

The results suggest that both chlorpromazine and chloracyzine increase the renal circulation. The increased blood flow is apparently due to dilatation of the renal vessels, the efferent vessels being dilated more than the afferent because the filtration fraction is reduced. Published data suggest that vasodilatation caused by chlorpromazine takes place on account of its central action, whereas chloracyzine, which has no pronounced effect on the central nervous system [10], exerts a peripheral (myotropic, sympatholytic, cholinolytic) action [8].

In the present experiments, as in those described by other workers [3,12], chlorpromazine inhibited diuresis, probably through an increase in the secretion of antidiuretic hormones [1,2]. Support for this explanation is also given by observations indicating that reabsorption plays a leading role in the observed changes in diuresis. So far as the effect of chloracyzine on diuresis is concerned, the mechanism of this action has not yet been explained.

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