Magnesium Ion Blockade of Regional Vasoconstriction

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IN PREVIOUS studies of vasoactive cations the magnesium ion was shown to inhibit potassium constriction of the mesenteric arterial bed.[9] Neutralization occurred as a quantitative phenomenon when the cations were simultaneously administered intra-arterially. In contrast, kalemic constriction was not reversed by conventional sympathetic dilating or blocking agents.[10] On the basis of these observations it was suspected that magnesium ion may reduce vasomotor tone and improve regional blood flow under circumstances where other drugs prove ineffective.

The generally accepted peripheral arterial response to magnesium ion is vasodilation which is thought to result from two different pharmacologic mechanisms.[6, 12] An indirect curare-like action retards acetylcholine release and interferes with transmission of nerve impulses at the neuromuscular junction and sympathetic ganglia.[1] A direct action of the cation reduces the responsiveness of vascular smooth muscle to sympatho-mimetic amines by alteration of membrane potential or of enzymatic processes or both.[4] Available evidence favors the second effect as the means by which kalemic constriction was locally antagonized and suggested that magnesium ion could also neutralize the non-sympathetic vasoconstrictors. With a view toward restoring effective regional circulation and function through a reduction of vasomotor tone when vasoconstriction is refractory to the usual measures, experiments were designed to investigate, magnesium ion blockade of adrenergic and non-adrenergic constriction of the renal and mesenteric arterial systems.

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Material and Methods

Magnesium ion (Mg^{++}) as the hydrated sulfate salt ($MgSO_4 \cdot 7H_2O$) was instilled into the trunk vessel of the arterial bed under study either by constant infusion with a motor driven pump or as a bolus by hand injection. Instillations were made directly into the artery through an indwelling hypodermic needle or via a cannulated small branch vessel. Blood flows were measured proximal to the site of infusion with calibrated non-cannulating flow probes from a dual channel, square wave electromagnetic flow-meter. Variations in flow rate were ascribed to active changes in the caliber of the vessel in the absence of any significant alteration in systemic pressure. Flow artifacts due to retrograde flushing past the probe, instillation of excessive volumes of fluid and obstruction to antegrade flow by forceful injection were avoided. Systemic pressure was obtained from a cannulated carotid or femoral artery. All measurements including the electrocardiogram were inscribed by a direct writing physiologic recorder.

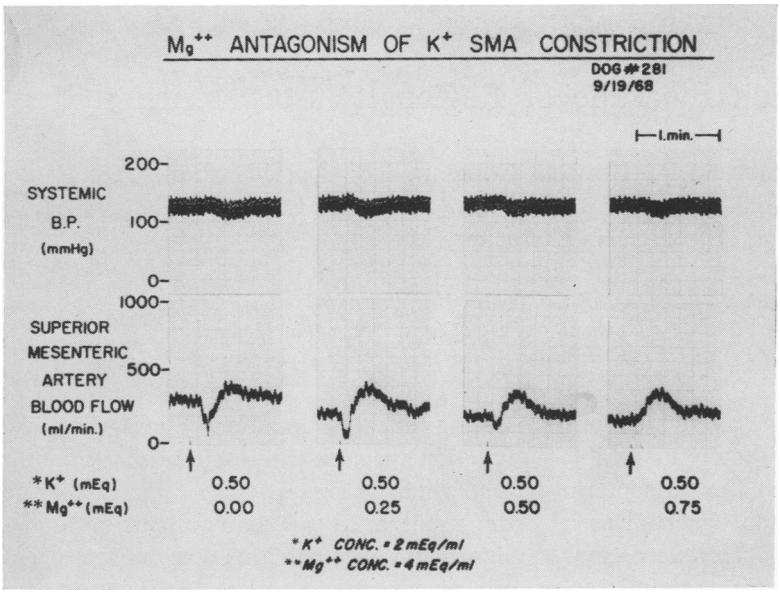

FIG. 1. Reduction in mesenteric blood flow caused by intra-arterial potassium injection is progressively antagonized by increasing amounts of magnesium ion.

