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Effect of Intrarenal Arterial Infusion of Magnesium on Renin Release in Dogs (39315)

PAUL C. CHURCHILL AND H. JAY LYONS

Department of Physiology, Wayne State University School of Medicine, Detroit, Michigan 48201

There is ample evidence that renin secretion is influenced by sodium load or concentration in the vicinity of the macula densa (8, 16). Other ionic species such as calcium (6, 10, 11) and potassium (1, 12) have been shown to affect renin secretion. The present research was undertaken to directly assess the effect of intrarenal arterial infusion of magnesium upon renin release in anesthetized dogs.

Methods. These experiments were performed on 15 adult (18–56 kg) mongrel dogs, fasted overnight, and anesthetized with sodium pentobarbital (30 mg/kg body weight, iv, with supplements given as required). Arterial, venous, left renal venous, and bilateral ureteral catheters were inserted; in four dogs, the right renal vein was also catheterized (4). 26-gauge needle, connected by a polyethylene catheter to a Harvard syringe pump, was introduced into the left renal artery near its aortic origin. Systemic arterial blood pressure was continuously monitored using a Narco pressure transducer and a multichannel Narco Physiograph.

Following this preparation, a priming solution of inulin and *p*-aminohippuric acid (5.0 g of inulin + 1.0 g of PAH in 100 ml of 150 m*M* NaCl, 1 ml/kg body weight) followed by a sustaining infusion (0.5 g of inulin + 0.5 g of PAH in 100 ml of 150 m*M* NaCl, 0.2 ml/min/kg body weight) were administered via the venous catheter. An infusion of 150 m*M* NaCl was begun in the renal artery at the rate of 0.6 ml/min, and after a 30–45-min equilibration period, two consecutive 10-min clearance periods were observed. Then $MgCl_2$ (0.8 *M*) was substituted for the 150 m*M* NaCl and infused at the same rate into the renal artery. Following a 30-min equilibration period, two additional 10-min clearance periods were observed. Then 150 m*M* NaCl was substituted for the $MgCl_2$ solution, and following a 30-min equilibration period, two recovery clearance periods were observed.

Arterial and renal venous blood was collected at clearance midpoints in heparinized, ice-cold plastic syringes and centrifuged at 4°. Ethylenediamine tetraacetate (1 mg) was added to duplicate 0.5-ml plasma samples which were then frozen until the renin assay could be done. A New England Nuclear Radioimmunoassay Kit (Boston, Mass.) was utilized for renin determinations. Plasma samples were thawed on ice, inhibitors of converting enzyme activity were added (10 μl of 1.7% dimercaprol in peanut oil and 10 μl of 6.6% 8-hydroxyquinoline in water, per ml of plasma), and the samples were incubated at 37°. Samples of 20 μl were removed at 1 and 2 hr incubation and angiotensin I concentration was determined by radioimmunoassay. Plasma renin activity was expressed as nanograms of angiotensin I per milliliter of plasma per hour incubation (ng A-I/ml/hr).

Sodium and potassium concentrations in the plasma and urine were determined by flame photometry using an internal lithium standard (Instrumentation Laboratories). Sodium and potassium excretion rates were calculated as the products of the urine concentrations (U_{Na} and U_K) and urine flow rate *(V)*. Magnesium was determined by atomic absorption spectrophotometry (Perkin-Elmer). Renal arterial Mg^{2+} concentration was calculated as the sum of the renal venous Mg^{2+} and the Mg^{2+} excreted/RPF. Inulin in urine and in trichloroacetic acid plasma filtrates was determined by the method of Harrison (5). Inulin clearance was calculated and used as the measure of glomerular filtration rate (GFR). PAH was determined by the method of Smith *et al.* (13). Renal plasma flow (RPF) was determined from the clearance of PAH corrected by its extraction. Paired Student's *t* test was used for the assessment of significance.

Results. The influence of intrarenal arterial $MgCl_2$ infusion on the plasma Mg^{2+} was determined in six dogs. The results are presented in Table I. The femoral arterial,

TABLE I. EFFECT OF INTRARENAL ARTERIAL Mg^{2+} INFUSION ON PLASMA MAGNESIUM CONCENTRATION[a]

Plasma Mg^{2+} concentration (mEq/liter)	Control		Magnesium Infusion		Recovery	
	Clearance 1	Clearance 2	Clearance 3	Clearance 4	Clearance 5	Clearance 6
Arterial	1.29 ±0.04 (7)	1.23 ±0.06 (6)	2.98 ±0.28 (6)	4.10 ±0.58 (6)	3.19 ±0.43 (7)	3.03 ±0.42 (7)
Left renal venous	1.23 ±0.04 (7)	1.17 0.06 (6)	4.22 ±0.76 (6)	5.72 ±0.99 (6)	3.04 ±0.40 (7)	2.74 ±0.31 (7)
Right renal venous	1.27 ±0.07 (3)	1.25 ±0.05 (2)	2.67 ±0.07 (3)	3.68 ±0.69 (4)	2.90 ±0.70 (3)	2.57 ±0.06 (2)
Renal arterial (calculated)	1.30 ±0.04 (6)	1.20 ±0.04 (6)	4.60 ±0.81 (6)	6.25 ±1.05 (6)	3.05 ±0.46 (6)	2.82 ±0.35 (6)

