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Effects of Metaraminol Perfusion of Kidney, Liver, or Brain on Renal Response to Saline Infusion in the Dog. (31830)

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Exaggerated natriuresis occurs in hypertensive subjects in response to infusion of sodium(1). It appears that some feature of the hypertensive state itself is responsible for the natriuretic response since this phenomenon occurs in subjects with hypertension of varying pathogeneses(2-6) and can also be induced in man(7) or dog(8) made hypertensive pharmacologically with metaraminol.

It is uncertain, however, whether the factor responsible for exaggerated natriuresis in the hypertensive dog is some local pharmacologic effect of metaraminol such as increased vascular resistance in some key organ, or if increased systemic blood pressure itself acts to promote an augmented natriuretic response. Patients with labile plood pressure may exhibit exaggerated natriuresis even while normotensive(9), and sympathectomy may inhibit an exaggerated natriuretic response even in subjects whose hypertension persists(10). These observations suggest that the exaggerated natriuretic response may be related to arteriolar constriction within some organ rather than to hypertension itself. If the local effects of metaraminol such as vasoconstriction could be induced in the absence of systemic hypertension, the role of pharmacologic effects of this drug in specific organs apart from that of hypertension itself might then be examined. In the present study, therefore, metaraminol was delivered in subpressor doses into the kidney, liver or brain of the dog while an infusion of saline was given systemically. Exaggerated natriuresis was not observed.

Methods. Sixteen mongrel dogs were studied following withdrawal of food and fluids for 18 hours. Anesthesia was induced with pentobarbital, 30 mg per kilogram, which was supplemented as necessary during study. Aqueous vasopressin, 5 units, was given subcutaneously ½ hour prior to study and was continued intravenously with the saline infusion at a rate of 4 milliunits per minute. Blood pressure was determined with a mercury manometer connected to a femoral artery catheter and arterial blood samples were withdrawn at appropriate intervals for analysis.

In 5 of these dogs the renal response to sodium infusion was examined during administration of metaraminol directly into the renal artery. The ureters were catheterized through a lower abdominal incision to obtain urine samples from the separate kidneys. The left renal artery was exposed extraperi-

toneally through a flank incision, and urine was collected prior to any infusion for the determination of control values for creatinine clearance and sodium excretion of the separate kidneys. A no. 23 needle was then inserted into the left renal artery and metaraminol was delivered at a rate of 5 μg per minute (0.1 ml per minute) while a systemic infusion of normal saline was given at 1.0 ml per minute. Twenty minutes later a one-hour collection of urine was begun to evaluate the effects of continued infusion of saline and unilateral administration of metaraminol. In previous studies insertion of a needle into the renal artery has been found not to alter renal function. In order to confirm that renal vasoconstriction occurred with the dose of metaraminol which was used, 4 control animals were studied in identical manner except that para-amino-hippurate (PAH) and inulin were infused throughout the study after an appropriate priming injection.

Seven dogs were studied to examine the renal effects of systemic infusion of saline while metaraminol was delivered directly to the liver. In 4, the portal vein was cannulated with a narrow polyethylene cannula introduced through a small tributary vein. A control urine collection was obtained prior to any infusion. Normal saline was then given intravenously at a rate of 1.0 ml per minute while metaraminol was delivered into the portal vein at 10 μg per minute (0.1 ml per minute). A one-hour urine collection was then obtained starting 20 minutes after the infusions were begun. In the other 3 dogs, following collection of a control urine specimen, a cannula was placed in the hepatic artery through a small branch vessel and infusion of metaraminol was begun as into the portal vein, while saline was given intravenously. A one-hour urine collection was then obtained as above.

The remaining 4 dogs were studied for the renal effects of systemic infusion of saline during perfusion of the brain with subpressor doses of metaraminol. The vertebral arteries were occluded near their origin to assure perfusion of the entire brain with metaraminol. A control urine collection was then obtained prior to any infusion. The internal carotid arteries were then both cannulated with a narrow polyethylene tube inserted through a small branch of the external carotid. Infusion of metaraminol was begun into each internal carotid artery at a rate of 5 μg per minute (0.1 ml per minute) while systemic infusion of normal saline at 1.0 ml per minute was given into a peripheral vein. After 20 minutes a one-hour collection was begun to be compared to the control collection.

In order to confirm that the surgical manipulations in these animals would not themselves prevent natriuresis if an appropriate stimulus was provided, further study was performed in 5 control dogs. In these animals cannulation of one renal artery (one dog), the portal vein (one dog), the hepatic artery (2 dogs) or the carotid arteries (one dog in which vertebral occlusion was also performed) was accomplished as in the study animals. Following collection of a baseline sample, saline was infused as before at the rate of 1.0 ml per minute but in these animals the cannulated organ was not perfused with metaraminol. Instead pressor infusion of metaraminol was given systemically during saline infusion. After 20 minutes a one-hour collection was begun to be compared to the baseline collection.