The study included 20 dogs weighing 11 to 22 Kg. that were anesthetized with intravenous sodium pentobarbital, 25 mg./Kg. All animals were intubated and maintained on a mechanical ventilator with ambient air. The peritoneal cavity was entered through a midline incision for exposure and isolation of the superior mesenteric or renal arteries. A minimum of one hour elapsed after completing the operative procedure before the cation infusion began. Magnesium ion concentration in all instillations was 4 mEq./ml. (concentration of stock solution of magnesium sulphate was 50%).

Two groups of experiments were carried out. In the first series of 14 dogs, known concentrations of potassium ion (as the chloride salt), neosynephrine, norepinephrine, epinephrine, angiotensin and pitressin were injected into the renal or superior mesenteric artery. The dose was selected in accordance with the body weight or in an amount sufficient to cause a reduction in blood flow greater than 50% of the control value. No effort was made to adjust the pH or maintain isotonicity. Magnesium ion was simultaneously injected in graded amounts until substantial reversal of vasoconstriction was obtained as indicated by the recorded flows.

In a second series of six experiments, one of three vasopressor agents was administered intravenously while right and left renal blood flows and urine volumes were individually measured. The rate of constrictor drug infusion was adjusted either to maintain the mean systemic pressure between 180 and 200 mm. Hg or to produce a sustained reduction in blood or urine flow or both. The concentrations of norepinephrine, angiotensin and pitressin were 16 mg., 1 mg. and 20 units per L., respectively. Cumulative 10-minute urine samples were obtained from indwelling ureteral cannulae and the sodium concentrations determined by flame photometry. Intravenous 5% glucose in saline, 1 to 4 ml./min., was given as a fluid load and maintained throughout the experiment. Magnesium was selectively infused into the left renal artery at rates of 0.8 to 4.0 mEq./ml. prior to or after pressor administration, and the changes in blood

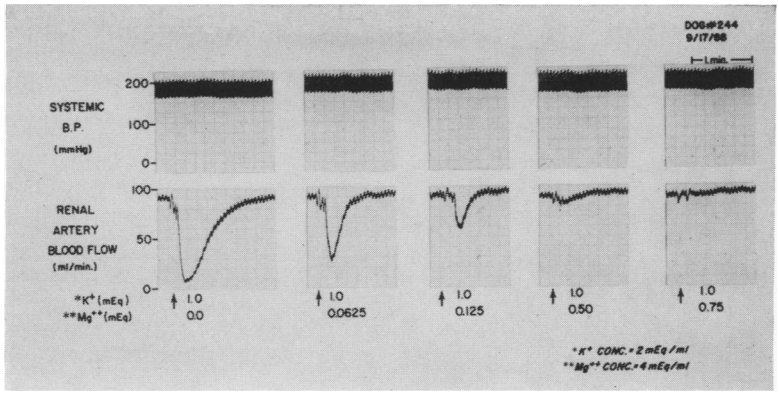

FIG. 2. Renal artery vasoconstriction in response to intra-arterial potassium injection blocked by simultaneous administration of magnesium ion in increasing doses.

flow, urine volume and sodium excretion were observed.

Results

Group I. Neutralizing Dose of Magnesium Ion

Potassium Ion. Bolus injections of potassium ion caused abrupt falls in the superior mesenteric (Fig. 1) and renal artery flows (Fig. 2). Graded increments in the simultaneously injected magnesium ion progressively blocked kalemic constriction of both beds.

Adrenergic Vasoconstrictors. The typical renal artery responses to norepinephrine and epinephrine were antagonized by magnesium ion (Fig. 3). The reversal by magnesium ion of sympathetic amine con-

