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Significance of Magnesium in Animals

Tohru Matsui

Magnesium (Mg) metabolism differs among animal species because the digestive system and feeds are different. The diseases related to Mg nutrition are rare in pigs and poultry under practical conditions because their diets are formulated as containing an appropriate level of Mg. On the other hand, Mg deficiency is not rare in grazing animals because Mg in pasture is affected by several factors such as soil and plant species and maturity, and thus Mg concentration is largely varied in pasture. Grass tetany in ruminants is induced by the reduction of Mg absorption resulting from low Mg intake with high potassium and nitrogenous compounds, and with the reduction of ruminal fermentation. Additionally, cold stress stimulates the incidence of tetany through decreasing Mg concentration in the cerebrospinal fluid. Excess Mg is one of the factors inducing urolithiasis in cats and cattle, and enterolithiasis in horses. However, Mg level in the practical diets alone cannot induce these diseases. Cat urolithiasis is developed in combination with alkaline urine, and cattle urolithiasis and horse enterolithiasis are developed in combination with high phosphorus intake. The diseases related to Mg nutrition are mainly developed in combination with other dietary factors and/or environmental factors in ruminants, horses, and cats.

Comparative Aspects of Magnesium Metabolism

The digestive system is widely different among animal species. Herbivores consume high fibrous feeds (rich in cellulose) originated from plants and their digestion is largely owing to microbial fermentation in the rumen (a forestomach) of ruminants, such as cattle and sheep, or in the large intestine of monogastric herbivores, such as horses and rabbits. These sites of microbial digestion are large because longer transit time is necessary for sufficient fermentation. Carnivores natively obtain most of their feed by eating other animals, and their digestion is mainly owing to digestive enzymes and microbial digestion is minimal. Thus, the alimentary tract is short and simple in carnivores. In omnivores such as dogs, pigs, and rats, both enzymatic and microbial

digestion are important and the structure of digestive tract is intermediate between carnivores and herbivores.

Apparent absorption of magnesium (Mg) is different among animal species (Table 31.1). Magnesium absorption is generally lower in ruminants than in other animals. In ruminants, sheep absorb Mg 1.7-times more efficiently than cattle because the ratio of surface area to content is higher in the major site of Mg absorption of sheep.[1] The efficiency of Mg absorption is higher in horses than in ruminants. Magnesium absorption is less in pigs than in rats. Dietary phytate (inositol hexaphosphate) is known to decrease Mg solubility in intestinal digesta of monogastric animals and suppresses Mg absorption.[2] Practical diets of pig contain whole grains, oilseed meals, and bran that are rich in phytate, but rats are usually given semipurified diets without containing phytate. Thus, Mg absorption may be different between these omnivore species. Because cats have a relatively short intestine resulting in a rapid passage rate of digesta, the digestibility for many natural feedstuffs is generally lower in cats than in rats and dogs.[3] The absorption of Mg also may be less in cats than in rats.

Ruminants mainly absorb Mg from the rumen.[4] The major site of Mg absorption is the distal small intestine[5] or the ileum and the colon[6] in rats. There have been few reports showing the major site of Mg absorption in other domestic animals. Pigs were reported to absorb Mg in the ileum and the colon.[7] Cats and dogs predominantly absorbed Mg from the large intestine.[8] The major site of Mg absorption was the small intestine in horses[9,10] and rabbits.[11]

There are two pathways for Mg absorption, that is, paracellular route and transcellular route.[6] The paracellular route consists of tight junctions and intercellular space between the epithelial cells, which depends on the passive driving force and the permeability of this route for Mg. The transcellular route consists of the influx through the apical membrane of epithelial cells and the

Table 31.1. Magnesium absorption in some species.

	Apparent absorption (% of intake)	Major site of absorption
Cattle	23.3 ± 7.8^{a}	Forestomach (rumen)
Sheep	32.8 ± 9.0^{b}	Forestomach (rumen)
Horse	51.2 ± 5.6^{c}	Small intestine
Pig	39.2 ± 9.7^{d}	Ileum and colon
Rat	60.8 ± 14.5^{e}	Ileum and colon
Cat	39.3 ± 12.9^{f}	Large intestine

Values are mean ± standard deviation (SD).

