Evidence for Suppression of Parathyroid Gland Activity by Hypermagnesemia

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ABSTRACT The effect of hypermagnesemia, produced by $MgCl_2$ infusion, on the activity of parathyroid glands, as assessed by changes in levels of serum calcium (S_{Ca}) and in the fraction of filtered phosphate excreted (C_P/C_{Cr}), was studied in 11 intact and 4 thyroparathyroidectomized (T-PTX) dogs. To exclude the effect of diurnal variation in C_P/C_{Cr} on the results, studies were initiated in both morning and afternoon hours and each study with $MgCl_2$ infusion was paired with a control experiment in the same dog not receiving $MgCl_2$. During $MgCl_2$ infusion, serum phosphorus rose progressively. Despite this rise, the levels of C_P/C_{Cr} fell in all experiments and were significantly different from values observed at the same time of the day in the paired control experiments. The concentrations of total S_{Ca} fell by 1.0–2.4 mg/100 ml with a proportional decrease in the levels of the diffusible and ionized fractions. The pattern of the fall in C_P/C_{Cr} during $MgCl_2$ resembled that observed after $CaCl_2$ infusion (seven dogs) and that which acutely followed thyroparathyroidectomy (seven dogs). When parathyroid extract was given to dogs receiving $MgCl_2$ infusion both C_P/C_{Cr} and S_{Ca} rose, and $MgCl_2$ infusion did not affect C_P/C_{Cr} and S_{Ca} in T-PTX dogs. These results indicate that hypermagnesemia suppresses the activity of the parathyroid glands, probably, by inhibiting production and (or) release of the hormone, without interfering with end-organ response. An increase in serum magnesium of 1.7–2.0 mg/100 ml was capable of producing the suppressive effect. Evaluation of the effect of simultaneous modest hypocalcemia and hypermagnesemia suggests that a decrease in the level of serum calcium is more potent than an increase in the concentration of serum magnesium in the regulation of parathyroid activity.

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INTRODUCTION

Although it is well documented that the concentration of ionized calcium in the plasma is of primary importance in regulating parathyroid hormone secretion (1–3), evidence exists suggesting that the level of blood magnesium may also play a role in the regulation of the activity of the parathyroid glands. In the rat, magnesium deficiency and hypomagnesemia may stimulate the parathyroid glands (4–6). Gitelman, Kukolj, and Welt (7) reported data in nephrectomized rats compatible with the concept that hypermagnesemia may suppress the activity of the parathyroid glands in the rat; their studies, however, do not exclude the possibility that the hypocalcemic effect of magnesium injections could have been produced by mechanism(s) other than the inhibition of the parathyroid glands. In four experiments utilizing the in vivo perfusion of isolated parathyroid glands in goats and sheep with perfusate containing high concentration of magnesium, there was an inverse correlation between the level of parathyroid hormone in the affluent blood and the concentration of magnesium in the perfusate in three experiments; this correlation was highly significant in only one study (8).

The relation between magnesium metabolism and the activity of parathyroid glands in the dog and man has not been delineated. Magnesium deficiency in the dog may be associated with normal or low levels of serum calcium (9–12); the effect of acute hypermagnesemia on the activity of the parathyroid glands has not been studied in the species. In man, magnesium deficiency

and hypomagnesemia may be accompanied by hypocalcemia (13), which cannot be corrected by the administration of parathyroid extract, suggesting that the skeleton is rendered resistant to the action of parathormone. The repeated injections of magnesium salts (14) and oral magnesium loading (15) to humans were associated with a decrease in phosphate excretion; these results were not attributed to inhibition of parathyroid glands. Furthermore, the relative importance of simultaneous changes in the concentration of serum calcium and magnesium in the regulation of the activity of parathyroid glands is not known.

The present study was undertaken to evaluate the effect of acute hypermagnesemia on the activity of the parathyroid glands in the dog as assessed by changes in the concentration of serum calcium and in the fraction of filtered phosphate excreted. The influence of a simultaneous hypermagnesemia and hypocalcemia on the activity of these glands was also studied.

METHODS

52 experiments were carried out during pentobarbital anesthesia in 18 intact and 11 thyroparathyroidectomized (T-PTX) mongrel dogs weighing 16–25 kg. An oral water load of 500 ml was given to the animals in each experiment

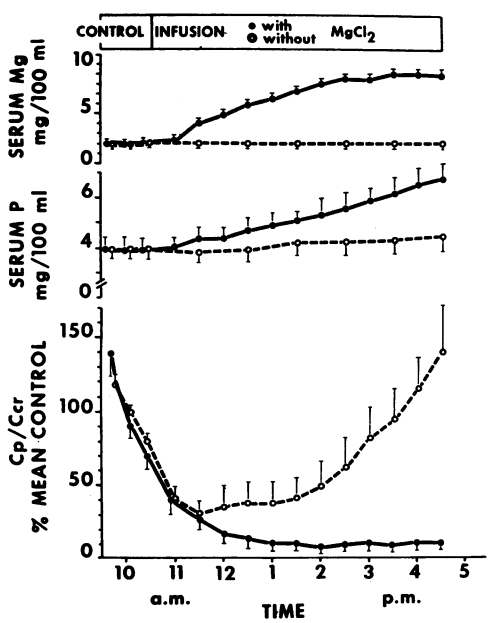

FIGURE 1 Morning studies. The changes in mean levels of serum magnesium (Mg) and phosphorus (P) and in the fraction of filtered phosphate excreted (C_P/C_{Cr}) in seven intact dogs with and without the infusion of $MgCl_2$ (100 μg Mg^{++}/kg per min). In order to reduce the variability in absolute fraction of C_P/C_{Cr} from one experiment to another, the changes in C_P/C_{Cr} are expressed as the per cent of the mean of the three control clearances in each individual experiment. The brackets represent ±1 SE.

