Phosphaturic Effect of Dopamine in Dogs

POSSIBLE ROLE OF INTRARENALLY PRODUCED DOPAMINE IN PHOSPHATE REGULATION

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ABSTRACT A possible role for dopamine in phosphate handling by the dog kidney was investigated by intrarenal artery infusions of dopamine. Dopamine increased fractional phosphate excretion both in the presence and absence of control of parathyroid hormone and calcitonin. In addition, dopamine increased both renal blood flow and sodium excretion; however, the phosphaturia was independent of these changes; since 30 min after completion of dopamine infusion, renal blood flow and sodium excretion returned to control levels and phosphate excretion remained elevated. For comparison, the vasodilator isoproterenol increased renal blood flow and sodium excretion without a significant change in fractional phosphate excretion. Thus, the phosphaturic effect of dopamine is probably independent of its vasodilator effect. The phosphaturic effect of dopamine could not be accounted for by subsequent conversion to norepinephrine, since norepinephrine was antiphosphaturic in the dog.

The effect of endogenous dopamine on renal phosphate excretion was investigated by intrarenal infusion of the precursor dopa. Dopa was phosphaturic both in the presence and absence of parathyroid hormone and calcitonin. In dogs pretreated with carbidopa, which blocks conversion of dopa to dopamine, dopa was no longer phosphaturic, although the kidney remained responsive to dopamine. It is postulated that dopamine may play a role in the intrarenal regulation of phosphate excretion.

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INTRODUCTION

Dopamine is not only a precursor of norepinephrine, but also has independent biologic activity. It is well established that infusions of a low dose of dopamine in the renal artery increase renal blood flow and sodium excretion (1). The first objective of the present studies was to evaluate the possible effect of exogenous dopamine on phosphate excretion.

The kidney contains a large amount of aromatic amino acid decarboxylase, which converts 3-(3,4-dihydroxyphenyl)-L-alanine (dopa) to dopamine (2–4). This enzyme system may account in part for the increased renal dopamine content during dopa infusions in dogs and rats (5–7). Therefore, we hypothesized that endogenous dopamine, i.e., intrarenally produced dopamine, might also have a role in renal phosphate handling.

These hypotheses were tested in dogs by infusions in the renal artery of either dopamine or dopa in the absence or presence of an inhibitor of aromatic amino acid decarboxylase. In addition, plasma parathyroid hormone (PTH)[1] level was controlled, since catecholamines have been shown to stimulate PTH release (8, 9).

METHODS

Effect of exogenous dopamine on phosphate excretion

Group 1. After three 10-min control clearance periods, dopamine (105 μg/kg·min) was infused in the renal artery of dogs with intact parathyroid glands. After 10 min for equilibration, three 10-min experimental clearance periods were obtained.

Group 2. Since dopamine (and dopa) was dissolved in sodium acetate buffer (20 mM, pH 5.55), the vehicle alone was infused in the experimental clearance periods.

[1] *Abbreviation used in this paper:* PTH, parathyroid hormone.

Group 3. To rule out a possible role of altered PTH secretion, dopamine (0.88 μg/kg·min) was infused in dogs with control of PTH. This was achieved by a surgical thyroparathyroidectomy at the beginning of experiments, immediately followed by a constant infusion of bovine PTH (10 mU/kg·min), continued throughout the entire protocol. This procedure will be referred to as "control of PTH."

Group 4. To evaluate the effect of vasodilation per se, isoproterenol (25 ng/kg·min) was infused in experimental periods in dogs with control of PTH.

Effect of dopa on phosphate excretion

Group 5. Clearance periods were obtained as in group 1, before, during, and after intrarenal infusion of L-dopa (50 μg/kg·min) in dogs with intact parathyroid glands.

Group 6. The same experiment was repeated in the absence of PTH. Dogs were thyroparathyroidectomized 18 h before experiments. The completeness of thyroparathyroidectomy was confirmed by decreases in plasma calcium and increases in plasma phosphate concentrations in each animal.

Effect of L-dopa in presence of an inhibitor of aromatic amino acid decarboxylase

Inhibition of aromatic amino acid decarboxylase was obtained by an intravenous infusion of L-(−)-α-hydrazino-3,4-dihydroxy-α-methyl hydrocinnamic acid monohydrate (carbidopa).[2] This compound is preferentially accumulated within the kidney when infused intravenously (10). Watanabe et al. have recently reported that 50 mg/kg of carbidopa, infused over a period of 15 min in dogs, markedly inhibits L-dopa-induced catecholamine synthesis in the kidney[3] (11).

