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Inhibition by chlorpromazine of the effects of dopamine on the dog kidney

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Dopamine-induced vasodilatation in the renal artery of the dog is reversed by chlorpromazine while the vasodilatation produced by isoprenaline is not. Pronethalol has the entirely opposite actions on this preparation. The infusion of dopamine into the renal artery enhances the kidney output of water, sodium, potassium and urea. These effects are also reversed by chlorpromazine.

Chlorpromazine has been reported to block dopamine effects in the brain (Nyback, Sedvall & Kopin, 1967; Gey & Pletscher, 1968; Nyback & Sedvall, 1968). However, this action has not been unequivocally demonstrated. Dopamine causes vasodilatation when injected into the renal artery of the dog (McNay & Goldberg, 1966; Goldberg, Sonneville & McNay, 1968). Since this effect is not blocked by β-adrenergic agents or by atropine it has been suggested by these authors that dopamine acts via specific "dopaminergic" receptors in the renal vascular bed.

The present study was designed to determine whether chlorpromazine interferes with the effect of dopamine on the renal artery.

EXPERIMENTAL

Materials and methods

Mongrel dogs of either sex, 8 to 15 kg, were anaesthetized with sodium pentobarbitone (30 mg/kg, i.v.). The left renal artery was isolated by lumbar incision and retroperitoneal dissection. The left ureter was sectioned and the proximal end cannulated with a ureteral catheter, inserted up to the pelvis for collecting urine. Intra-arterial injections (1 ml) or infusions were made through a polyethylene catheter of 1·3 mm external diameter introduced through the left femoral artery up to the renal artery. Blood flow in the left renal artery was measured by means of a flow-probe connected to a Nycotron electromagnetic flow-meter. Both instantaneous and mean flows were recorded. The zero-flow base line and the electrical zero were determined immediately after application of the flow-probe and at intervals throughout each experiment by mechanical occlusion of the artery distal to the flow-probe. Sodium and potassium concentrations in the samples of urine were analysed by flame photometry; urea was measured according to Dupré. Systemic blood pressure was measured with a capacitance transducer from the femoral artery and recorded on a multichannel polygraph. The heart rate was counted from blood pressure tracings.

The following experimental design was used to examine the effect of dopamine and chlorpromazine on urine excretion. Isotonic NaCl was infused through the arterial catheter at 1 ml/min for 10 min, the urine excreted by left kidney was collected during this time. Dopamine (50 μg/ml) was then added to isotonic saline

solution which was infused for 12 min at the rate of 1 ml/min. The urine was collected starting 2 min after the beginning of the dopamine infusion.

This procedure was repeated 3 times and the values obtained were considered control values. Chlorpromazine (3 mg/kg) was then infused over 5 min. Ten min after, the chlorpromazine saline and dopamine infusions were repeated and urine was collected.

RESULTS

Inhibition by chlorpromazine of the haemodynamic effects of dopamine on the renal artery

Six dogs were used and the results are in Tables 1 and 2. The intra-arterial injections of dopamine ranging from 1 to 5 μg produced a dose-related increase in the renal blood flow; the average maximum increase was 35 $\pm$ 12%. Higher doses produced a diminished response (10 μg) or a vasoconstrictor response (20 μg).

Table 1. *Changes in the renal blood flow induced by intra-arterial dopamine, before and after chlorpromazine (3 mg, i.a.)*

Dog No.	% Changes in blood flow produced by different doses of dopamine									
	Before chlorpromazine					After chlorpromazine*				
	1 μg	2	5	10	20	1 μg	2	5	10	20
1	+20	+30	+38	+15	—15	0	0	0	— 5	—10
2	+12	+25	+31	+10	—22	0	0	— 5	—15	—20
3	+24	+38	+41	+21	—30	+5	0	—10	—20	—40
4	+11	+34	+26	— 5	—	0	0	— 5	—25	—
5	+13	+22	+38	+15	—10	0	0	0	—10	—
6	+20	+29	+36	+10	—15	0	0	0	—15	—
Means	+16	+29	+35	nc	nc	0	0	— 7	—15	nc
$\pm$ s.d.	8	9	12			5		3	10	

* Dopamine was injected 15 to 25 min after chlorpromazine.

Table 2. *Changes in the renal blood flow induced by intra-arterial injections of isoprenaline after chlorpromazine or pronethalol*

Dog No.	% Changes in renal blood flow produced by different doses of isoprenaline								
	Isoprenaline			Isoprenaline after chlorpromazine*			Isoprenaline after pronethalol		
	1 μg	1 μg	5 μg	1 μg	2 μg	5 μg	1 μg	2 μg	5 μg
1	+30	+50	+60	+20	+50	+60			
2	+25	+45	+55	+25	+40	+50			
3	+15	+30	+45	+15	+30	+50			
4	+20	+35	+45	+20	+30	+45			
5	+15	+25	+50	+20	+35	+45			
6	+25	+40	+55	+25	+45	+65			
Means ..	+22	+37	+51	+20	+36	+52			
s.d.	10	7	5	5	9	7			
7	+20	+35	+55				0	2	+10
8	+15	+30	+45				2	5	+10
9	+20	+40	+60				0	0	+ 5
Means ..	+18	+35	+53				0	+ 2	3·8
+ s.d. ..	3	5	7				2	2	5

* Isoprenaline was injected 15 to 20 min after chlorpromazine.