[a]Calculated from 35 publications in dairy cattle given diets containing appropriate amounts of magnesium and potassium.

[b]Calculated from 37 publications in lambs given diets containing appropriate amounts of magnesium and potassium.

[c]Calculated from seven publications in horses given diets containing sufficient amounts of magnesium.

[d]Calculated from 12 publications in growing pigs given diets containing sufficient amounts of magnesium.

[e]Calculated from 27 publications in growing rats given AIN diets.

[f]Calculated from 11 publications in cats given diets containing sufficient amounts of magnesium.

efflux across the basolateral membrane. The Mg concentration was 5 m*M* in the liquid phase of ileal digesta of pigs given a conventional diet[12] and the luminal Mg concentration ranged between 4 and 13 m*M* in the rumen.[13] The intracellular concentration of ionized Mg ranged between 0.5 and 1.0 m*M* in ruminal epithelial cells[14] and between 0.4 and 0.7 m*M* in Caco-2 intestinal cells.[15] Additionally, ionized Mg concentration is 0.4 to 0.6 m*M* in blood. Therefore, the intracellular concentration of ionized Mg is generally considered lower than its luminal concentration and is close to its concentration in blood. The entry of ionized Mg into the epithelial cells does not require energy but the efflux is energy dependent.[8]

Coudray and colleagues[16] suggested that the active transport of Mg was important only under conditions of extremely low dietary Mg in rats because the amount of absorbed Mg linearly increased with increasing dietary Mg up to the requirement level. Some researchers also reported that Mg was primarily absorbed by a passive diffusion at usual Mg intake in rats.[17,18] Additionally, metabolic inhibitors and an adenosine triphosphatase (ATPase) inhibitor did not affect transepithelial Mg transport, which also supported passive transport as the major route of Mg absorption.[19]

As reviewed by Schweigel and Martens,[8] ruminants mainly absorb Mg through transcellular route across the rumen epithelium by the secondary active transport. Ruminants obtain dietary energy as volatile fatty acids produced by ruminal microbes. Additionally, ruminal microbes degrade dietary nitrogenous components (protein and nonprotein nitrogen) to ammonia and they reconstitute protein from ammonia. The microbial protein largely contributes to protein nutrition of ruminants. Magnesium absorption increases with increasing readily fermentable carbohydrates in diets. The ingestion of readily fermentable carbohydrates rapidly raises ruminal concentration of volatile fatty acids and CO_2/HCO_3^-, which stimulate directly Mg uptake by the epithelial cells. The high intake of nitrogenous substances increases ruminal ammonia concentration through the fermentation because the degradation of dietary protein is higher than microbial protein synthesis in this condition, which transiently reduces Mg absorption. Additionally, the reduction of ruminal pH increases Mg absorption through rising Mg solubility. The concentrations of volatile fatty acids and ammonia affect ruminal pH and Mg absorption. The high concentration of potassium (K) in the rumen largely and directly suppresses Mg uptake by the epithelial cells.

Magnesium is endogenously excreted in both urine and feces. Urinary Mg excretion was largely more than the endogenous fecal excretion in sheep[20] and cats[21] given Mg at the requirement level. On the other hand, the endogenous fecal excretion was as much as urinary excretion in rats.[16] Horses secreted a half of absorbed Mg into the large intestine[10] or the endogenous fecal loss of Mg was more than urinary excretion in horses given Mg at its requirement level.[22] Urinary Mg excretion increases with dietary Mg in most animals and it is known that there is a good correlation between Mg absorption and its urinary excretion. The endogenous excretion into feces was reported to

increase with increasing dietary Mg in rats[16] and in sheep.[23] However, the relationship between dietary Mg and its endogenous excretion into feces is still controversial.

The concentration of Mg is approximately 5 m*M* in cow's milk. A cow producing 30 kg of milk would loss 150 mmol Mg/day into the milk, which approximately corresponds to half of absorbed Mg.[24] The Mg concentration in milk was relatively stable in Mg-deficient cows but the milk production decreased.[25] Rats secreted Mg into milk at approximately 40% of apparently absorbed Mg.[26] The Mg concentration was approximately 1.6 m*M* in mare's milk and mares lost Mg at 12 to 40 mmol/day into milk.[27] Lactating mares absorb 160 mmol Mg/day when dietary Mg is satisfied with its requirement.[28] Therefore, the absorbed Mg is fourfold more than its secretion into milk in horses. Lactation stimulates Mg absorption due to increasing feed intake and efficiency of Mg absorption. The positive balance of Mg may be maintained even in lactating cows when a sufficient amount of Mg is given.

