REFLEX MECHANISM OF MAINTENANCE OF MAGNESIUM HOMEOSTASIS

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Local stimulation of the liver by $MgCl_2$ solution in unanesthetized dogs caused reflex excretion of magnesium through a change in tubular processes. The presence of receptors selectively sensitive to Mg in the liver is postulated. Information from these receptors was shown to spread among the vagus nerves.

KEY WORDS: *magnesium; reflex; liver; receptors; kidney.*

The maintenance of ionic homeostasis is one of the most important conditions for the functioning of physiological systems. Information on regulation of the balance of monovalent cations is now available [1, 9, 10], but there are hardly any data on the maintenance of the stability of the concentration of bivalent cations, notably Mg. The Mg concentration in the blood plasma is known to vary within very narrow limits [13, 15, 19, 20], and changes in its content in diet are accompanied by changes in its excretion with the urine [5, 11-13, 16, 19, 20]. A system for regulating magnesium excretion must evidently exist in the body, and its organization and function have been inadequately studied. The liver, lying in the pathway of the many substances entering via the digestive system, has been shown to be an interoceptive zone responsible for activating various reflex mechanisms aimed at maintaining water and electrolyte equilibrium [1, 7-10, 14, 17]. Previously osmoreceptors [7, 8, 10, 13], volume receptors [18], and K^+ [1, 9] and Na^+ [1, 17] receptors have been discovered in this organ. Presumably the Mg receptors, the origin of the magnesium excreting reflex, are located in the liver also.

This paper describes an investigation aimed at continuing the study of the magnesium excretion regulating system.

EXPERIMENTAL METHOD

Chronic experiments were carried out on dogs weighing 9-18 kg with ureters exteriorized in the abdominal wall and with a gastric fistula. The animals were kept on an ordinary diet. The main series of experiments was carried out on dogs in which a thin polyethylene tube was inserted through the splenic vein into the portal vein, by means of which $MgCl_2$ solutions could be injected. In control experiments solutions were injected into the general circulation through a catheter fixed into a subcutaneous vein of the hind limb [2], so that unknown to the animal the solutions could be injected into the bloodstream and blood taken for analysis. Some experiments were carried out on dogs after bilateral supradiaphragmatic vagotomy. The dog was fixed to a frame and stable diuresis was maintained at the rate of 3-4 $ml/(min \cdot m^2)$ by injecting water periodically through the fistula. Twenty minutes after establishment of the stable background, 0.3% $MgCl_2$ solution was injected in a dose of 0.5 ml/kg through the tube into the portal vein or intravenously in the course of 5 min. Changes in diuresis were analyzed by measuring 5-min samples of urine. The concentration of Na and K in each sample was determined by flame photometry and the Mg concentration by a fluorometric method [3]. The rate of glomerular filtration was estimated from the endogenous creatinine clearance. At the beginning of the experiment, 5 min after injection of the stimulus, and twice in the course of the observations, the concentration of these ions in the blood plasma from the systemic circulation was determined.

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TABLE 1. Changes in Renal Function after Injection of 0.3% $MgCl_2$ Solution into Portal Vein (A) and into General Circulation (B)

Period of observation	A (n=15) diuresis, ml/(min·m²)	percent excretion of fluid	increase in excretion of Mg compared with initial background, μeq/(min·m²)	excretable fraction of Mg, difference from background, percent
Initial background	3,56±0,16	6,22±0,53	2,71	5,63
Injection				
1 (15)	4,00±0,22	7,00±0,65	+0,70±0,24 a	+1,41±0,43 a
2 (15)	3,51±0,27	6,63±0,82	+3,98±0,75 a	+8,94±1,69 a
3 (15)	3,72±0,31	6,92±0,82	+3,49±0,78 a	+7,68±1,60 a
4 (10)	4,22±0,31	7,76±0,61	+2,19±0,38 a	+5,08±0,70 a
5 (15)	2,65±0,39a	5,08±0,85	+2,41±0,39 a	+6,37±0,70 a
6 (15)	1,49±0,26a	2,87±0,62a	+2,48±0,46 a	+6,26±1,20a
7 (15)	1,26±0,21 a	2,33±0,52a	+2,25±0,37 a	+7,46±2,23 a
8 (10)	1,72±0,28a	3,20±0,69a	+2,06±0,57a	+5,65±1,67 a
9 (10)	2,74±0,31a	5,01±0,87	+1,13±0,48a	+2,60±0,82 a
	4,27±0,28a	7,63±0,64	—0,08±0,39	+0,02±0,77