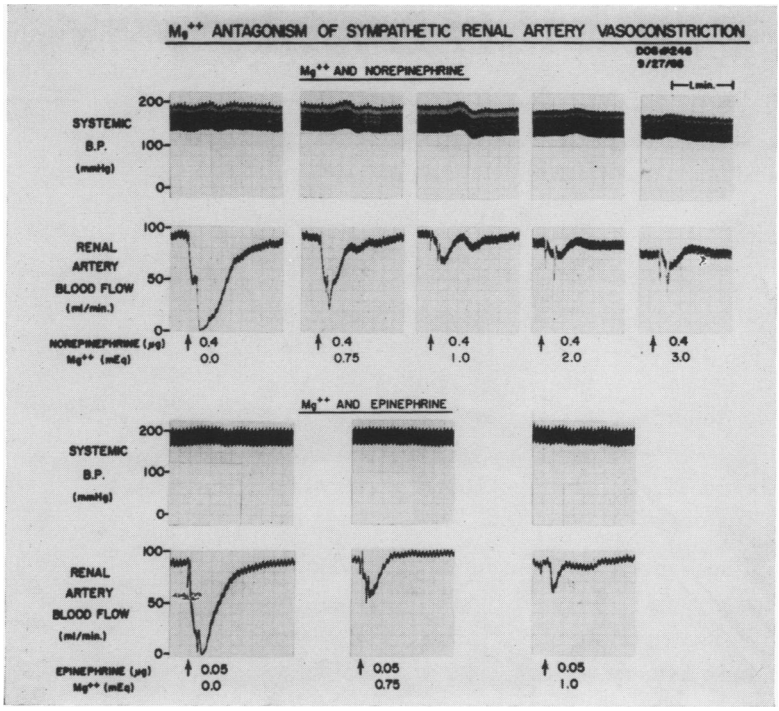

FIG. 3. Typical renal artery response to intra-arterial adrenergic vasopressors antagonized by simultaneous injection of magnesium ion.

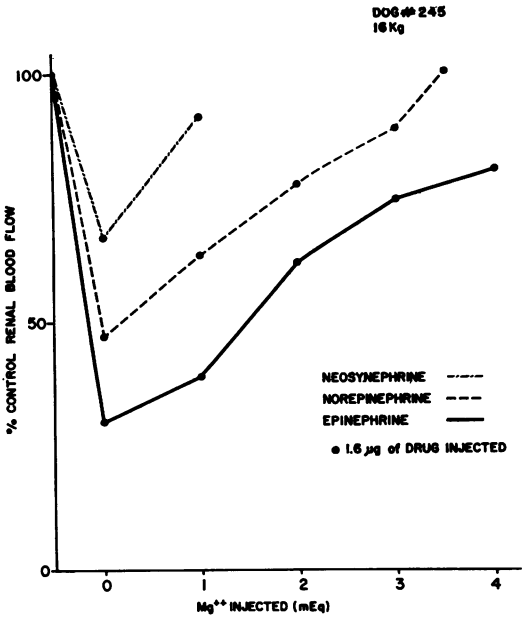

FIG. 4. Comparative magnesium ion antagonism of renovascular constriction induced by 1.6 mg. (0.1 mg./Kg.) of neosynephrine, norepinephrine and epinephrine injected intra-arterially.

striction of the renal (Fig. 4) and superior mesenteric (Fig. 5) beds were similar. In both regions neosynephrine required the least quantity of magnesium ion to neutralize its effect.

Non-Adrenergic Vasoconstrictors. Magnesium ion neutralized the angiotensin and pitressin mediated vasoconstriction of the superior mesenteric (Fig. 6) and renal (Fig. 7) arterial systems, respectively. Systemic pressures were not appreciably altered by the amount of the cation required for complete inhibition of clinical doses of the non-adrenegic pressors.

Group II. Continuous Renal Artery Infusion of Magnesium Ion

Intravenous angiotensin caused a decline in right and left renal blood blows and an increase in systemic pressure. There was some recovery with passage of time. Selective infusion of magnesium ion into the left renal artery promptly reversed the ipsilateral vasoconstriction and restored flow beyond the baseline value (Fig. 8). Cessation of the infusion was followed by a reduction in blood flow. It is evident that circulating magnesium ion gains the right renal arterial bed since blood flow on this side increased slightly within a minute after the onset of the magnesium infusion.

Nor-epinephrine caused a substantial depression in renal blood flow, urine volume and sodium excretion in the right kidney which was not selectively infused with magnesium ion. In comparison, the treated left kidney exhibited significant increases in these functional values (Fig. 9). There were no appreciable changes in systemic pressure at the rates of intra-arterial cation administration used in these experiments.

Similarly, magnesium ion reversed the pitressin induced reduction in renal blood flow, urine volume and natruresis (Fig. 10) without altering the level of systemic pressure or expanding the narrowed pulse pressure. The contralateral kidney showed slight functional improvement within the same ten minute collection period as a result of the recirculated magnesium ion.