Analyses for osmolality, sodium, potassium, inulin, PAH, and creatinine were performed by standard methods(11,12). Excretion rates and clearance values were corrected for a surface area of one square meter. In each study the position and patency of the infusion needles or cannulas was confirmed at the end of the procedure.

Results. Data are presented in Table I showing the renal response to saline infusion in 5 dogs during metaraminol perfusion of one kidney. During the control period after exposure of the left renal artery the function of the two kidneys was comparable as judged by similar values for urine flow (V), osmolar and creatinine clearance and basal excretion rate for sodium ($U_{Na}V$) and potassium (U_KV). During perfusion of the left kidney with metaraminol the clearance of endogenous creatinine (C_{cr}) was decreased disproportionately in one dog (#4), presumably be-

TABLE I. Effects of Intravenous Administration of Saline in Dogs Receiving Metaraminol Infusion into One Renal Artery.

Dog #	Infusion*	V, ml/min R	V, ml/min L	C_{osm}, ml/min R	C_{osm}, ml/min L	C_{cr}, ml/min R	C_{cr}, ml/min L	$U_{Na}V$, μEq/min R	$U_{Na}V$, μEq/min L	U_KV, μEq/min R	U_KV, μEq/min L	Mean BP, mm Hg
1	None	.10	.089	.50	.41	24	18	31	22	14	12	105
	Saline I.V.; metaraminol into L. renal artery	.11	.095	.51	.43	21	16	18	15	26	17	105
2	None	.34	.35	.72	.53	39	25	14	20	16	17	120
	Saline I.V.; metaraminol into L. renal artery	.16	.14	.53	.29	32	23	7	7	14	10	130
3	None	.12	.11	.33	.30	39	38	18	5	7	10	105
	Saline I.V.; metaraminol into L. renal artery	.29	.18	.59	.41	43	49	21	8	32	23	105
4	None	.15	.18	.63	.80	30	36	24	37	26	34	135
	Saline I.V.; metaraminol into L. renal artery	.094	.024	.36	.036	23	1.3	12	4	17	1	135
5	None	.090	.094	.41	.37	47	44	4	6	8	8	130
	Saline I.V.; metaraminol into L. renal artery	.13	.10	.47	.36	45	31	5	5	17	12	130

* Normal saline infusion was given at a rate of 1.0 ml per minute; metaraminol bitartrate was infused at a rate of 0.1 ml per minute (5 μg per minute).

cause of excessive vasoconstriction. In the other animals the glomerular filtration rate (GFR) as estimated from C_{cr} was not markedly depressed in the kidney receiving metaraminol. $U_{Na}V$ was decreased during perfusion by metaraminol in 3 dogs and changed little in the other 2. In the control kidney the change in $U_{Na}V$ was similar to that of the test kidney in each instance. U_KV in the kidney perfused with metaraminol was increased in 3 dogs and decreased in 2. The sum of sodium and potassium excretion (a measure of delivery of sodium to the distal Na^+-K^+ exchange site) was decreased by metaraminol in 2 dogs, increased in one and unchanged in 2. In 3 out of 4 control animals infusion of this same dose of metaraminol into the left renal artery reduced the clearance of para-amino-hippurate (C_{PAH}) by an average of 29% while C_{PAH} in the corresponding right kidneys decreased only 11%.

Data are presented in Tables II and III showing the renal response to saline infusion in 7 dogs during metaraminol perfusion of the liver. C_{cr} was not strikingly altered by this procedure. In 4 dogs in which the liver was perfused *via* the portal vein (Table II) $U_{Na}V$ was unchanged during saline infusion in one, decreased in one and increased in 2. In these 2 animals the natriuresis remained less than that observed in normotensive dogs given saline infusion(8). In the 3 animals in which hepatic perfusion was performed *via* the hepatic artery (Table III) $U_{Na}V$ decreased in 2 and was unchanged in one. Changes in U_KV tended to be in the same direction as changes in $U_{Na}V$.

Data are presented in Table IV showing the renal response to saline infusion in 4 dogs during metaraminol perfusion of the brain. C_{cr} was not strikingly altered by this procedure. $U_{Na}V$ decreased in 2 dogs, was unchanged in 1, and increased in 1. Changes in U_KV were similar to those observed in $U_{Na}V$.

No significant pressor effect resulted from metaraminol perfusion of individual organs.