Period of observation	B (n=14) diuresis, ml/(min·m²)	percent excretion of fluid	increase in excretion of Mg compared with initial background, μeq/(min·m²)	excretable fraction of Mg, difference from background, percent
Initial background	3,46±0,12	6,08±0,22	2,79	7,60
Injection				
1 (15)	3,63±0,23	6,80±0,41	—0,56±0,32 a, b	—0,02±0,41
2 (15)	3,79±0,28	7,03±0,60	+0,86±0,38	+2,36±0,99 a, b
3 (15)	3,40±0,24 a	6,64±0,51	+0,51±0,25 b	+2,39±0,62 a, b
4 (10)	3,36±0,23b	6,38±0,38b	+0,28±0,24 b	+1,83±0,63a, b
5 (15)	3,56±0,24b	6,67±0,46	+0,57±0,28b	+2,35±0,75 a, b
6 (15)	3,15±0,28 b	6,29±0,57 b	+0,04±0,34 b	+1,89±0,77 a, b
7 (15)	2,99±0,35 b	6,01±0,69b	—0,08±0,31 b	+2,05±1,01 b
8 (10)	3,01±0,35 b	5,88±0,74b	—0,24±0,39 b	+0,74±1,04b
9 (10)	3,42±0,28	6,52±0,55	—0,22±0,40	+0,33±1,05
	3,73±0,25	7,14±0,42 a	—0,59±0,61	+0,11±1,00

Legend: 1) Each period of observation (1-9) corresponds to time (in min) shown in parentheses. 2) a: $P < 0.05$ compared with initial background; b: statistically significant differences between indices of responses to injection of stimulus into portal vein and into general circulation; calculated by comparison of arithmetic mean values of independent distribution [4].

EXPERIMENTAL RESULTS

Injection of $MgCl_2$ into the portal vein evoked a complex response which, depending on the character of the change in renal function, could be divided into two phases. The first phase (Fig. 1), lasting 46 ± 2 min, was characterized by absence of any change in the excretion of water, Na, and K, but by a marked (on average by 2.2 times) increase in Mg excretion. The second phase, lasting 74 ± 2 min, began with muscular tremor, at first affecting individual groups of muscles, but later spreading to the whole body. There was a parallel decrease in water excretion and an increase in Na and Mg excretion. There was also a tendency for an increase in the potassium excretion. The tremor stopped after 25-35 min but the renal response lasted on average until 65 ± 3 min. The concentration of ions in the blood plasma (in meq/liter) was maintained within the background limits [for example, background: Mg 1.10 ± 0.06, Na 145 ± 1, K 4.70 ± 0.06; after injection of stimulus: Mg 1.11 ± 0.05 ($P > 0.1$), Na 143 ± 1 ($P > 0.05$), K 4.58 ± 0.06 ($P > 0.1$); after 45 min: Mg 1.02 ± 0.07 ($P > 0.1$), Na 142 ± 1 ($P < 0.05$), K 4.69 ± 0.06 ($P > 0.1$)]. The changes in the renal indices were almost independent of filtration and were determined by processes in the tubules.

In the next series fourteen experiments were carried out on five dogs, in which 0.3% $MgCl_2$ solution was injected through the limb vein. The results are given in Table 1. In eleven experiments these injections gave no result whatever, but in the other three experi-

