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MAGNESIUM TRANSPORT IN THE GASTROINTESTINAL TRACT

M. Schweigel and H. Martens

Department of Veterinary Physiology, Freie Universität Berlin, Oertzenweg 19b, 14163 Berlin, Germany

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1. ABSTRACT

Magnesium is an essential (macro) mineral in vertebrates with many biochemical and physiological functions including activation of enzymes, involvement into metabolic pathways, regulation of membrane channels and muscle contraction. Despite these important functions, Mg^{++} homeostasis is not regulated by hormones, but depends on absorption from the gastrointestinal tract, requirement of the body, and excretion via the kidneys. The present review summarizes data on epithelial Mg^{++} transport in the gut via paracellular and cellular pathways. Paracellular movement of Mg^{++} is only important in leaky epithelia as in the small intestine. The transcellular transport of Mg^{++}, luminal uptake and basolateral extrusion, require membrane proteins which increase the low permeability of the membranes and facilitate the movement of Mg^{++} through these lipid bilayers. Proposals have been made how these proteins could mediate Mg^{++} transport. There is now a growing body of evidence for a PD-dependent luminal Mg^{++} uptake via a carrier or channel. Furthermore, PD-independent uptake mechanisms have been demonstrated which may be represented by $Mg^{++}/2cation^{+}$ exchange or co-transport of Mg^{++} with anions. The mechanism of a basolateral extrusion is not clear. A Na^{+}/Mg^{++} exchange, well characterized in non-polar cells, has been suggested which leads to the proposal that there is a secondary active transport system for Mg^{++}. It can readily be learned from this fragmentary knowledge of transepithelial Mg^{++} transport that future research must be directed to a study of the relevant membrane proteins (carriers or channel for Mg^{++}) in order to close the gap between the incompletely described epithelial Mg^{++} transport mechanisms and the well established transport systems, e.g., sodium or glucose.

2. INTRODUCTION

Magnesium is an essential mineral in vertebrates and is the fourth abundant cation in the body, within the cell second only to potassium. It has long been known that a large number of enzymes, in particular those involving phosphate compounds such as ATPases, kinases and phosphatases, require Mg^{++} for activation (36). Mg^{++} is involved with several physiogical and biochemical processes including synthesis of RNA, DNA or protein and stabilization of membranes (102). Recently, it has been shown that Mg^{++} plays an important role in the regulation of membrane channels (81, 95) as well as excitation-contraction coupling in skeletal muscle (53). Knowledge of the functional compartmentation of intracellular Mg^{++} led to a better understanding of these multiple effects (35, 63).

It can be recognized from these many functions that Mg^{++} depletion causes disturbances which may have potentially serious consequences for patients (5) and which are life-threatening, for example in ruminants where hypomagnesemia leads to tetany (74).

Surprisingly, despite the essential role of Mg^{++} for many vital functions, Mg^{++} metabolism is not under control of hormonal regulation. The reasons for the missing hormonal regulation are not clear, but the consequences are quite evident: Mg^{++} homeostasis is mainly determined by (1) absorption from the gastrointestinal tract, (2) requirement of the body, and (3) excretion via the kidneys.

It is the intention of this review to summarize data on the first step of Mg^{++} homeostasis: Localization and mechanisms of epithelial Mg^{++} transport in the gastrointestinal tract. Transport of Mg^{++} across biological

membranes has comprehensively been reviewed (6, 25) and will only be considered under the aspect of comparative physiology. Mg^{++} absorption from the gut is influenced by certain dietary components, as reviewed by Brink and Beynen (11). Hardwick et al. (43) summarized data on the influence of vitamin D and Ca^{++} on Mg^{++} absorption.