Control data are presented in Table V showing the renal response to saline infusion in 5 dogs during systemic pressor infusion of metaraminol in dogs having renal artery, portal vein, hepatic artery or carotid arteries cannulated. In these animals both $U_{Na}V$ and the sum of $U_{Na}V + U_KV$ increased in all animals although increase in $U_{Na}V$ was minimal in one animal with very low initial sodium output (#19). Sodium excretion in these 5 animals was augmented by 271, 75, 50, 1500 and 178%, respectively.

Discussion. The natriuretic response of the

normal dog to infusion of saline at a rate of one ml per minute averages about 15 μEq per minute(8). This response is augmented to over 200 μEq per minute in dogs receiving pressor infusions of metaraminol(8). The doses of metaraminol delivered to individual

TABLE II. Effects of Intravenous Administration of Saline in Dogs Receiving Metaraminol Infusion into the Portal Vein.

Dog No.	Infusion*	V, ml/min	C_{osm}, ml/min	C_{cr}, ml/min	$U_{Na}V$ μEq/min	U_KV, μEq/min	Mean BP, mm Hg
6	None	.20	.71	50	32	26	140
	Saline I.V.; metaraminol into portal vein	.33	1.2	67	53	41	130
7	None	.20	.33	29	8	29	120
	Saline I.V.; metaraminol into portal vein	.22	.31	30	9	31	105
8	None	.15	.90	74	6	35	120
	Saline I.V.; metaraminol into portal vein	.21	.94	67	9	45	120
9	None	.12	.87	69	19	28	150
	Saline I.V.; metaraminol into portal vein	.11	.63	64	1	19	150

* Normal saline infusion was given at a rate of 1.0 ml per min; metaraminol bitartrate was infused at a rate of 0.1 ml per min (10 μg per min).

TABLE III. Effects of Intravenous Administration of Saline in Dogs Receiving Metaraminol Infusion into the Hepatic Artery.

Dog No.	Infusion*	V, ml/min	C_{osm}, ml/min	C_{cr}, ml/min	$U_{Na}V$ μEq/min	U_KV, μEq/min	Mean BP, mm Hg
10	None	.31	1.1	78	49	45	130
	Saline I.V.; metaraminol into hepatic artery	.16	.58	84	4	34	120
11	None	.16	.89	63	5	30	130
	Saline I.V.; metaraminol into hepatic artery	.16	1.0	63	4	38	135
12	None	.63	2.0	59	117	35	145
	Saline I.V.; metaraminol into hepatic artery	.29	1.2	52	44	32	140

* Normal saline infusion was given at a rate of 1.0 ml per min; metaraminol bitartrate was infused at a rate of 0.1 ml per min (10 μg per min).

TABLE IV. Effects of Intravenous Administration of Saline in Dogs Receiving Metaraminol Infusion into Both Internal Carotid Arteries.

Dog No.	Infusion*	V, ml/min	C_{osm}, ml/min	C_{cr}, ml/min	$U_{Na}V$ μEq/min	U_KV, μEq/min	Mean BP, mm Hg
13	None	.26	1.7	85	84	60	135
	Saline I.V.; metaraminol into both internal carotids	.22	1.7	86	63	43	135
14	None	.25	1.1	66	44	28	130
	Saline I.V.; metaraminol into both internal carotids	.45	1.6	67	110	49	115
15	None	.31	1.4	69	35	52	150
	Saline I.V.; metaraminol into both internal carotids	.31	1.2	57	34	45	130
16	None	.25	1.0	48	60	39	145
	Saline I.V.; metaraminol into both internal carotids	.13	.40	38	7	16	135

* Normal saline infusion was given at a rate of 1.0 ml per min; metaraminol bitartrate was infused at a rate of 0.1 ml per min (5 μg per min) into each internal carotid artery.

TABLE V. Effects of Intravenous Administration of Saline in Dogs Receiving Systemic Pressor Infusion of Metaraminol, Following Cannulation of Renal, Carotid or Hepatic Artery or Portal Vein.

Dog #	Infusion*	V, ml/min R	V, ml/min L	C_{osm}, ml/min R	C_{osm}, ml/min L	C_{cr}, ml/min R	C_{cr}, ml/min L	$U_{Na}V$, μEq/min R	$U_{Na}V$, μEq/min L	U_KV, μEq/min R	U_KV, μEq/min L	Mean BP, mm Hg
	Left renal artery cannulated											
17	None	.10	.12	.36	.41	28	33	23	26	11	12	140
	Saline + metaraminol I.V.	.35	.46	1.3	1.3	43	33	78	104	47	38	180
	Portal vein cannulated											
18	None	.29		1.4		53		101		30		135
	Saline + metaraminol I.V.	.41		1.4		46		177		36		180
	Hepatic artery cannulated											
19	None	.12		.77		56		8		17		135
	Saline + metaraminol I.V.	.22		1.4		65		12		50		180
	Hepatic artery cannulated											
20	None	.13		.85		50		4		34		140
	Saline + metaraminol I.V.	.37		1.5		46		64		35		180
	Carotid arteries cannulated; vertebral arteries occluded											
21	None	.28		1.1		45		18		41		85
	Saline + metaraminol I.V.	.54		1.4		55		50		54		150