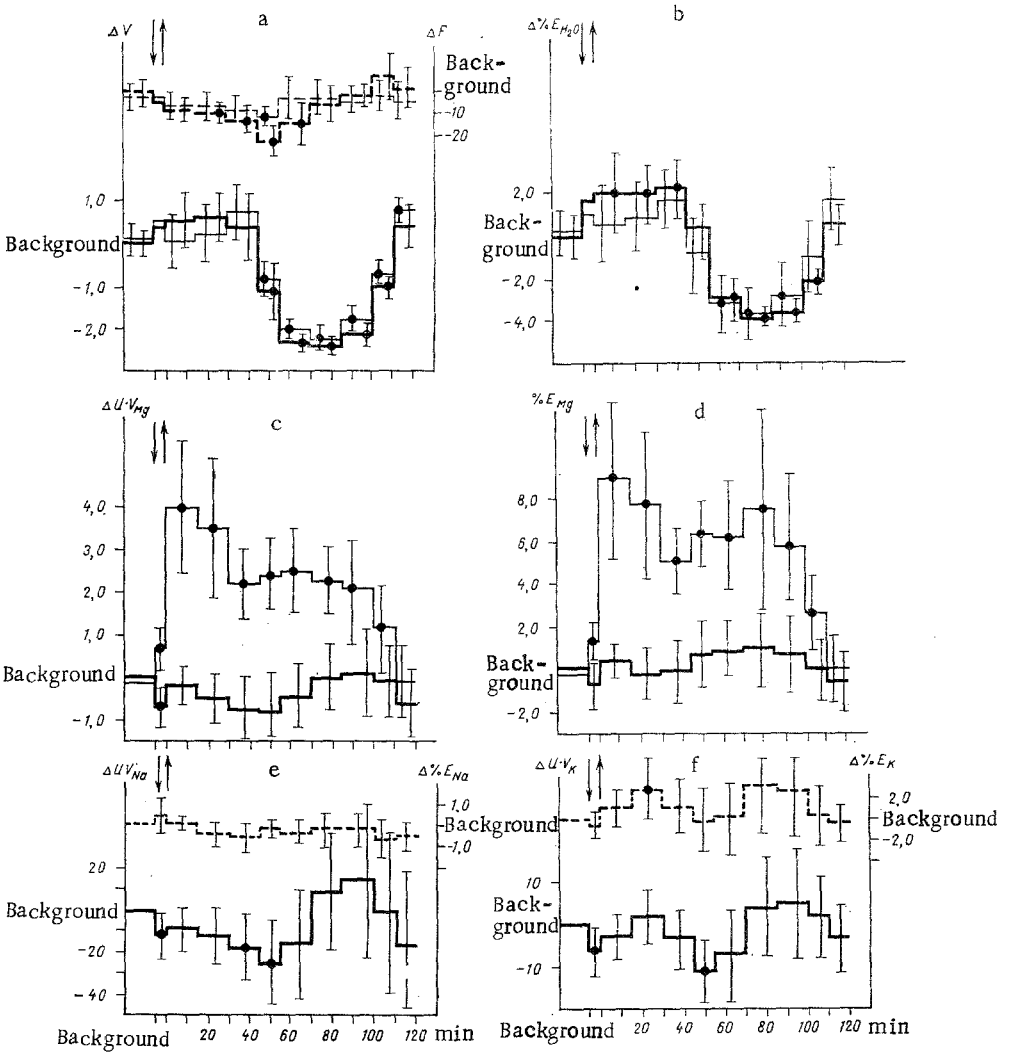

Fig. 1. Changes in renal function after injection of 0.3% $MgCl_2$ solution into portal veins of dogs. In a-d: thin lines represent intact animals, thick lines vagotomized; a) continuous lines, diuresis [in ml/(min•m²)]; broken lines, rate of glomerular filtration [in ml/(min•m²)]; b) percentage of excretion of fluids c) changes in excretion of Mg [in μeq/(min•m²)]; d) changes in excretable Mg fraction; e) continuous line, change in Na excretion [in μeq/(min•m²)]; broken line, change in excretable Na fraction; f) continuous line, change in K excretion [in μeq/(min•m²)]; broken line, change in excretable K fraction. Changes in excretion of ions and their excretable fractions and changes in diuresis, filtration, and percentage excretion of fluid calculated as difference from background. Confidence limits shown at P = 0.05 level. Abscissa, time in 10-min intervals. Arrows mark beginning and end of injection of solution.

ments a weak response similar to that obtained by intraportal injection and evidently due to the accumulation of the circulating cation in the liver was obtained. The plasma Mg concentration, just as in the main series of experiments, remained stable [background: 1.10 ± 0.04 meq/liter, after injection: 1.11 ± 0.05 meq/liter (P > 0.1); after 45 min: 1.09 ± 0.05 meq/liter (P > 0.1)]. The results suggest that the response takes place by a reflex mechanism.

It was shown previously [1] that impulses activating ion-regulating reflexes for monovalent cations spread from the receptive fields of the liver mainly along the vagus nerves. It was decided to study the pathway of spread of information for the magnesium excreting re-

flex. For this purpose fourteen experiments were carried out on five dogs after bilateral supradiaphragmatic vagotomy. The results, which are shown in Fig. 1, indicate that changes in diuresis in the vagotomized animals were the same as in the intact dogs; the reflex tremor also developed. Meanwhile, the vagotomy completely abolished the reflex excretion of Mg ions in response to injection of $MgCl_2$ solution. The experiments with vagotomy confirm the view that the response is reflex in nature and they show that information from the hepatic Mg receptors, like those from receptors of other ions, travel along the vagus nerve.

The study of the mechanism of the reflex tremor arising after injection of $MgCl_2$ into the portal veins was not one of the aims of this investigation. However, it should be pointed out that the tremor was evidently of central origin, for tremor of the muscles of the hind limbs did not develop after division of the spinal cord at the level T11-L1.

It can be postulated on the basis of these results that specialized Mg receptors are located in the liver; stimulation of these receptors activates a reflex mechanism resulting in increased excretion of Mg by the kidneys and restoration of the disturbed homeostasis through changes in tubular processes.

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