Magnesium Deficiency

The main manifestation of Mg deficiency induces retarded growth, hyperirritability and tetany, peripheral vasodilation, anorexia, muscular incoordination, and convulsion.[29] Typical ingredients of feeds contain sufficient amounts of Mg and thus practical diets usually contain adequate Mg in many species and Mg deficiency is rare. Although the Mg concentration in forages generally satisfies its requirement of ruminants, the Mg concentration varies largely with plant species, maturity of plants, and with the soil and climate in which plants are grown. Therefore, Mg in forages is occasionally low and hypomagnesemia is observed in grazing herbivores. Hypomagnesemia in ruminants is classified into a rapidly developing type and a slowly developing type.[30]

Acute Type of Hypomagnesemia (Grass Tetany)

Grass tetany results from hypomagnesemia that occurs suddenly in early spring just after the initiation of grazing.[29] Grass tetany is seldom developed in horses grazing pastures that develop grass tetany in cattle.

The reduction of Mg absorption is considered as a major factor of the pathogenesis, which results from low Mg in diets and factors reducing Mg bioavailability. Grass tetany is found in areas where dairying or beef production is highly developed. Pastures in areas with intensive livestock production are generally rich in K and nitrogenous components due to frequent fertilization with manure. Grazing cattle on such pastures entails the risk of hypomagnesemia, primarily due to K-suppressing Mg absorption.[31] Additionally, excess nitrogenous components raise ruminal ammonia concentration, which reduces Mg absorption.[31]

The feed intake is reduced by the rapid change of environment after the initiation of grazing, which decreases Mg absorption. Lactating cows are more susceptible to development of grass tetany because of Mg secretion into milk. Furthermore, the susceptibility to grass tetany is increased in order ruminants. Bone Mg concentration is lower in order animals. The reduction of available Mg in bone was possibly related to the higher incidence of grass tetany in older cows.[32] The administration of a pyrophosphate analogue suppressed bone resorption in sheep, which did not affect plasma Mg concentration in sheep given an adequate amount of Mg[33] but the pyrophosphate analogue enhanced the reduction of plasma Mg concentration in sheep given a Mg-deficient diet.[34] On the other hand, Robson nd colleagues[35] reviewed the relationship between bone resorption and the plasma Mg concentration and they suggested that bone Mg was not important for maintaining the plasma Mg concentration. Therefore, the relationship between bone resorption and the incidence of hypomagnesemia is not clear in old ruminants. The Mg absorption was low in old ruminants,[36] which may be related to higher incidence of grass tetany in older animals.

The onset of grass tetany is more closely associated with the Mg concentration in the cerebrospinal fluid (CSF) than with blood Mg. The Mg concentration in CSF was lower in clinically affected cows than in nontetanic cows but plasma Mg concentration was almost similar between them.[37] The low Mg concentration in CSF was associated with alterations in monoamine concentrations in the central nervous systems that played an important role in both voluntary and involuntary motor function.[38] Therefore, the disturbance of monoamine concentrations was considered to play a role in the etiology of hypomagnesemic tetany.

The Mg concentration is higher in CSF than in plasma and the difference of Mg concentration is generated by its active transport. Mild hyperkalemia lowered Mg concentration in CSF of sheep.[39] Therefore, Mg influx into CSF may be inhibited by high concentration of K in blood. The initiation of grazing in early spring stresses animals through the rapid changes in environment. A stress reaction involving the adrenal–glucocorticoid axis increased circulating K concentration and lowered Mg transport across the choroidal plexus, which was one of causes of this disease.[35] Thus, dietary and environmental factors synergistically develop grass tetany.