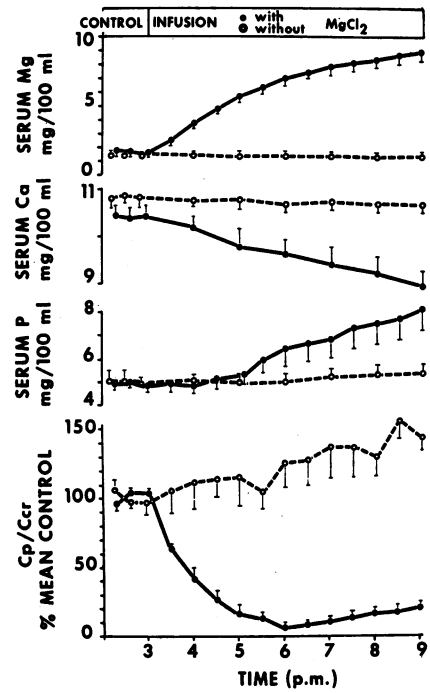

FIGURE 2 Afternoon studies. The changes in mean levels of serum magnesium (Mg), calcium (Ca), and phosphorus (P) and in the fraction of filtered phosphate excreted (C_P/C_{Cr}) in four intact dogs with and without the infusion of $MgCl_2$ (100 μg Mg^{++}/kg per min). The changes in C_P/C_{Cr} are expressed as in Fig. 1.

1 hr before the induction of anesthesia. Respiration was controlled by a Harvard respiratory pump, which was adjusted initially with a stroke volume of 10 ml/kg body weight and at a rate of 30 strokes/min. Blood pH was measured several times during each study with a Radiometer pH meter (London Co., Westlake, Ohio), and the stroke volume of the respirator was adjusted thereafter to maintain blood pH within normal range; usually, little adjustment was necessary. Glomerular filtration rate was measured by exogenous creatinine clearance. Urine was collected from a retention catheter, and the bladder was washed with air at the end of each period. Blood was obtained at the midpoint of each clearance period from an indwelling needle in the femoral vein. The following studies were performed.

Experiments with the infusion of magnesium chloride (15 dogs, 38 experiments). After three control clearance periods, each of 20 min duration, magnesium chloride was added to 0.45% saline, and this solution was infused at 1 ml/min for 6 hr to deliver 100 μg Mg^{++}/kg per min in each experiment unless noted otherwise; clearance collections of 30 min duration were obtained throughout. To exclude the effect of the diurnal variation in phosphate excretion on the results, experiments were initiated in both morning (morning studies) and afternoon (afternoon studies) hours, and each experiment with infusion of $MgCl_2$ was paired with a control study in which the same animal received only 0.45% saline at 1 ml/min for 6 hr over the same period of the day during which the $MgCl_2$ infusion was given. 5–10 days separated studies in the same dog.

Seven intact dogs, in which studies began in the morning hours, received the infusion of $MgCl_2$ between 10:30 a.m. and 4:30 p.m. Four of these dogs were restudied with a second infusion of $MgCl_2$ while they also received intramuscular injections of 100 U of parathyroid extract (supplied courtesy of Dr. A. S. Ridolfo, Eli Lilly & Co., Indianapolis, Ind.) at 10:30 a.m., 12:30 p.m., and 2:30 p.m.

Four intact dogs, in which experiments were started in the afternoon hours, received the usual $MgCl_2$ infusion between 3:00 p.m. and 9:00 p.m. These animals were restudied with the amount of $MgCl_2$ reduced to deliver 40 μg Mg^{++}/kg per min from 3:00 p.m. to 6:00 p.m., and the experiments were then continued until 9:00 p.m. with only 0.45% saline infused.

The effect of $MgCl_2$ was also evaluated in four T-PTX dogs. Thyroparathyroidectomy was performed under pentobarbital anesthesia 2–3 days before the first study. The complete removal of the parathyroid glands was confirmed by the appearance of hypocalcemia. The dogs received liberal amounts of calcium and phosphate in their diet, and they remained in good condition for at least 10 days. Both a control experiment and a study with the infusion of $MgCl_2$ were carried out in each dog between 3:00 p.m. and 9:00 p.m.

Experiments with calcium chloride infusion (seven dogs, seven experiments). After three control clearance periods of 20 min duration, $CaCl_2$ was added to 0.45% saline, and the solution was infused at 2 ml/min to deliver 5 mg Ca^{++}/kg per hr from 11:30 a.m. to 2:30 p.m. The calcium chloride infusion was replaced by 0.45% saline alone, and the experiment continued for an additional 3 hr, with clearance collections obtained throughout the entire study.

Experiments during and immediately following thyroparathyroidectomy (seven dogs, seven experiments). After three control clearance periods of 20–30 min each, thyroparathyroidectomy was performed between 11:00 a.m. and 12:30 p.m. Clearance studies were obtained during the surgical procedure and for 4 additional hr thereafter.

Blood and urine samples were analyzed for creatinine by the Jaffe reaction (16) and for phosphate by the method of Fiske and Subbarow (17), and calcium and magnesium were measured by the Perkin Elmer atomic absorption spectrophotometer, model 303. Diffusible calcium and magnesium and ionized calcium were measured in ultrafiltrates of serum prepared anaerobically in Lavietes chambers at room temperature (18). The concentration of ionized calcium was measured by a micromodification of the method of Ettori and Scogan (19). Water content of serum was determined by refractometry (Goldberg refractometer, American Optical Corp., Scientific Instrument Div., Buffalo, N. Y.).