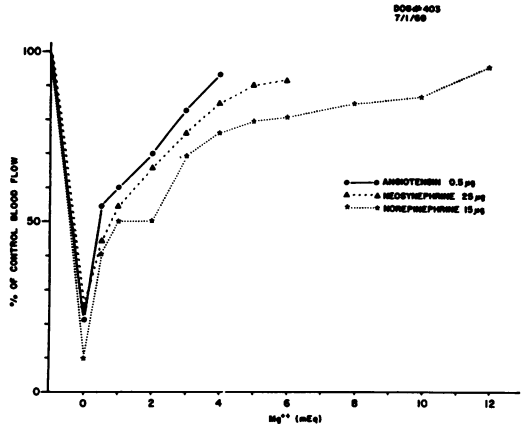

FIG. 5. Comparative magnesium ion blockade of constriction of the superior mesenteric vascular bed due to intra-arterial injections of angiotensin, neosynephrine and norepinephrine.

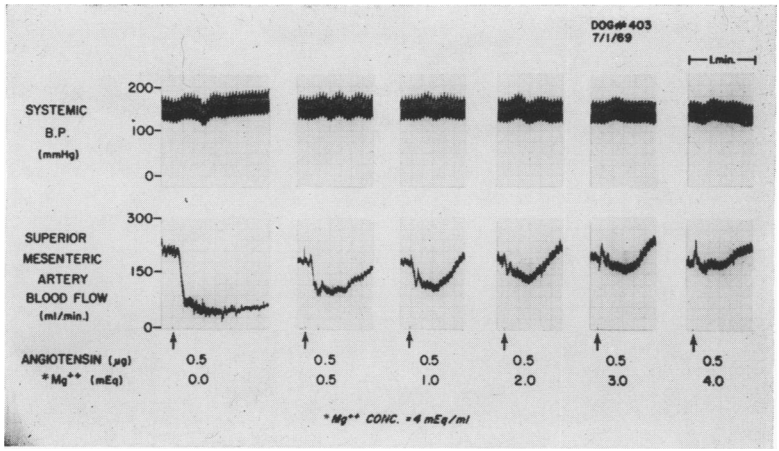

FIG. 6. Fall in superior mesenteric artery blood flow due to intra-arterial angiotensin inhibited by simultaneous injection of magnesium ion in progressively increasing doses.

Discussion

These studies indicate magnesium ion is a potent inhibitor of vascular constriction due to adrenergic and non-adrenergic mediators. In the chain reaction of smooth muscle relaxation, the cation exerts its effect at a site peripheral to that of the pressor amines. This was confirmed in a separate series of experiments in which alpha and beta adrenergic blocking agents failed to reverse magnesium neutralization of vaso-active sympathetic compounds. Suppression of pitressin, angiotensin and potassium induced vaso-constriction suggests that the cation modifies fundamental ionic processes to reduce vasomotor tone.[6] Bohr has proposed a final common pathway for the smooth muscle contractile process (or its inhibition) that involves intracellular coupling and release of ionized calcium.[2] The subsequent chemo-mechanical transduction is regulated through magnesium ion which controls cell membrane transport of potassium ion and thereby the action potential at the effector.[6]

A continuous regional infusion of magnesium was required for sustained local inhibition of systemic vasopressors. Pretreatment of the vascular bed was without effect. At infusion rates greater than 1.6 mEq./min., administration of magnesium ion was associated with a progressive reduction in systemic pressure and eventually a decline in renal blood flow. In four of six experiments the infusion rate was maintained at 0.8 mEq./min. This caused no appreciable change in blood pressure over an average period of 4 hours and was only slightly less effective in neutralizing the pressor agent. Under the conditions of these experiments it was concluded that 0.8 mEq. represented the approximate clearance rate

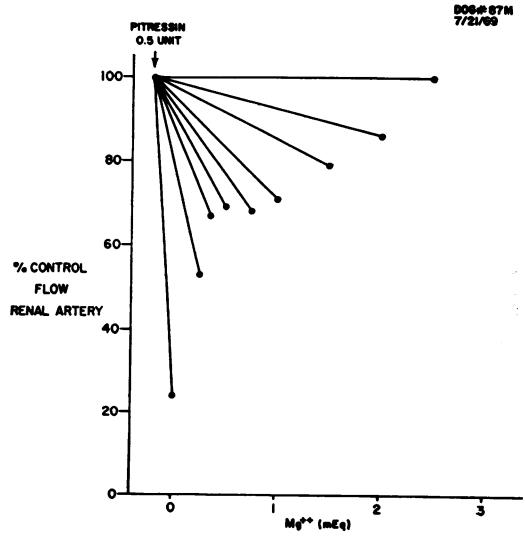

FIG. 7. Blockade of pitressin induced renal vasoconstriction by magnesium ion; complete inhibition of 0.5 u achieved with 2.5 mEq. of the cation.