Slow Type of Hypomagnesemia

Subclinical hypomagnesemia is observed in cattle for several months especially during winter. When a plasma Mg concentration reaches critically low level, it is accompanied by clinical symptoms such as moderate incoordination, tetany, and hyperirritability. This disease is called winter tetany.[40] Winter tetany is developed by low dietary Mg, low quality of feeds, and environmental stresses such as extremely cold and wet weather.[40] The reduction of energy intake suppresses ruminal fermentation, which decreases volatile fatty acids

and CO_2 concentrations, and elevates ammonia concentration in the rumen. Additionally, the reduction of energy intake increases ruminal pH because of high ammonia and low volatile fatty acid concentrations in the rumen. These changes decrease Mg absorption in the rumen.

Hypomagnesemia is observed in calves consuming whole milk for an extended period, particularly calves suckling cows that are subclinically hypomagnesemic. This disease is called milk tetany.[40] The etiology of this disease is a simple deficiency of Mg. The Mg requirement was calculated as 1.3 g/kg dry matter in a 75-kg suckling calf gaining at 1 kg/day.[41] Magnesium concentration was 1 g/kg dry matter in milk.[42] Therefore, the fast-growing calves may be susceptible to development of milk tetany. Additionally, Mg absorption decreases with growth, that is, 70% for a 50-kg calf and 30% for 75-kg calf[41] and hypomagnesemia occurs in older suckling calves.

Spontaneous atherosclerosis (AS) is considered to occur in almost all animal species, including wild ruminants. Although AS is rare in adult ruminants, AS is developed in calves consuming whole milk for an extended period. A sclerosis of arteries was also found in calves given artificial magnesium-deficient diets. The margarine-fed calves developed hypomagnesemia and severe arteriosclerosis that could be prevented with Mg supplementation. Thus, Mg deficiency is considered as a trigger of AS in calves.[43]

Excess Magnesium

Magnesium toxicosis has not been reported and does not appear in many animals given natural feedstuffs but would be most likely to occur using excess supplementation with Mg. On the other hand, excess Mg may induce urolithiasis of ruminants (Figure 31.1) and cats, and enterolithiasis of horses (Figure 31.2) in practical conditions. Excess Mg-induced uroliths are com-

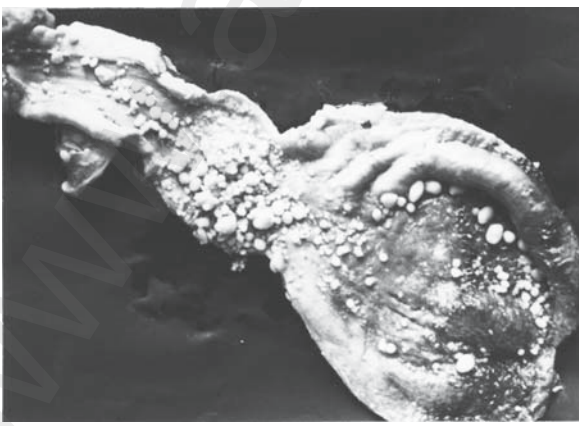

Figure 31.1. Uroliths in the bladder and urinary duct of beef cattle. (Courtesy of H. Yano, Kyoto University, Kyoto, Japan.)

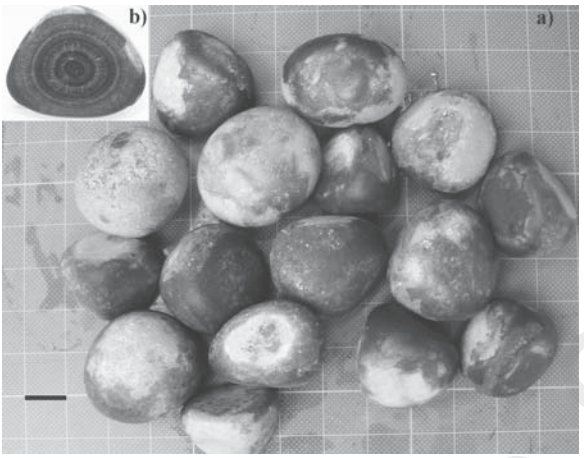

Figure 31.2. Enteroliths from the large intestine of a horse. Transverse section of an enterolith. Scale bar = 2 cm. (Courtesy of Y. Tajima and T. Ueno, Equine Research Institute, Japan Racing Association, Utsunomiya, Japan.)