RESULTS

In the anesthetized but otherwise intact dog, phosphate excretion displays a distinct diurnal pattern (Figs. 1

TABLE I

Detailed Protocal of Two Experiments, One without (Control) and One with $MgCl_2$ Infusion (i.v. Mg), Carried Out in Dog No. 1

	Time	C_{Cr}		S_{Mg}		S_{Ca}		$\frac{S_P}{\text{Control}}$	$\frac{C}{C_{Cr}} \times 100$	
		Control	i.v. Mg	Control	i.v. Mg	Control	i.v. Mg	i.v. Mg	Control	i.v. Mg
		ml/min		*mg/100 ml*		*ml/min*		*mg/ 100 ml*		
a.m.	8:00 Oral water load, 500 ml									
	8:30 Anesthesia with pentobarbital Priming dose of creatinine (500 mg) Infusion started: 7 mg creatinine/min delivered in 0.45% saline at 1 ml/min									
	9:30–9:50	44.8	41.9	1.25	1.68	8.9	9.3	3.9	16.1	18.9
	9:50–10:10	48.4	39.6	1.25	1.68	8.9	9.3	3.9	16.1	18.9
	10:10–10:30	49.0	44.5	1.38	1.68	9.0	9.3	4.0	7.8	13.9
	10:30 In i.v. Mg experiment, $MgCl_2$ added to infusate to deliver 100 μg mg/kg per min									
	10:30–11:00	40.6	41.1	—	2.10	—	—	4.2	5.2	6.1
	11:00–11:30	43.6	42.8	1.38	3.49	9.1	9.0	4.3	2.5	3.0
	11:30–12:00	45.9	43.0	—	4.55	—	—	4.2	4.9	0.6
p.m.	12:00–12:30	45.2	42.7	1.50	5.53	8.9	9.0	4.2	2.5	0.4
	12:30–1:00	41.4	42.1	—	6.55	—	—	4.5	1.9	0.2
	1:00–1:30	43.5	42.2	1.45	7.27	8.8	8.8	4.9	1.2	0.2
	1:30–2:00	51.2	41.7	—	7.78	—	—	5.1	1.4	0.3
	2:00–2:30	51.2	41.8	1.45	8.00	8.8	8.6	5.2	3.1	0.2
	2:30–3:00	46.8	41.8	—	8.23	—	—	5.6	7.9	0.2
	3:00–3:30	45.0	41.0	1.39	8.25	8.8	8.3	5.7	13.7	0.3
	3:30–4:00	45.5	38.9	—	8.30	—	—	5.7	17.7	0.3
	4:00–4:30	46.1	41.5	1.39	8.38	8.8	8.1	6.0	15.6	0.4

Abbreviations: C_{Cr} = exogenous creatinine clearance; S_{Mg} = serum magnesium; S_{Ca} = serum calcium; S_P = serum phosphorus; C_P = phosphate clearance.

TABLE II

Detailed Protocol of Two Experiments, One without (Control) and One with $MgCl_2$ (i.v. Mg), Carried out in Dog No. 8 between 2:00 p.m. and 9:00 p.m.

Time	C_{Cr}		S_{Mg}		S_{Ca}		S_P		$\frac{C_P}{C_{Cr}} \times 100$	
	Control	i.v. Mg	Control	i.v. Mg	Control	i.v. Mg	Control	i.v. Mg	Control	i.v. Mg
	ml/min		*mg/100 ml*		*ml/min*		*mg/100 ml*			
p.m. 12:30	Oral water load, 500 ml									
1:00	Anesthesia with pentobarbital									
	Priming dose of creatinine (500 mg)									
	Infusion started: 7 mg creatinine/min delivered in 0.45% saline at 1 ml/min									
2:00–2:20	68.1	60.5	1.59	1.80	10.8	10.2	5.2	4.4	12.0	25.4
2:20–2:40	69.0	56.7	1.68	2.00	10.8	10.2	5.2	4.5	11.7	26.3
2:40–3:00	65.9	56.0	1.54	1.90	10.5	10.2	5.1	4.4	13.0	27.6
3:00	In i.v. Mg experiment, $MgCl_2$ added to infusate to deliver 100 μg mg/kg per min									
3:00–3:30	56.4	56.8		2.43				4.0	18.1	15.8
3:30–4:00	54.8	66.0	1.61	3.76	10.8	10.1	5.0	4.0	20.4	5.9
4:00–4:30	54.9	59.3		4.96				4.3	17.8	4.6
4:30–5:00	59.7	56.9	1.68	5.79	10.8	9.6	4.9	4.5	12.2	4.0
5:00–5:30	62.6	53.9		6.40				5.0	12.0	3.2
5:30–6:00	65.4	57.0	1.60	7.20	10.5	9.4	4.7	5.3	15.3	2.5
6:00–6:30	65.3	52.6		7.73				5.3	13.0	2.3
6:30–7:00	53.1	51.3	1.53	8.00	10.8	9.3	4.9	5.3	14.3	1.5
7:00–7:30	66.9	53.0		8.67				6.0	13.6	1.4
7:30–8:00	63.3	57.7	1.40	9.03	10.8	8.8	5.1	6.1	14.2	2.1
8:00–8:30	51.6	55.1		9.33				6.5	21.9	2.9
8:30–9:00	64.3	56.7	1.49	9.54	10.5	8.3	5.1	7.0	16.8	3.8

Abbreviations: C_{Cr} = exogenous creatinine clearance; S_{Mg} = serum magnesium; S_{Ca} = serum calcium; S_P = serum phosphorus; C_P = phosphate clearance.

and 2). The fraction of filtered phosphate excreted (C_P/C_{Cr}) is usually high in the early morning hours, and it decreases to a nadir between 11 a.m. and 1 p.m.; C_P/C_{Cr} then increases gradually to reach the same values observed during early morning hours between 3:00 p.m. and 4:00 p.m. Fractional phosphate excretion either remains stable or increases slightly thereafter. The possibility that prolonged anesthesia of 8 hr may have affected the pattern of phosphate excretion could not be excluded. In contrast to the results in the intact dogs, the fraction of filtered phosphate excreted fell in the afternoon hours in the T-PTX dogs. It is possible that the diurnal excretory pattern of phosphate may be altered by thyroparathyroidectomy.