Group 7. After control clearance periods, carbidopa (50 mg/kg dissolved in 60 ml of saline, pH 1) was infused intravenously over a period of 15 min in dogs with control of plasma PTH level. Control studies were then performed with carbidopa alone infused during experimental periods. All dogs treated with carbidopa were artificially ventilated (Harvard Apparatus Co., Inc., Millis, Mass., respiration pump); blood gases and pH were measured in eight animals and remained constant.

Group 8. After control clearance periods and carbidopa infusion, an intrarenal infusion of L-dopa (50 μg/kg·min) was started and 15 min were allowed for equilibration before experimental clearance periods were obtained.

Group 9. After control clearance periods and carbidopa infusion, dopamine was infused in the renal artey and experimental clearance periods were obtained.

Effect of norepinephrine

Group 10. In dogs with control of PTH, clearance periods were obtained before and during infusion of norepinephrine. In six dogs given a 5 ml/min infusion of either 5% dextrose ($n = 4$) or saline ($n = 2$), three 10-min control collections were obtained, then a norepinephrine infusion was started and the infusion rate adjusted (0.20 μg/kg·min, range: 0.14–0.29) to increase blood pressure by about 20 mm Hg. 1 h was allowed for equilibration before three 10-min experimental collections were obtained.

All dogs were fed a standard pellet diet providing approximately 1% calcium and 0.8% phosphate. They were allowed free access to water, and food was withheld approximately 18 h before the experiment. They were anesthetized with sodium pentobarbital (30 mg/kg body wt), and the trachea was intubated. Catheters were placed in a jugular vein and in a femoral artery and vein for infusions and blood sampling. Ureters were cannulated. 60 min before the initial clearance periods, all dogs received a priming dose of inulin, and a maintenance infusion of inulin in isotonic saline was administered at 1 ml/min throughout the experiments to maintain an inulin concentration of 0.25 mg/ml.

Changes in total renal blood flow were measured by an electromagnetic flowmeter, the probe placed on the left renal artery between the 20-gauge needle for infusions and its aortic origin.

Plasma and urine concentrations were measured as follows: inulin by the anthrone method (12), phosphate by the method of Young (13), sodium by flame photometry, and calcium by atomic absorption.

The data for each variable were averaged for clearance periods before, during, and after catecholamine infusions. Student's t test for paired or unpaired comparisons was used for statistical analysis, with a P value less than 0.05 considered to represent a statistically significant change.

RESULTS

Effect of exogenous dopamine on phosphate excretion (Table I). Intrarenal infusions of dopamine in dogs with intact parathyroid glands increased the fractional excretions of phosphate and sodium and increased renal blood flow (Table I). Fractional excretion of phosphate was increased both during ($+ 6.25 \pm 0.88\%$, $P < 0.01$) and 30 min after discontinuing dopamine infusions, ($+ 5.17 \pm 1.08\%$, $P < 0.01$). Fractional excretion of sodium was increased only during the infusions ($+ 0.90 \pm 0.20\%$, $P < 0.01$).

To rule out an effect due to stimulation of PTH or calcitonin, dopamine was infused in the renal artery of dogs with control of plasma PTH. The same pattern of response was observed (Table I, group 3).

To determine whether another renal vasodilating agent can reproduce the phosphaturic effect of dopamine, isoproterenol was infused in the renal artery of dogs with control of PTH. Control of PTH was important since isoproterenol stimulates PTH release (8, 9). Isoproterenol increased renal blood flow and fractional excretion of sodium, but did not change systemic blood pressure (Table I, group 4). Fractional phosphate excretion was not significantly changed either during ($P < 0.20$) or after ($P < 0.50$) infusions. Although plasma phosphate concentration decreased slightly during infusions of isoproterenol, there was no change in the filtered load of phosphate.

Effect of dopa on phosphate excretion (Table II). Intrarenal artery infusions of dopa in intact dogs were phosphaturic. Fractional phosphate excretion was in-

[2] Kindly supplied by Dr. C. A. Stone, Merck Sharp & Dohme, Div. of Merck Co., Inc., West Point, Pa.

[3] Watanabe et al. infused a mixture of labeled and unlabeled (300 μg/kg·min) L-dopa infused over a period of 30 min; in control and carbidopa-treated dogs, the renal catecholamine content was then 1,396.2±433 cpm, and 30.5 ±10.8 cpm, respectively (11).