posed of Mg ammonium phosphate (P) and are determined as struvite (Mg ammonium P hexahydrate) in cats and dogs. Crystallization of Mg ammonium P depends on the urinary concentration of its components, that is, the product of $[Mg^{2+}] \times [NH_4^+] \times [PO_4^{3-}]$ and urinary pH affecting NH_4^+ and PO_4^{3-} concentrations.[44]

Urolithiasis is an important clinical problem, especially in dogs and cats. Uroliths are mainly composed of struvite or calcium oxalate in these animals. Although the formation of struvite stone in dogs usually results from a urinary tract infection with urea-splitting microbes that increase urinary ammonium concentration, the majority of struvite uroliths are observed in sterile cats forming sterile urine.[45] Thus, the diet is the major causal factor inducing urolithiasis in cats. Since the cat evolved as a desert animal, it has the capacity to produce highly concentrated urine in order to conserve water. Cats usually consume diets rich in animal protein, which produces net amounts of acid from sulfur amino acids and acidifies urine. Urinary P and ammonia concentrations are higher in cats than in other animals, although urinary pH and Mg may be lower in cats than in other animals (Table 31.2).

Urinary Mg excretion increases with Mg intake in animals including cats. Excess Mg is linked to struvite urolithiasis. The dietary Mg over 0.35%

Table 31.2. Urinary concentrations of factors affecting struvite formation in some species.

	Magnesium m*M*	Phosphorus m*M*	Ammonia m*M*	pH	References
Cow	19	0.9	10.5	8.3	Vagnoni et al.[46]
Rat	19	12	45	6.97	Amanzadeh et al.[47]
Cat	3.1	81	118	6.37	Cottam et al.[48]

produced struvite urolithiasis.[49] Pet food industries reduce Mg content in commercial cat foods and Mg concentration ranges from 0.05% and 0.3% in many commercial cat foods. Thus, dietary Mg is not critical at present. Nevertheless, excess Mg should be avoided and low-Mg diets are considered advantageous in the prevention of struvite urolithiasis. Cats produce acidic urine with a pH of 6.0 to 7.0 in the normal situation. Struvite remains largely in solution below pH 6.6, while the crystallization may occur spontaneously if the urinary pH rises above 7.1.[50] High levels of dietary Mg did not induce urolithiasis when acidic urine was produced.[51] Therefore, urinary pH may be more important factor than the urinary Mg concentration in cats. However, urine acidification together with a low Mg intake increases the risk of calcium oxalate urolithiasis in cats.[52]

Ruminants ingest plant materials that contain large amounts of K and organic anions. Organic anions are protonated during catabolism and then oxidized to water and CO_2 (base forming), leaving K and HCO_3^- to be excreted into urine. Therefore, urinary pH is higher in ruminants than in some other animals (Table 31.2). The alkaline urine may also stimulate the development of urolithiasis in ruminants. Although the urinary Mg concentration is not high in cattle, excess Mg increases its concentration. Urinary P and ammonia concentrations are low in ruminants because they excreted mainly P and ammonia into the digestive tract via saliva (P and ammonia) or via transport across ruminal wall (ammonia). However, excess P and protein increase urinary P and ammonia. A field survey indicated that dietary Mg was positively correlated with both the morbidity and mortality rates due to urolithiasis in fattening lambs.[53] However, some researchers suggested that high dietary Mg per se did not develop urolithiasis and that high dietary P was required for the urolith formation in calves[54] and lambs.[55]

Enterolithiasis is a serious problem in horses. The enteroliths consist primarily of Mg ammonium P. Prominent clinical features were recurrent mild abdominal pain, gaseous distension, and minimal intestinal motility. Most obstructing enteroliths were found near the beginning of the small colon. Horses with enterolithiasis represented 15.1% of patients admitted for treatment of colic, and 27.5% of patients undergoing celiotomy for treatment of colic.[56] Enteroliths ranged from 200 g to 9 kg, but generally weighed 450 g to 3 kg.[57] Horses secrete Mg and P into the large intestine, which may stimulate the incidence of enterolithiasis. Wheat bran was reported as a dietary factor inducing enterolithiasis because of its high concentration of P and Mg.[58]

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