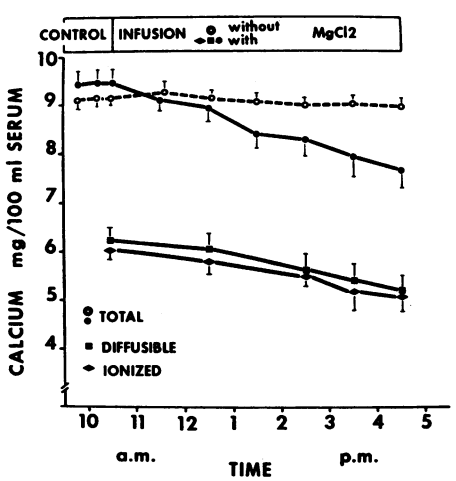

FIGURE 3 The effect of $MgCl_2$ infusion on the mean levels of total, diffusible, and ionized serum calcium in the serum intact dogs shown in Fig. 1. The brackets indicate ±1 SE.

The detailed protocols of an experiment with magnesium chloride infusion and its paired control study, both initiated during the morning hours, are presented in Table I, and representative protocols of similar studies began in the afternoon hours are shown in Table II. The summaries of the morning and afternoon experiments are depicted in Figs. 1 and 2, respectively. The concentrations in serum of total, diffusible, and ionized calcium in seven dogs receiving an infusion of $MgCl_2$ from 10:30 a.m. to 4:30 p.m. are presented in Fig. 3. The infusion of $MgCl_2$ caused a gradual increase in the

TABLE III

Detailed Protocol of an Experiment with $MgCl_2$ and the Intramuscular Injection of Parathyroid Extract Carried Out in Intact Dogs between 9:30 a.m. and 4:30 p.m.

	Time	C_{Cr}	S_{Mg}	S_{Ca}	S_P	$\frac{C_P}{C_{Cr}} \times 100$
		ml/min	*mg/100 ml*	*mg/100 ml*	*mg/100 ml*	
a.m.	8:00 Oral water load, 500 ml					
	8:30 Anesthesia with pentobarbital Primary dose of creatinine (500 mg) Infusion started: 7 mg creatinine/min delivered in 0.45% saline at 1 ml/min					
	9:30–9:50	37.5	1.34	8.8	4.6	25.3
	9:50–10:10	37.5	1.34	8.8	4.6	21.1
	10:10–10:30	37.0	1.47	8.8	4.6	17.6
	10:30 $MgCl_2$ added to infusate to deliver 100 μg mg/kg per min Intramuscular injection of 200 U of parathyroid extract					
	10:30–11:00	39.1	1.97	—	5.2	24.3
	11:00–11:30	39.2	2.10	8.7	5.1	30.6
	11:30–12:00	43.2	4.59	—	5.2	31.3
p.m.	12:00–12:30	38.6	5.88	9.0	5.4	39.4
	12:30 Intramuscular injection of 200 U of parathyroid extract					
	12:30–1:00	36.9	6.55	—	5.5	44.3
	1:00–1:30	36.4	6.82	9.3	5.5	32.7
	1:30–2:00	38.5	7.70	—	6.1	35.6
	2:00–2:30	36.9	8.03	9.6	6.1	39.2
	2:30 Intramuscular injection of 200 U of parathyroid extract					
	2:30–3:00	37.9	8:40	—	6.5	37.9
	3:00–3:30	38.8	9.10	9.9	6.8	33.6
	3:30–4:00	38.2	9.73	—	7.0	35.2
	4:00–4:30	38.6	10.26	10.2	7.5	30.0

Abbreviations: C_{Cr} = exogenous creatinine clearance; S_{Mg} = serum magnesium; S_{Ca} = serum calcium; S_P = serum phosphorus; C_P = phosphate clearance.

serum concentration of total magnesium to levels of 8–11 mg/100 ml at the end of the experiment; since there was no significant change in the per cent diffusibility of serum magnesium, the increments in levels of diffusible magnesium were proportional to changes of the total concentration of this ion. The hypermagnesemia was associated with a decrease in the concentration of total serum calcium of 1.0–2.4 mg/100 ml and a proportional fall in levels of the diffusible and ionized fractions of calcium. The decrement in the concentration of serum calcium was gradual, and the mean value for the entire group was significantly lower than the control level by the 5th hr of $MgCl_2$ infusion ($P = 0.02$).

The serum concentration of inorganic phosphorus increased from 4.0 ±0.37 to 6.8 ±0.58 mg/100 ml (mean ±SE) in the morning studies and from 4.9 ±0.20 to 8.1 ±0.91 mg/100 ml in the afternoon studies. Despite this increase in the level of serum phosphorus and the subsequent rise in filtered phosphate, the fraction of filtered phosphate excreted fell markedly and remained low as long as the magnesium infusion was continued. In studies initiated in the morning hours, the fall in C_P/C_{Cr} during the first 2 hr of the $MgCl_2$ coincided with the decrease in C_P/C_{Cr} observed as part of the normal diurnal variation; therefore, it was not possible to assess the level of serum magnesium at which a change in C_P/C_{Cr} had first occurred. However, the studies started in the afternoon hours would allow such an evaluation. When the concentration of serum magnesium increased by 2.0–3.0 ml to levels of 3.5–4.5 mg/100 ml, there was a significant fall in C_P-C_{Cr} ($P < 0.01$).

When parathyroid extract was administered to four animals receiving $MgCl_2$ infusion, the concentration of serum calcium rose by 1.0–2.0 mg/100 ml (from 8.9 ±0.16 to 10.4 ±0.44 mg/100 ml). The levels of serum phosphorus increased from 4.1 ±0.42 to 6.9 ±0.30 mg/100 ml, and the magnitude of this increase was similar to that observed in experiments with only $MgCl_2$ infused. Fractional phosphate excretion increased to more than 250% of values observed before PTE administra-