TABLE I

Effect of Dopamine and Isoproterenol on Phosphate and Sodium Excretions

	FE_{PO_4}	FE_{Na}	RBF	GFR	Plasma PO_4	Blood pressure
	%	%	*ml/min*	*ml/min*	*mM*	*mm Hg*
Dogs with intact parathyroid glands						
Group 1: dopamine infusion (1.05 μg/kg·min) (n = 9)						
C	10.5±2.2	0.94±0.26	207±30	43.1±4.0	1.95±0.14	131±5
E	16.8±2.7‡	1.83±0.34‡	262±32‡	47.7±5.9	2.01±0.14	135±5
PI	15.8±2.1‡	0.84±0.17	201±27	42.3±4.1	2.02±0.14	140±5*
Group 2: sodium acetate (20 mM, pH 5.55) (n = 9)						
C	15.3±1.8	1.41±0.26	—	39.8±5.8	1.47±0.10	141±4
E	15.4±1.7	1.62±0.27	—	39.1±6.2	1.47±0.10	140±4
PI	14.4±1.8	1.25±0.27	—	44.3±6.4	1.49±0.12	144±4
Dogs with control of plasma PTH level						
Group 3: dopamine infusion (0.88 μg/kg·min) (n = 8)						
C	17.7±3.6	0.74±0.11	257±26	43.2±3.6	1.96±0.08	130±7
E	24.2±4.5‡	1.37±0.23‡	327±30‡	44.2±4.5	1.93±0.09	131±7
PI	23.0±4.2*	1.11±0.21	266±35	40.9±4.0	1.92±0.10	135±7*
Group 4: isoproterenol infusion (25 ng/kg·min) (n = 7)						
C	11.8±4.4	1.04±0.26	234±26	40.7±6.8	1.75±0.11	126±5
E	15.4±4.2	2.01±0.54*	278±31‡	43.8±6.6	1.65±0.11‡	125±6
PI	14.2±5.2	1.21±0.19	235±31	45.7±8.4	1.89±0.16	128±6

FE, fractional excretion; RBF, renal blood flow; GFR, glomerular filtration rate; C, E, and PI, control, experimental, and postinfusion periods, respectively.

* $P < 0.05$.

‡ $P < 0.01$.

creased, both during (+ 6.4±1.2%, $P < 0.01$) and 30 min after discontinuing dopa infusions (+ 5.9±1.4%, $P < 0.01$). Fractional sodium excretion was increased only during infusions (+ 0.95± 0.30%, $P < 0.01$).

In the absence of PTH or calcitonin (Table II, group 6), dopa remained phosphaturic: + 4.6±1.2%, $P < 0.01$ during, and + 5.6±1.3%, $P < 0.01$ after dopa infusions.

TABLE II

Effects of L-Dopa on Phosphate and Sodium Excretions

	FE_{PO_4}	FE_{Na}	RBF	GFR	Plasma PO_4	Plasma Ca	Blood pressure
	%	%	*ml/min*	*ml/min*	*mM*	*mM*	*mm Hg*
L-Dopa infusions (50 μg/kg·min)							
Group 5: dogs with intact parathyroid glands (n = 9)							
C	14.6±2.2	1.09±0.20	202±20	42.9±6.4	1.73±0.09	2.28±0.18	121±4
E	21.1±2.8‡	2.03±0.39‡	225±22*	44.6±8.2	1.77±0.11	2.31±0.17	124±5
PI	20.5±2.6‡	1.31±0.29	182±25	40.6±4.7	1.79±0.10	2.30±0.17§	128±3
Group 6: 18-h thyroparathyroidectomized dogs (n = 9)					1.58±0.16§	2.76±0.17§	
C	4.6±1.2	0.43±0.13	206±12	55.7±6.6	2.00±0.09	2.19±0.11	135±4
E	9.2±2.2‡	0.63±0.18	237±20*	58.9±6.1	1.96±0.08	2.16±0.10	136±4
PI	10.2±2.1‡	0.48±0.10	197±20	59.3±8.3	1.94±0.10	2.09±0.12	136±4

FE, fractional excretion; RBF, renal blood flow; GFR, glomerular filtration rate; C, E, and PI, control, experimental, and postinfusion periods, respectively.

* $P < 0.05$.

‡ $P < 0.01$.