* Normal saline infusion was given at a rate of 1.0 ml per minute; metaraminol bitartrate was infused at a rate of .02 ml per minute (200 μg per minute) and was turned on and off to maintain mean BP between 160 and 200 mm Hg.

organs in the present study were calculated to equal approximately what the same organ must have received in previous studies when hypertension was produced during the systemic infusion of metaraminol and exaggerated natriuresis resulted. When one-tenth the pressor dose of metaraminol is infused directly into the renal artery vasoconstriction is achieved as evidenced by selective decrease in C_{PAH} in the perfused kidney. One dog in the present study also developed decreased C_{cr} in the perfused kidney and we have found that higher doses of metaraminol uniformly cause anuria.

In the present study the kidney receiving metaraminol in dosage adequate to cause renal vasoconstriction nevertheless failed to develop exaggerated natriuresis in response to systemic administration of saline.

One-fifth the pressor dose of metaraminol (approximately the amount reaching the liver on first passage during a systemic infusion adequate to cause exaggerated natriuresis) was infused into the portal vein or hepatic artery while saline was administered systemically. Exaggerated natriuresis was not observed.

Metaraminol was infused into each internal carotid artery in a dosage one-tenth that needed to cause hypertension and exaggerated natriuresis when given systemically with saline. Infusion of sodium under these conditions failed to elicit exaggerated natriuresis.

In dogs subjected to similar surgery but given pressor doses of metaraminol during administration of saline, natriuresis could be induced. These data indicate that surgical trauma and anesthesia were not responsible for prevention of natriuresis in the study animals.

It therefore appears that metaraminol does not directly sensitize the dog kidney to respond to saline infusion with enhanced natriuresis. This finding supports previous observations which suggested that exaggerated natriuresis was of extra-renal origin(13). It remains possible that the significant vasoconstrictor effect of metaraminol is exerted on some organ other than the kidney and causes release of some natriuretic factor during saline infusion. The present data offer evidence that neither the liver nor the brain is such an organ and therefore tend to support the thesis that high blood pressure itself plays a necessary role in the enhanced natriuretic response to infusion of saline in the hypertensive dog.

Summary. The exaggerated natriuretic response to infusion of saline observed in hypertensive man or dog might be related to vasoconstriction within some key organ rather than

to elevation of blood pressure. To examine this thesis saline infusion was administered to 16 mongrel dogs while individual organs were perfused with subpressor doses of metaraminol. The dose of metaraminol was that which the organ would receive during a systemic pressor infusion known to result in exaggerated natriuresis in the dog. The local pharmacologic effects of metaraminol on kidney, liver or brain did not result in an augmented natriuretic response to the infusion of saline. These data are therefore consistent with the view that hypertension itself is necessary for the appearance of exaggerated natriuresis in response to saline infusion in the dog.

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Effect of Advancing Age on Thyrotropin Content of the Pituitary and Blood Of the Rat.*† (31831)

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The effect of advancing age from 25 to 115 days on the thyroid hormone secretion rate (TSR) of female rats was reported(1). It was observed that the TSR of the same rats at 25 days was 1.52 μg L-thyroxine (L-T_4)/100 g BW and gradually declined to a level of 0.88 μg/100 g BW at 115 days. An explanation of the mechanism involved in the decline in TSR during this period has been sought. Since the secretion and discharge of thyrotropin (TSH) is clearly involved in TSR, it seemed of interest to determine the change in the pituitary and blood content of TSH during advancing age up to maturity.

Levey(2) determined TSH concentration in the pituitary of rats by a bio-assay from birth to 56 days of age and noted a progressive increase from 13 mU/mg to over 100 mU/mg. However, he was unable to determine the level of TSH in the serum samples because they were all below the minimum sensitivity of the bio-assay method(3).

Since Levey showed a progressive increase in pituitary TSH in young rats with age, whereas our study showed a progressive decrease in TSR during the same period of growth, it seemed of interest to repeat the study of the changes in pituitary TSH but at the same time assay the plasma concentration of TSH. Instead of a bio-assay of TSH as used by Levey, the TSH of both pituitary and plasma was assayed by an immuno-

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