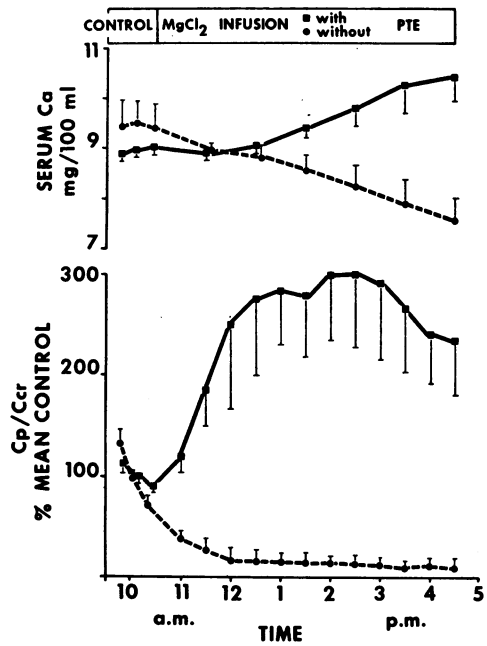

FIGURE 4 The mean values of serum calcium (Ca) and the changes in the fraction of filtered phosphate excreted (C_P/C_{Cr}) in four intact dogs receiving $MgCl_2$ infusion (100 μg Mg^{++}/kg per min) with and without the administration of parathyroid extract (PTE). The changes in C_P/C_{Cr} are expressed as in Fig. 1.

tion. The per cent change in C_P/C_{Cr} noted in dogs receiving $MgCl_2$ and PTE was significantly different from that observed in the same dogs receiving only $MgCl_2$. A detailed protocol of an experiment with the administration of $MgCl_2$ and PTE is presented in Table III. The changes in the concentration of serum calcium and in C_P/C_{Cr} observed in four dogs receiving $MgCl_2$ infusion, with and without PTE administration, are shown in Fig. 4.

Representative experiments in a T-PTX dog, with and without $MgCl_2$ infusion, are shown in Table IV. The summary of changes in the concentrations of serum calcium and in C_P/C_{Cr} in all such studies is presented in Fig. 5. The infusion of $MgCl_2$ caused a significant rise in the concentration of serum phosphorus (from 5.5 $\pm$0.37 to 7.4 $\pm$0.21 mg/100 ml) and a slight decrease in the levels of serum calcium. However, in these T-PTX animals, the levels of serum calcium and the changes in C_P/C_{Cr} were not different during $MgCl_2$ infusion from observations made in control studies carried out without $MgCl_2$ infusions in the same dogs.

The infusion of 40 μg Mg^{++}/kg per min caused a smaller rise in the concentration of serum magnesium to 4.27 $\pm$0.07 mg/100 ml after 3 hr of the infusion; by this time, serum calcium had fallen from 10.8 $\pm$0.14 to 9.8 $\pm$0.26 mg/100 ml and C_P/C_{Cr} had decreased markedly (Table V). This fall in C_P/C_{Cr} was significant ($P < 0.05$) after serum magnesium had increased by 1.7–2.0 mg/100 ml to a mean level of 3.28 $\pm$0.09 mg/100 ml. Following the discontinuation of $MgCl_2$ infusion, there was a gradual fall in serum magnesium, serum calcium remained low, but C_P/C_{Cr} rose abruptly and often reached values greater than those seen before the infusion of $MgCl_2$ (Table V). A summary of four such experiments is presented in Fig. 6. These studies demonstrate that C_P/C_{Cr} may increase in the presence of relative hypocalcemia despite the same degree of hypermagnesemia which otherwise causes C_P/C_{Cr} to fall.

Detailed protocols of an acute experiment during T-PTX and of that with the infusion of $CaCl_2$ are presented in Tables VI and VII, respectively. The removal of the parathyroid glands was followed by a fall in the concentration of serum calcium by 1.0–2.0 mg/100 ml and by a marked decrease in C_P/C_{Cr}; the decrease in serum calcium level was significant ($P < 0.05$) by 2–3 hr after the removal of the parathyroid glands. The infusion of $CaCl_2$ with the subsequent hypercalcemia was also followed by marked fall in C_P/C_{Cr}. The pattern and the magnitude of changes in C_P/C_{Cr} following either thyroparathyroidectomy or calcium infusion closely resembled those observed during the infusion of $MgCl_2$ (Fig. 7).

DISCUSSION

Although certain data are available suggesting that hypermagnesemia may suppress the activity of the parathyroid glands in vivo, such an effect has not been established with certainty. Gitelman, Kukolj, and Welt (7) showed that the injection of magnesium chloride to nephrectomized rats resulted in a small but significant decrease in the serum concentration of ionized calcium when compared with nephrectomized rats receiving only saline; the injection of magnesium chloride did not affect the level of ionized calcium in the blood when given to hypocalcemic parathyroidectomized and nephrectomized rats. These data are consistent with the hypothesis that hypermagnesemia may suppress the activity of the parathyroid glands but are not conclusive. The possibility that hypermagnesemia may interfere with the action of parathyroid hormone on bone was not excluded. Buckle, Care, Cooper, and Gitelman (8) performed in vivo perfusion of isolated parathyroid glands of one sheep and three goats with a blood perfusate containing magnesium in a concentration of 3.0–5.7 mg/100 ml. A decrease in the level of parathyroid hormone (PTH) in the effluent blood occurred. However, only in two goats did the change in PTH concentration exceed 1 SD (1.6 ng PTH/ml) for their immunoassay for measuring parathyroid hormone; furthermore, in one of these goats, the correlation between the level of parathyroid in the effluent blood and the magnesium concentration in the perfusate was not statistically significant.

TABLE IV

Detailed Protocol of Two Experiments, One without (Control) and One with $MgCl_2$ Infusion (i.v. Mg), Carried Out in the Same Thyroparathyroidectomized Dog between 2:00 p.m. and 9:00 p.m.