§ Plasma calcium and phosphate measurements before thyroparathyroidectomy.

TABLE III

Effect of Catecholamines on Phosphate and Sodium in Carbidopa-Treated Dogs with Controlled Plasma PTH Level

	FE_{PO_4}	FE_{Na}	RBF	GFR	Plasma PO_4	Blood pressure
	%	%	*ml/min*	*ml/min*	*mM*	*mm Hg*
Group 7: Carbidopa alone (n = 8)						
C	14.3±4.3	1.04±0.25	183±20	38.0±3.4	1.68±0.12	117±3
E	13.4±3.3	1.75±0.53	168±25	33.9±3.5	1.49±0.11‡	118±4
Group 8: Carbidopa and L-dopa (50 μg/kg·min) (n = 9)						
C	14.8±4.8	1.34±0.38	181±19	32.0±3.3	1.63±0.13	120±3
E	17.1±4.6	1.55±0.38	171±17	34.7±4.0	1.54±0.12	126±4*
Group 9: Carbidopa and dopamine (0.46 μg/kg·min) (n = 4)						
C	24.4±4.5	1.65±1.01	230±7	32.4±4.8	1.19±0.13	109±4
E	37.2±2.5*	2.23±1.01‡	252±4*	35.2±1.6	1.19±0.11	116±4

FE, fractional excretion; RBF, renal blood flow; GFR, glomerular filtration rate; C and E, control and experimental periods, respectively.

* $P < 0.05$.

‡ $P < 0.01$.

Effect of dopa on phosphate excretions in presence of aromatic amino acid decarboxylase inhibitor (Table III). Infusion of carbidopa alone did not significantly change the fractional excretions of either phosphate or sodium, but significantly decreased plasma phosphate concentration (−0.19±0.03 mM, $P < 0.001$) (Table III, group 7).

Dopa was not significantly phosphaturic in the presence of carbidopa. Mean fractional phosphate excretion tended to increase; however, this change in the mean was due to only two out of the nine dogs and might be explained by a variable response of mongrel dogs to inhibition of aromatic amino acid decarboxylase (Table III, group 8).

TABLE IV

Effect of Norepinephrine on Phosphate Excretion in Dogs with Control of Plasma PTH Level

	FE_{PO_4}		Plasma PO_4	
Dogs	C	NE	C	NE
	%		*mM*	
1	15.4	2.7	1.18	0.89
2	9.8	2.0	1.62	1.25
3	27.8	4.9	1.89	1.09
4	14.8	0.5	1.50	1.07
5	21.6	7.2	2.04	2.21
6	30.5	17.5	1.79	1.75
Mean	20.0	5.8	1.67	1.38
SEM	3.3	2.5	0.12	0.20
P	<0.001		<0.10	

C, control, NE, norepinephrine.

In the presence of carbidopa the kidney was still responsive to dopamine; there was a significant increase in renal blood flow and phosphate and sodium excretions (Table III, group 9).

Effect of intravenous infusions of norepinephrine on phosphate excretion (Table IV). Norepinephrine was infused in dogs with control of plasma PTH level to produce a mild increase in blood pressure (+19±3 mm Hg) without a decrease in renal hemodynamics. Renal plasma flow and glomerular filtration rate were 127±6.6 and 45.4±5.0 ml/min before and 142±8.3 and 50.5±5.6 ml/min during norepinephrine infusions. As shown in Table IV, there was a consistent decrease in fractional excretion of phosphate. Since plasma phosphate concentration tends to decrease during norepinephrine infusions, the decrease in fractional phosphate excretion may be a consequence of changes in plasma phosphate rather than a direct effect of norepinephrine. There were no significant changes in fractional sodium excretion, 1.62±0.48% before and 1.41±0.44% during infusions.

DISCUSSION

The present study in dogs was designed to investigate a possible role of dopamine in renal phosphate handling. Infusion of dopamine into the renal artery of dogs with intact parathyroid glands or into the renal artery of thyroparathyroidectomized dogs with control of plasma PTH produced a phosphaturia. Thus the phosphaturic effect of dopamine is independent of changes in PTH or calcitonin.