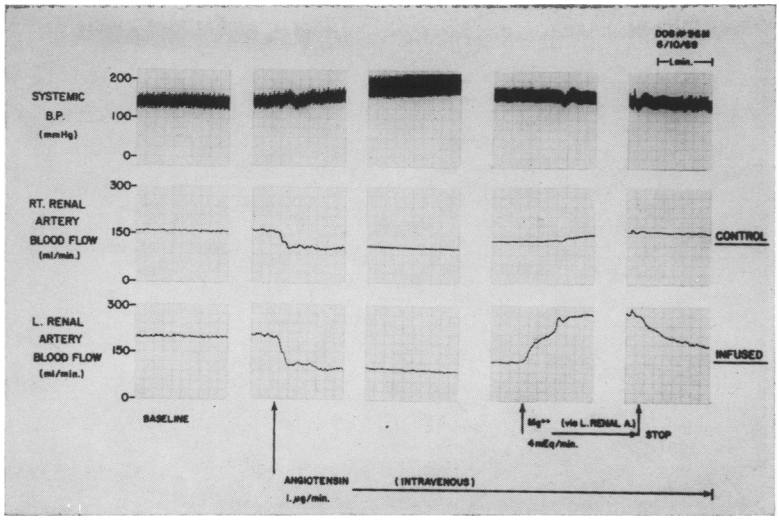

FIG. 8. Intravenous angiotensin causes a substantial reduction in blood flow to both kidneys. Selective magnesium ion infusion into the left renal artery results in a prompt ipsilateral vasodilation; delayed, modest increase in contralateral flow ascribed to re-circulation of magnesium ion.

of magnesium ion through renal excretion and/or intracellular deposition.[11] Cessation of cation administration resulted in a gradual fall in renal blood flow, urine volume and sodium excretion over a 10 to 20-minute period to pre-infusion values.

Neither angiotensin nor pitressin have recognized pharmacologic antagonists equivalent to the alpha blocking agents of the sympathetic amines. Few reports deal with magnesium as an inhibitor of the non-sympathetic pressors.[8] From our observations it would appear that within the range of physiologic doses magnesium readily blocks the ability of these drugs to constrict vascular smooth muscle. The potassium-magnesium antagonism demonstrated in these experiments is active against kalemic constriction; kalemic vasodilation remains unaffected.[10] This cationic interaction has been investigated extensively in chemical cardioplegia and merits further study as it applies to the peripheral circulation.[7, 9]

The superiority of regional over systemic blockade to preserve visceral blood flow against excessive vasoconstriction has been emphasized by Gump and his associates.[5] These investigators selectively infused phenoxybenzamine into a renal bed constricted by hemorrhage or sympathetic pressor amines. An effective blood flow was restored at relatively low doses without the serious hypotension that regularly attends systemic use. The results of our study suggest magnesium ion would serve a similar role and perhaps offer several advantages. Unlike the adrenergic blocking agent, the action of the cation is rapid in onset, short-lived and antagonistic to amine and non-amine vasoconstrictors. The intensity and duration of the block may be better controlled through precise regulation of the rate and concentration of the magnesium infusion. Since the cation activates all intracellular processes for the generation and transfer of energy-rich phosphates and governs transmembrane sodium-potassium flux,[13] it may stabilize the cell and help maintain its viability under conditions of marginal flow.[3]