Time	C_{Cr}		S_{Mg}		S_{Ca}		S_P		$\frac{C_P}{C_{Cr}} \times 100$	
	Control	i.v. Mg	Control	i.v. Mg	Control	i.v. Mg	Control	i.v. Mg	Control	i.v. Mg
p.m. 12:30	Oral water load, 500 ml									
1:00	Anesthesia with pentobarbital									
	Priming dose of creatinine (500 mg)									
	Infusion I started: 7 mg creatinine/min delivered in 0.45 saline at 1 ml/min									
2:00–2:20	69.0	59.8	1.50	1.47	7.4	7.6	5.8	4.9	10.3	15.7
2:20–2:40	69.0	66.8	1.54	1.50	7.4	7.6	5.7	4.9	9.5	14.9
2:40–3:00	70.0	67.2	1.53	1.54	7.4	7.5	5.4	4.9	8.5	12.3
3:00	In i.v. Mg experiment, $MgCl_2$ added to infusate to deliver 100 μg mg/kg per min									
3:00–3:30	82.0	71.3		2.75				4.7	8.3	6.0
3:30–4:00	84.5	74.7	1.51	3.85	7.4	7.4	4.4	4.4	1.2	6.1
4:00–4:30	85.4	72.5		4.65				4.4	1.7	5.7
4:30–5:00	79.0	77.4	1.49	5.60	7.4	7.5	5.1	4.5	2.4	2.6
5:00–5:30	78.2	72.7		6.70				4.7	1.9	1.8
5:30–6:00	80.5	68.6	1.45	7.35	7.3	7.3	5.3	4.9	1.8	1.8
6:00–6:30	85.4	76.5		8.25				5.6	4.8	2.3
6:30–7:00	79.3	76.4	1.48	9.35	7.4	7.3	5.0	5.8	6.0	6.5
7:00–7:30	81.5	80.7		10.15				6.10	6.3	8.4
7:30–8:00	83.2	77.7	1.48	10.85	7.3	7.4	4.9	6.40	8.0	9.0
8:00–8:30	84.0	78.1		11.55				6.90	10.2	12.0
8:30–9:00	85.1	80.8	1.50	12.10	7.3	7.4	4.9	7.30	8.6	14.6

Abbreviations: C_{Cr} = endogenous creatinine clearance; S_{Mg} = serum magnesium; S_{Ca} = serum calcium; S_P = serum phosphorus; C_P = phosphate clearance.

The results of the present study demonstrate that acute hypermagnesemia is associated with a significant decrease in the concentration of both total and ionized serum calcium, a rise in the level of blood inorganic phosphorus, and a marked fall in the fraction of filtered phosphate excreted. Theoretically, several mechanisms could be responsible for these changes. Magnesium infusion is associated with an increase in urinary calcium excretion (20–22), and such losses might conceivably cause a fall in serum calcium levels. Total urinary calcium excretion, which was measured in six dogs, varied from 25 to 90 mg over the entire 6 hr period of $MgCl_2$ infusion. This amount of calcium is less than the theoretical loss necessary to cause the observed decrease in serum calcium levels, calculated from the assumption that calcium is distributed in extracellular fluid; since this is a gross underestimate of the distribution of miscible calcium (23), it is apparent that the fall in the levels of serum calcium cannot be explained by the urinary losses of this ion.

Stimulation of secretion of calcitonin can produce a fall in serum calcium (24), and studies of Radde, Witterman, and Pensuwan (25) suggest that the early fall in levels of serum calcium caused by $MgCl_2$ in the rat could be due to enhanced secretion of calcitonin. How-

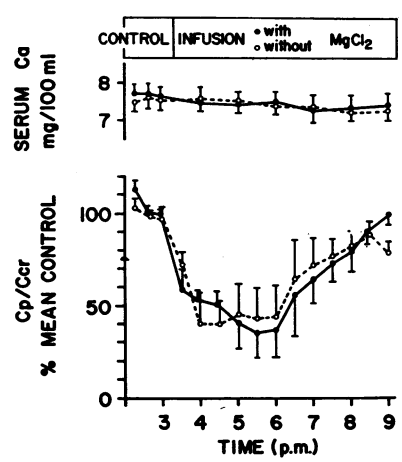

FIGURE 5 The changes in mean levels of serum calcium (Ca) and in the changes in the fraction of filtered phosphate excreted (C_P/C_{Cr}) in four thyroparathyroidectomized dogs without and with $MgCl_2$ infused (100 μg Mg^{++}/kg per min). The changes in C_P/C_{Cr} are expressed as in Fig. 1.

TABLE V

Detailed Protocol of an Experiment in Which a Smaller Amount of $MgCl_2$ was Infused into Intact Dog No. 8 for a Shorter Period of Time

Time	C_{Cr}	S_{Mg}	S_{Ca}	S_P	$\frac{C_P}{C_{Cr}} \times 100$
	ml/min	*mg/100 ml*	*mg/100 ml*	*mg/100 ml*	
p.m. 12:30	Oral water load, 500 ml				
1:00	Anesthesia with pentobarbital				
	Priming dose of creatinine (500 mg)				
	Infusion I started: 7 mg creatinine/min delivered in 0.45% saline at 1 ml/min				
2:00–2:20	50.0	1.74	11.2	5.0	25.5
2:20–2:40	52.4	1.69	11.2	4.9	26.4
2:40–3:00	52.8	1.68	11.1	5.0	23.0
3:00	Infusion II started: 40 ug mg/kg per min delivered in 0.45% saline at 1 ml/min				
3:00–3:30	54.2	2.04		5.1	15.3
3:30–4:00	57.4	2.87	10.5	4.7	9.8
4:00–4:30	48.8	3.16		4.7	5.5
4:30–5:00	58.1	3.72	10.3	4.9	1.5
5:00–5:30	46.2	4.08		5.4	1.4
5:30–6:00	58.1	4.13	10.0	5.6	2.6
6:00	Infusion II discontinued				
6:00–6:30	60.6	3.88		5.7	5.9
6:30–7:00	60.0	3.45	9.8	6.0	13.6
7:00–7:30	64.1	3.44		6.4	17.0
7:30–8:00	66.2	3.30	9.6	6.5	28.4
8:00–8:30	64.2	3.11		6.3	36.2
8:30–9:00	67.0	2.76	9.6	6.4	40.6

Abbreviations: C_{Cr} = exogenous creatinine clearance; S_{Mg} = serum magnesium; S_{Ca} serum calcium; S_P = serum phosphorus; C_P = phosphate clearance.

ever, perfusion of the thyroid glands of goats with blood containing a high concentration of magnesium failed to augment the secretion of calcitonin (26). In addition, studies reported by Kleeman, Bernstein, and Chapman suggest that the homeostatic regulation of the levels of serum calcium in the dog is not affected by removal of the thyroid glands (27). Following the administration of calcitonin, a decrease in serum calcium level occurs much more rapidly than was observed in the present study during the infusion of $MgCl_2$; furthermore, calcitonin does not cause a decrease in urinary excretion of phosphate (26). Although the present study does not exclude the possibility that infusion of $MgCl_2$ may stimulate secretion of calcitonin in the dog, it is unlikely that such an event could be responsible for the present results.