Intra-arterial injections of 5 μg of dopamine did not influence the systemic blood pressure and the heart rate. The intra-arterial injection of isoprenaline, 1 to 5 μg, produced a dose-related increase in renal blood flow (Table 2). These results are in agreement with those of McNay & Goldberg (1966).

The intra-arterial injection of chlorpromazine produced no changes in the renal blood flow, but ten to 20 min after the chlorpromazine the vasodilatating effect of dopamine was completely abolished or reversed (Table 1) while the effect of isoprenaline remained unchanged (Table 2).

On the other hand, in three experiments the vasodilating effect of isoprenaline was blocked by intra-arterial injection of pronethalol (5 mg/kg) while the vasodilatation produced by dopamine was not influenced by β-blocking agents. The vasoconstriction in the renal artery produced by high doses of dopamine was reversed by phentolamine (1 mg/kg, i.p. 5–10 min before the dopamine) but only diminished by chlorpromazine (3 mg/kg, i.a. 20 min before the dopamine) (Table 1).

Inhibition by chlorpromazine of the dopamine effect on urine excretion

These experiments were made in 6 dogs. The results are in Table 3. The infusion of dopamine (3 μg/kg min^{-1}) increased water excretion by 18% and the excretion of

Table 3. *Effect of dopamine before and after chlorpromazine on the urinary excretion of sodium, potassium and urea in dogs*

	Urine volume and composition during infusion				
Dog No.	Urine ml/10 min	Urea (g %)	Na m-equiv/litre	K	% Change in urine vol/10 min
	Saline				
1	5	10	204	12	
2	10	1·7	296	24	
3	12	5·7	255	12	
4	7	6·6	300	26	
5	7	9	168	20	
6	8	8	220	19	
means ..	8	6·8	240	19	
s.d. ..	3	5	70	7	
	Dopamine				
1	6·5	14	276	17	13
2	13	10·6	444	35	13
3	15	7·3	292	19	12·5
4	9	8·9	335	35	12
5	8	27	278	30	11·1
6	10	11	258	23	12·5
means ..	10	13	313	26	12·3
s.d. ..	4·5	4	130	9	0·8
	Dopamine after chlorpromazine				
1	4·5	10	215	12	—10
2	10	5	300	26	0
3	11	5	245	15	— 5
4	6	6	315	27	—12
5	5	7	155	18	—20
6	7	6·5	200	17	—12
means ..	7	6	221	19	— 9
s.d. ..	2	4	80	7	6

Each of the values is the average of three determinations. Chlorpromazine was given intra-arterially at the dose of 3 mg/kg 15–20 min before dopamine infusion.

urea, sodium and potassium by 100, 40 and 10% respectively. The infusion of dopamine (3 μg/kg min^{-1}) increased the renal blood flow but did not change the systemic blood pressure or the heart rate.

Chlorpromazine did not significantly modify the renal blood flow, the urinary output, and the urinary composition after saline infusion. But given before the infusion of dopamine, it decreased the blood flow by 20% while not affecting urea, sodium and potassium excretion (see Table 3).

DISCUSSION

In agreement with Goldberg & others, I found that the vasodilatation induced by dopamine in the renal artery, unlike that induced by isoprenaline, is not antagonized by β-blockade. On the other hand, the renal vasodilatation caused by dopamine is inhibited by chlorpromazine, although it does not inhibit the vasodilating effect of isoprenaline.

These results support the hypothesis that dopamine is acting upon specific receptors in the renal vascular bed and the concept that chlorpromazine inhibits dopaminergic receptors in brain (Nyback & others, 1966; Nyback & Sedvall, 1968; Gey & Pletscher, 1968). The vasoconstriction response to high doses of dopamine is probably mediated by an action upon α-adrenergic receptors. In fact, this effect is reversed by phentolamine (McNay & Goldberg, 1966). However, chlorpromazine, which is also an α-blocking agent (Courvoisier, Fournel & others, 1953; Jourdan, Duchene-Marullaz & Boisser, 1955), diminished the vasoconstriction produced by dopamine, but did not reverse it, indicating that chlorpromazine inhibits the receptors related to the vasodilatation more effectively than it does those mediating vasoconstriction. The finding that dopamine enhances water, electrolyte and urea output by its kidney deserves further investigation. That this effect is also inhibited by chlorpromazine suggest that it is mediated by specific dopaminergic receptors. Whether the dopamine effect on urine excretion is secondary to its effect on renal blood flow remains to be elucidated.

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