Summary

Magnesium ion blockade of sympathetic and non-sympathetic vasopressors was dem-

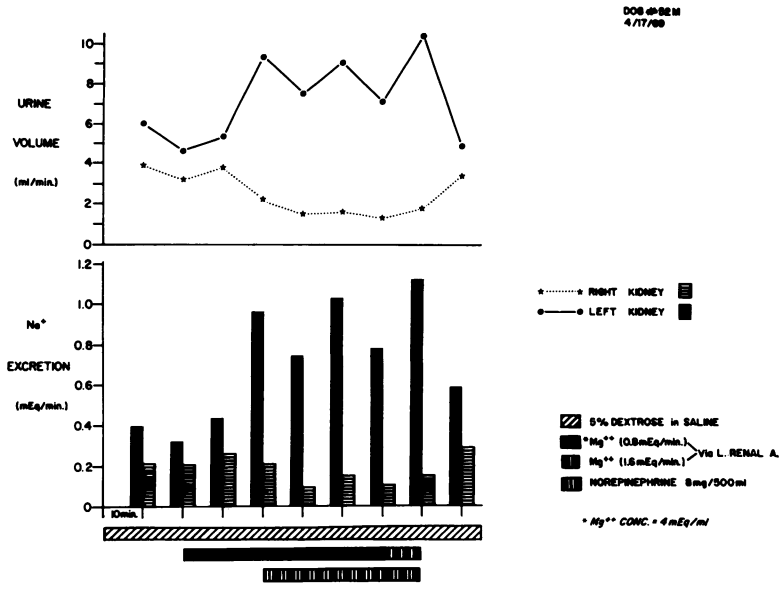

FIG. 9. Selective left renal artery infusion of magnesium ion prior to intravenous norepinephrine. Ipsilateral increase in urine volume and natruresis contrasts with depression of these values on the side unprotected by the cation blockade.

onstrated in the renal and mesenteric arterial beds. Vascular smooth muscle constriction induced by neosynephrine, epinephrine, norepinephrine, angiotensin, pitressin and potassium was inhibited by simultaneous intra-arterial injections of the cation.

Blockade of the renal bed was achieved with selective magnesium ion infusions of 0.8 to 4 mEq./min. into the renal artery.

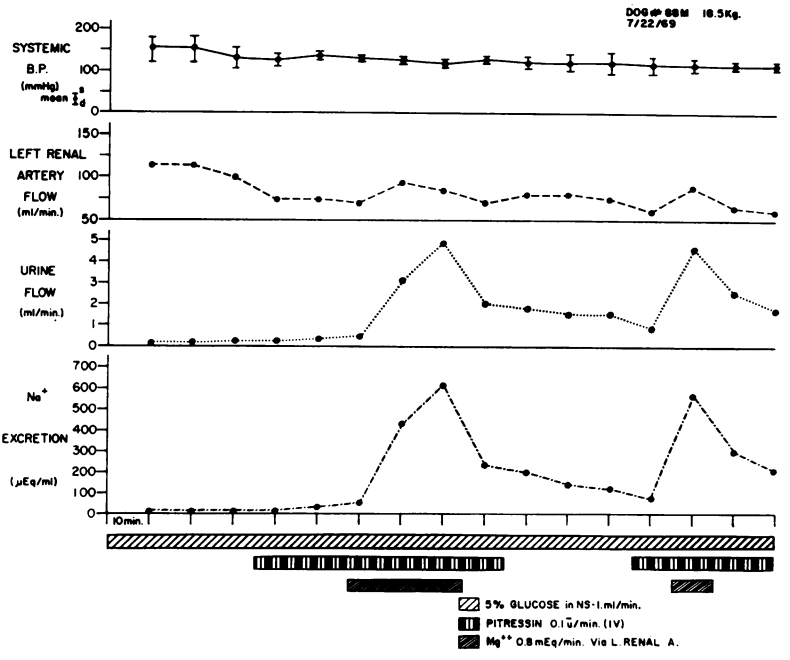

FIG. 10. Pitressin renal effects reversed by selective magnesium ion infusion. Regional arterial blockade manifested by parallel increases in blood flow, urine volume and sodium excretion.

Renovascular constriction caused by intravenous norepinephrine, pitressin or angiotensin was neutralized or reversed. The increase in renal blood flow was reflected in gains in urine volume and sodium excretion. The advantages of magnesium ion as an agent to inhibit regional vasoconstriction include rapid onset of action, brief duration of effect, effectiveness against a variety of vasoconstrictors and ability to control the blockade.

Acknowledgments

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