The fall in fractional excretion of phosphate observed during $MgCl_2$ infusion occurred at a time of the day when phosphate excretion is normally stable or rising. A decrease in C_P/C_{Cr} could either be due to a reduction in filtered phosphate or to enhanced tubular reabsorption of phosphate. During $MgCl_2$ infusion, glomerular filtration rate remained stable and the levels of serum phosphate increased; hence, filtered load of phosphate was elevated at a time when urinary excretion was falling, indicating an increase in the tubular reabsorption of phosphate.

Several features of the present study favor the conclusion that the infusion of $MgCl_2$ produces its effect on serum calcium and phosphate excretion through inhibition of the activity of the parathyroid glands. The effects of acute hypermagnesemia on the concentration of serum calcium and on phosphate excretion were similar to those observed after parathyroidectomy; and the changes in urinary phosphate which occurred with hypercalcemia, which is known to inhibit activity of the parathyroid glands (1–3), closely resembled those noted with hypermagnesemia. Furthermore, the elevation in serum calcium and the marked increase in fractional phosphate excretion which followed the administration of parathyroid extract to hypermagnesemic dogs indicate that hypermagnesemia, per se, does not interfere

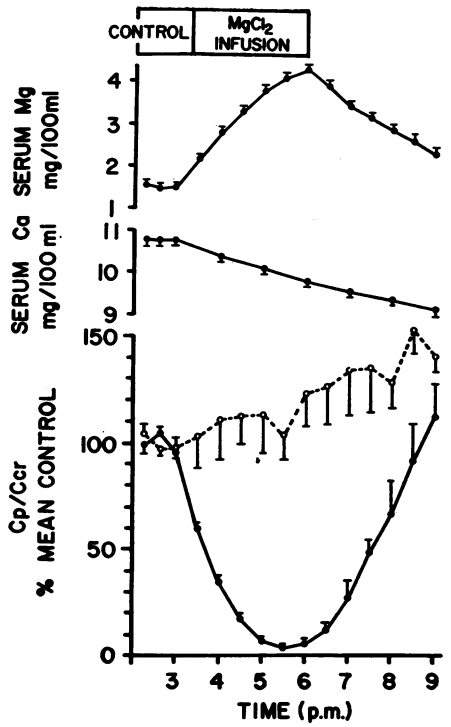

FIGURE 6 The mean levels of serum magnesium (Mg) and calcium (Ca) and changes in the fraction of filtered phosphate excreted (C_P/C_{Cr}) with a lower rate of magnesium infusion (40 μg Mg^{++}/kg per min) from 3 p.m. to 6 p.m. in the same four dogs shown in Fig. 2. The changes in C_P/C_{Cr} are expressed as in Fig. 1. The solid symbols (●) indicate observations with $MgCl_2$ and the open symbols (○), those without.

with the action of parathyroid hormone on its target organs, e.g., the skeleton and kidneys. Finally, hypermagnesemia failed to produce similar changes in serum calcium levels and phosphate excretion in thyroparathyroidectomized animals; this provides evidence that these effects of hypermagnesemia are mediated through the parathyroid glands and that hypermagnesemia, per se, does not significantly influence either the movement of calcium from bone or the excretion of phosphate by the kidneys. The mechanisms through which a rise in the concentration of magnesium in the blood may inhibit the activity of the parathyroid glands are not delineated in the present study; hypermagnesemia may inhibit the formation and (or) release of parathyroid hormone.

The rise in the concentration of serum phosphorus during hypermagnesemia is probably unrelated to the inhibition of the parathyroid glands or to the decrease in the urinary excretion of phosphate, since hyperphosphatemia occurred during hypermagnesemia, both in intact dogs receiving PTE and in the T-PTX animals. An increase in the level of serum phosphorus occurs

TABLE VI

Detailed Protocol of an Experiment with Thyroparathyroidectomy (T-PTX) Carried Out between 11 a.m. and 6:00 p.m.

	Time	C_{Cr}	S_{Ca}	S_P	$\frac{C_P}{C_{Cr}} \times 100$
		ml/min	*mg/100 ml*	*mg/100 ml*	
a.m.	8:15	Oral water load of 500 ml			
	9:00	Anesthesia with pentobarbital Priming dose of creatinine (500 mg) Infusion started to deliver 6 mg creatinine/min in 0.45% saline at 2 ml/min			
	10:00–10:20	55.4	9.8	5.2	17.5
	10:20–10:40	49.3	9.6	5.2	22.1
	10:40–11:00	52.1	9.6	5.0	23.8
	Thyroparathyroidectomy performed between 11:00 and 12:30 p.m.				
	11:00–11:30	44.4	9.7	4.7	23.0
	11:30–12:00	46.7	9.6	4.8	14.6
p.m.	12:00–12:30	42.8	9.3	4.9	6.8
	12:30–1:00	50.4	9.0	5.2	3.1
	1:00–1:30	53.7	8.8	5.0	3.4
	1:30–2:00	52.7	8.9	5.4	5.7
	2:00–2:30	54.3	8.6	5.8	0.7
	2:30–3:00	52.9	8.5	5.9	0.3
	3:00–3:30	48.9	8.5	5.8	0.9
	3:30–4:00	53.2	8.2	5.9	0.6

Abbreviations: C_{Cr} = exogenous creatinine clearance; S_{Ca} = serum calcium; S_P = serum phosphorus; C_P = phosphate clearance.

during calcium infusion, and this phenomenon has been attributed to a shift of phosphate from soft tissues to the extracellular space (28). It is possible that acute hypermagnesemia exerts a similar effect.