[a] Magnesium was infused into left artery (0.4 mEq Mg^{2+}/min) during clearances 3 and 4. Renal arterial plasma Mg^{2+} concentration was calculated as the sum of renal venous Mg^{2+} concentration and urinary Mg^{2+} concentration/RPF. Results are presented as means ± SEM. Number of observations in parentheses. All values during clearances 3–6 are signficantly above control levels ($p < 0.005$).

renal venous, and calculated renal arterial Mg^{2+} were significantly elevated throughout the infusion and recovery periods ($p < 0.005$). At these levels, we observed no indication of toxicity, such as a sharp drop in blood pressure or respiratory abnormalities.

As shown in Table II, there was a slight decline in mean arterial blood pressure and renal plasma flow throughout the experiment reaching significance ($p < 0.05$) during the fourth clearance period. Magnesium induced a significant diuresis ($p < 0.005$), and also a significant natriuresis in both the third ($p < 0.005$) and the fourth ($p < 0.01$) clearance periods, without significantly changing the plasma concentration of Na^+ and K^+ or the GFR. The same changes were observed in the right kidney, contralateral to the $MgCl_2$ infusion, but they were less dramatic and delayed.

The effect of Mg^{2+} on renin secretion is summarized in Table III. We observed no significant changes in arterial plasma renin activity during the experiment. The renal venous-arterial plasma renin activity (RV-A), was significantly increased during $MgCl_2$ infusion ($p < 0.025$). Also, there was an increase in renin secretion rate, RPF (RV-A), during $MgCl_2$ infusion (third clearance, $p < 0.01$; fourth clearance, $p < 0.025$). Renin secretion returned to baseline values during recovery.

Discussion. The present study extends the work of others who used rats (2), that Mg^{2+} administration produces a diuresis and natriuresis in dogs. In those animals in which function was monitored in both kidneys, the kidney contralateral to the $MgCl_2$ infusion also exhibited increased urine flow and sodium excretion. However, these responses were reduced and delayed from that seen in the other kidney (Table II).

Plasma Mg^{2+} concentrations on the order of 10 mEq/liter have been shown to produce respiratory abnormalities and sharp decreases in blood pressure (18). Although plasma Mg^{2+} never attained that level in the present experiments, a steady fall in blood pressure, which became significant after about 30 min of infusion, occurred throughout the experiment. Renal blood flow seemed to decrease in parallel with the changes in blood pressure, the fall becoming significant during the recovery period. Renin secretion increased significantly during Mg^{2+} infusion and rapidly returned to control levels in the recovery period. Although decreases in mean arterial blood pressure are known to stimulate renin secretion (16), it is doubtful that this mechanism was solely responsible for the observed renin stimulation. The increase in renin secretion was observed during the first Mg^{2+} clearance period, at which time blood pressure had not fallen significantly. Moreover, blood pressure was significantly reduced during recovery, when renin secretion had returned to normal.

The stimulation of renin during Mg^{2+} administration does not accord well with the macula densa theories proposed by Vander (16) or Thurau (14). According to these theories, Na^+ concentration, load, and transport play controlling roles in renin secretion. We found that $U_{Na}V$ increased (Na^+ reabsorption decreased) and renin secretion was stimulated during the infusion. However, during the recovery period, when

TABLE II. EFFECT OF INTRARENAL ARTERIAL Mg^{2+} INFUSION[a]