Although both renal blood flow and sodium excretion increased during dopamine infusion, the phosphaturia

may be independent of these changes, since 30 min after completion of dopamine infusion, renal blood flow and sodium excretion returned to control levels and phosphate excretion remained elevated. It is well established that most renal vasodilators produce a natriuresis; however, their effects on phosphate excretion are variable. Schneider et al. have reported that for comparable increases in renal blood flow and sodium excretion, acetylcholine and prostaglandin E_1 were phosphaturic, whereas bradykinin or prostaglandin E_2 were not phosphaturic (14). In addition, in the present studies another renal vasodilator, isoproterenol, was infused in the renal artery. Although isoproterenol increased renal blood flow and sodium excretion, there was no significant change in fractional phosphate excretion. There is, therefore, no *pari passu* relationship between renal vasodilatation and increased phosphate excretion by the kidney. Thus, for these reasons, including the persistence of the phosphaturia after return of blood flow and sodium excretion to control levels, it is likely that the phosphaturic effect of dopamine is independent of its vasodilator effect.

We next considered that the phosphaturic effect of dopamine could be explained by increased norepinephrine concentrations within the kidney. Increased norepinephrine content in the kidney has been reported after infusion of dopamine (7). In addition, subcutaneous injections of very high doses of norepinephrine have been shown to be phosphaturic in parathyroidectomized rats (15). In the present study, intravenous infusion of norepinephrine in dogs with control of PTH decreased the fractional excretion of phosphate. This decrease cannot be accounted for by decreases in renal hemodynamics, but could be exaggerated by the tendency of plasma phosphate concentration to decrease during infusions. Given the tendency for norepinephrine to be antiphosphaturic in the dog, it is unlikely that the phosphaturic effect of dopamine is due to conversion to norepinephrine.

With the background that exogenous dopamine produces a phosphaturia, we investigated a possible effect of endogenous dopamine on phosphate excretion by intrarenal infusion of the precursor of dopamine, dopa. Dopa is probably an inert compound (16–18), which, when infused, increases the renal content of dopamine (5–7). In intact dogs, renal artery infusions of dopa were phosphaturic. To rule out a role for PTH and/or calcitonin in this phosphaturia, the same experiments were performed in thyroparathyroidectomized animals and again dopa was phosphaturic. To determine whether the phosphaturia was due to dopa or its metabolite, dopamine, the phosphaturic effect of dopa was studied in the presence of carbidopa, which blocks conversion of dopa to dopamine. In dogs pretreated with carbidopa, dopa was no longer phosphaturic, although the kidney remained responsive to dopamine (Table III). Thus the phosphaturia associated with dopa was not due to dopa itself. Since the kidney can efficiently decarboxylate dopa to dopamine (2–4), it is likely that the phosphaturic effect of dopa is due to an increased renal content of endogenous dopamine. This interpretation is supported by the finding that the phosphaturia in the infused kidney was significantly higher than that of the contralateral organ.[4] However, phosphate excretion was significantly increased in the contralateral kidney, raising the possibility of a superimposed systemic effect. Although PTH and calcitonin have been eliminated, additional systemic factors cannot be ruled out. Similarly, since catecholamines have a very short half-life, the persistence of a phosphaturia after discontinuance of the infusion may indicate activation of a phosphaturic mechanism by dopamine that does not depend upon the continued presence of increased dopamine levels. Finally, it is noteworthy that carbidopa was not antiphosphaturic when given alone (group 7, Table III). Although interpretation of this finding is speculative, it may reflect that basal levels of renal dopamine may be very low under these experimental conditions and therefore an antiphosphaturic effect of decreased dopamine levels would be difficult to demonstrate. This finding does not exclude a possible regulatory role for endogenous dopamine in phosphate excretion.

In summary, the phosphaturic effect of dopamine is independent of changes in PTH, calcitonin, renal blood flow, and sodium excretion. It is not explained by an increase in norepinephrine biosynthesis, since norepinephrine infusions tend to decrease phosphate excretion in dogs. The phosphaturia was induced by either exogenous dopamine, or by an increase of the renal endogenous level, produced by infusion of dopa. The significance in man of this role of dopamine in renal phosphate regulation is difficult to assess at the present time. However, the plasma levels of dopa in the present study are in the same range as in patients undergoing L-dopa therapy. In the present study, the dopa concentration in the infused kidney was 4 μg/ml, whereas Goldberg et al. reported a 3 μg/ml peak concentration in a patient given a 1-g test dose of oral L-dopa (19).

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[4] Detailed data tables including results from the contralateral kidney are available on request from NAPS. See NAPS document 02807 (six pages). Order from ASIS/NAPS, c/o Microfiche Publications, 440 Park Avenue South, New York 10016.

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