TABLE VII

Detailed Protocol of an Experiment with Calcium Infusion into an Intact Dog Carried Out between 9:20 a.m. to 5:00 p.m.

	Time	C_{Cr}	S_{Ca}	S_P	$\frac{C_P}{C_{Cr}} \times 100$
		ml/min	*mg/100 ml*	*mg/100 ml*	
a.m.	7:45	Oral water load of 500 ml			
	8:30	Anesthesia with pentobarbital Priming dose of creatinine (500 mg) Infusion I started to deliver 6 mg creatinine/min in 0.45% saline at rate of 2 ml/min			
	10:00–10:30	37.6	10.5	3.2	24.7
	10:30–11:00	39.6	10.8	3.2	22.5
	11:00–11:30	35.0	10.4	3.3	22.9
	11:30	Infusion II started to deliver 5 mg Ca^{++}/kg per hr in 0.45% saline at 1 ml/min for 3 hr			
	11:30–12:00	39.9	11.2	3.4	17.8
p.m.	12:00–12:30	38.1	12.0	3.6	11.8
	12:30–1:00	31.5	12.8	3.8	4.4
	1:00–1:30	32.3	13.3	3.8	1.5
	1:30–2:00	33.8	13.7	4.4	1.2
	2:00–2:30	33.7	14.6	4.8	0.5
	2:30	Infusion II discontinued.			
	2:30–3:30	33.6	14.3	4.6	0.2
	3:30–4:30	30.0	13.1	4.4	0.3
	4:30–5:30	31.0	12.7	4.2	0.5

Abbreviations: C_{Cr} = exogenous creatinine clearance; S_{Ca} = serum calcium; S_P = serum phosphorus; C_P = phosphate clearance.

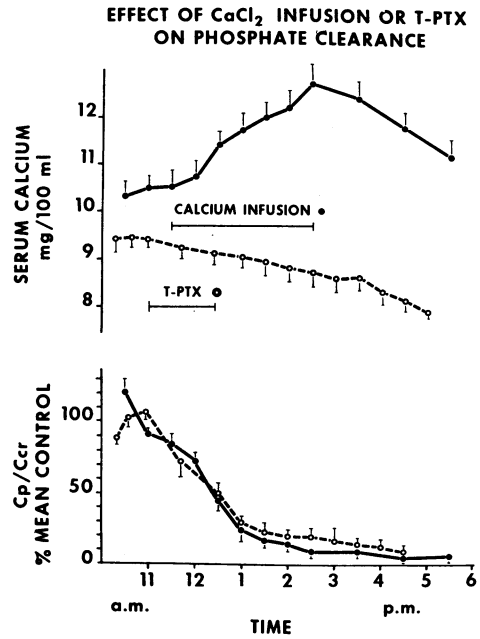

FIGURE 7 The changes in mean serum calcium and in the fraction of filtered phosphate excreted (C_P/C_{Cr}) with calcium infusion (seven dogs) and following thyroparathyroidectomy, T-PTX (seven dogs). The changes in C_P/C_{Cr} are expressed as in Fig. 1. The horizontal brackets encompass the period of time during which either calcium was infused or the parathyroid glands were surgically removed.

The results of the present study also permit an evaluation of the magnitude of increment in the concentration of serum magnesium which is required to inhibit the activity of the parathyroid glands. Data from the afternoon experiments, in which 100 μg Mg^{++}/kg per min was given, suggest that the activity of the parathyroid glands had already been suppressed as the concentration of serum magnesium increased by 2.0–3.5 mg/100 ml to levels of 3.5–5.0 mg/100 ml. Since the rate of rise in the level of serum magnesium was rapid in these experiments, it is possible that even a smaller increment in the concentration of serum magnesium may suppress the parathyroid glands. The results from the experiments in which a smaller amount of magnesium was infused (40 μg/kg per min), indeed demonstrate that a significant fall in C_P/C_{Cr} became evident with a rise in the level of serum magnesium of only 1.7–2.0 mg/100 ml and at a serum concentration of 3.1–3.5 mg/100 ml. Although alterations in C_P/C_{Cr} may be a sensitive index of changes in the function of the parathyroid glands, the measurement of the levels of the parathyroid hormone in the blood will permit a more precise evaluation of the minimal increment in the level of serum magnesium which is necessary to suppress the activity of the glands. Increments in the concentration of serum magnesium of 1.7–2.0 mg/100 ml may be encountered in man under certain physiological and pathological states (e.g. following ingestion of oral magnesium salts and in uremia); therefore, it is possible that the relation between the levels of serum magnesium and activity of the parathyroid glands has physiological significance.

McIntyre, Boss, and Throughton (29) suggested that an interrelationship between magnesium and parathyroid hormone is important in the regulation of serum magnesium level. The ability of the kidneys to alter urinary excretion of magnesium with changes in the concentration of magnesium in blood is probably one of the major factors controlling the serum level of this ion (30), and evidence has accumulated suggesting that parathyroid hormone causes enhanced renal tubular reabsorption of magnesium (22, 29). With hypermagnesemia and consequent inhibition of the parathyroid glands, tubular reabsorption of magnesium may fall with enhanced urinary excretion; hence, serum magnesium level would return toward normal.

In the present study, a small decrease in the level of serum calcium was associated with an increase in fractional phosphate excretion and, presumably, increased parathyroid activity, despite the presence of hypermagnesemia which was initially sufficient to decrease C_P/C_{Cr}. These observations suggest that a decrease in the levels of serum calcium is more potent than a rise in the level of magnesium in the regulation of parathyroid activity.

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