	Control		Magnesium infusion		Recovery	
	Clearance 1	Clearance 2	Clearance 3	Clearance 4	Clearance 5	Clearance 6
Mean arterial blood pressure (mm Hg)	138 ± 5 (15)	138 ± 5 (14)	133 ± 5 (15)	129 ± 5 (15)[3]	127 ± 4 (15)[3]	127 ± 4 (15)[3]
Plasma sodium concentration (mEq/L)	145 ± 1 (15)	146 ± 1 (14)	145 ± 4 (15)	145 ± 4 (15)	145 ± 1 (15)	145 ± 1 (15)
Plasma potassium concentration (mEq/L)	3.8 ± 0.1 (15)	3.8 ± 0.1 (14)	3.8 ± 0.1 (15)	3.9 ± 0.1 (15)	3.9 ± 0.1 (15)	3.8 ± 0.1 (15)
Renal plasma flow (ml/min)						
Rt.	174 ± 40 (4)	145 ± 23 (4)	140 ± 12 (4)	128 ± 6 (4)	135 ± 11 (4)	127 ± 4 (4)
Lt.	167 ± 20 (14)	159 ± 20 (15)	157 ± 17 (14)	140 ± 16 (14)	131 ± 11 (15)[2]	121 ± 9 (15)[3]
Glomerlar filtration rate (ml/min)						
Rt.	40.7 ± 8.3 (4)	31.4 ± 7.8 (4)	33.1 ± 4.2 (4)	33.1 ± 4.2 (4)	40.7 ± 7.4 (4)	40.6 ± 6.0 (4)
Lt.	34.2 ± 3.4 (15)	32.6 ± 3.3 (14)	31.2 ± 3.1 (15)	28.6 ± 3.0 (14)	31.3 ± 3.2 (15)	29.9 ± 2.8 (15)
Urine flow rate (ml/min)						
Rt.	0.23 ± 0.08 (4)	0.51 ± 0.20 (4)	0.79 ± 0.21 (4)	0.86 ± 0.31 (4)[2]	0.92 ± 0.17 (4)	1.10 ± 0.31 (4)[1]
Lt.	0.46 ± 0.09 (14)	0.56 ± 0.11 (15)	1.34 ± 0.25 (15)[4]	1.60 ± 0.23 (14)[4]	1.34 ± 0.39 (15)[4]	1.21 ± 0.33 (15)[2]
Sodium excretion rate (mEq/min)						
Rt.	43 ± 5 (4)	43 ± 10 (4)	101 ± 38 (4)	101 ± 44 (4)	59 ± 20 (4)	71 ± 29 (4)
Lt.	63 ± 14 (15)	74 ± 19 (15)	148 ± 41 (15)[4]	156 ± 38 (15)[3]	114 ± 42 (15)[1]	108 ± 38 (15)

[a] Magnesium was infused into the left renal artery (0.4 mEq Mg^{2+}/min) during clearances 3 and 4. Results are expressed as means ± SEM. Number of observations in parentheses. Signficance: [1] $p < 0.05$; [2] $p < 0.025$; [3] $p < 0.01$; [4] $p < 0.005$.

TABLE III. EFFECT OF INTRARENAL ARTERIAL Mg^{2+} INFUSION ON RENIN[a]

	Control		Magnesium infusion		Recovery	
	Clearance 1	Clearance 2	Clearance 3	Clearance 4	Clearance 5	Clearance 6
Arterial plasma renin (ng A-I/ml/hr)	16.8 ± 3.9 (15)	17.1 ± 4.2 (14)	17.5 ± 4.7 (15)	15.3 ± 4.2 (15)	13.1 ± 3.6 (14)	13.4 ± 3.8 (14)
Renal venous-arterial plasma renin (RV-A) (ng A-I/ml/hr)	4.01 ± 2.07 (15)	3.60 ± 2.26 (15)	6.86 ± 2.33 (15)[2]	5.89 ± 2.42 (15)[2]	4.38 ± 1.58 (14)	5.56 ± 2.13 (14)
Renal secretion rate RPF (RV-A) (ng A-I/ hr/min)	515 ± 340 (15)	446 ± 280 (15)	992 ± 341 (15)[3]	924 ± 412 (14)[2]	469 ± 158 (14)	491 ± 165 (14)

[a] Magnesium was infused into the left renal artery (0.4 mEq/min) during clearances 3 and 4. Results are expressed as means ± SEM. Number of observations in parentheses. All renin values are for the left kidney. Significance: [1] $p < 0.05$; [2] $p < 0.025$; [3] $p < 0.01$; [4] $p < 0.005$.

renin secretion had returned to control levels, plasma Mg^{2+} and $U_{Na}V$ were still elevated. Thus, the renin response was transient but any presumed stimulus should still have been operative. A simiar transience in response to Ca^{2+} might explain why some groups report a stimulation of renin secretion by Ca^{2+} (6, 10, 11, 19), while others find little or no effect (7, 9, 17).

It is difficult to reconcile these results with the observations of Cantin *et al.* (3). These workers report an increase in electrondense juxtaglomerular granules in Mg^{2+} deficiency. Since a good correlation has been demonstrated between pressor activity of renal extracts and the number of granules in JG cells (15), this suggests that Mg^{2+} might have been expected to decrease, rather than increase, renin secretion.

Summary. Magnesium chloride was infused into the renal artery of anesthetized dogs in order to determine its effect on renal function. Natriuresis and diuresis were observed during $MgCl_2$ infusion, but there appeared to be no effect on glomerular filtration rate (GFR), or plasma sodium or potassium concentrations. Although mean arterial blood pressure and renal plasma flow (RPF) decreased throughout the experiment, the fall was not significant until after stopping $MgCl_2$ infusion. A significant stimulation of renin secretion occurred during magnesium administration.

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