3. INTESTINAL MG^{++} TRANSPORT

3.1.Mg^{++} intake and absorption

Despite the large variation of apparent Mg^{++} digestibility in all species, there is the general observation that Mg^{++} absorption increases almost linearly with increasing Mg^{++} intake (44, 72, 73). These results from different species are consistent with observations in humans within the usual range of Mg^{++} intake (2.0 - 7.5 mg / kg / day). Mg^{++} absorption increased proportionately with increases in Mg^{++} intake and the fraction of Mg^{++} absorbed remained constant (50). The constant proportion of Mg^{++} absorption is in contrast to Ca^{++} (44) and suggests that intestinal regulation of Mg^{++} absorption is absent or of minor importance. Indeed, Petith and Schedl (78) concluded from studies with rats that adaptation of Mg^{++} absorption in the small intestine to Mg^{++} deficiency is minimal and mainly consists of reduced secretion, which probably reflects paracellular Mg^{++} transport which depends on the blood Mg^{++} concentration. In sheep high (unphysiological) blood Mg^{++} concentrations due to continuous intravenous Mg^{++} infusion, depressed Mg^{++} absorption from the gastrointestinal tract as shown by conventional balance studies (2). It is possible that this reduced Mg^{++} absorption is caused by secretion into the small instestine, because we found a linear and positive correlation between the blood Mg^{++} concentration and net secretion into the entire small intestine (Martens, unpublished) and because neither hypo- nor hypermagnesemia changed net Mg^{++} absorption from the rumen of sheep (70).

Thus, the present data do not support the conclusion that Mg^{++} absorption from the gut is regulated by requirement or intake. There is some evidence that passive and very likely paracellular backflow (secretion) in the "leaky" small intestine correlates with blood Mg^{++} concentration and hence may have minor effects on net absorption.

3.2. Site of Mg^{++} absorption

Kayne and Lee (49) have carefully reviewed the literature on the site of Mg^{++} absorption and concluded from *in vitro* studies with rats that "the distal small intestine, in particular the ileum, and the colon are the site where bulk of Mg^{++} is absorbed". Evaluating the data from studies in man with the entire, undisturbed intestinal tract led to a slightly different conclusion. Cumulative absorption of Mg^{++} after an oral dose of $^{28}Mg^{++}$ supports the assumption that the main site of Mg^{++} absorption is the small intestine and that no absorption occurred in the colon (49). Indeed, the available data are confusing, because in rats Mg^{++} absorption has been demonstrated to take place in the small intestine (4, 19, 20, 62, 78, 83), the caecum (82, 85, 93) and the colon (71, 85). Furthermore, the demonstration of net Mg^{++} absorption in isolated segments of the intestine or the appearance of $^{28}Mg^{++}$ in blood following oral administration, do not give conclusive information regarding the physiological meaning of this transepithelial passage of Mg^{++}. Kayne and Lee (49) recognized this possible complication and stated that "where and when Mg^{++} absorption occurs can only be ascertained in an intestine in which the natural physiological conditions .....are not altered..". These required conditions are almost accomplished by using animals with fistulas at different locations in the gut. This methods permits the continuous determination of Mg^{++} flow rates along the gastrointestinal tract in undisturbed animals. The data obtained are much more reliable and have shown that the site of net disappearance varies between species. In dogs (87) and in cats (103), Mg^{++} is predominantly absorbed from the large intestine. Similar observations have been made in pigs (77), where the proximal part of the small intestine exhibits a net secretion of Mg^{++}, while net absorption occurs in the ileum and colon (77). In horses, Mg^{++} is mainly absorbed from the small intestine (46), which is probably also the case in rabbits (1). The forestomachs are the main site of Mg^{++} absorption in the gut of ruminants (97).

There is no doubt that studies with fistulated animals significantly improved the knowledge of the site of Mg^{++} absorption. Furthermore, infusion of Mg^{++} into the fistula of animals fed with a Mg-deficient diet gives us the information as to where Mg^{++} is absorbed and how important Mg^{++} absorption is distal to the site of infusion for Mg^{++} homeostasis. This approach was successfully used in sheep to demonstrate that the forestomachs are the main site of Mg^{++} absorption and that this is essential for Mg^{++} homeostasis (97). Postruminal infusion of Mg^{++} in sheep fed a Mg-deficient diet did not normalise blood Mg^{++} concentrations (97), indicating that absorption of Mg^{++} from the small and large intestine is negligible and does not contribute to Mg^{++} homeostasis in these species (34, 97). These findings lead to a totally new understanding of Mg^{++} absorption and homeostasis in ruminants and significantly advanced knowledge of the pathogenesis of hypomagnesemia in this species.

Hence conclusions regarding the site of Mg^{++} absorption should rely on measurements of flow rates along the entire gastrointestinal tract. Even when the main site of Mg^{++} absorption has been determined with this method, the physiological meaning for Mg^{++} homeostasis can only be evaluated if the animal is fed with a Mg^{++} deficient diet and Mg^{++} is infused distal to the suggested absorption site. The response of blood Mg^{++} concentration to this experimental design gives the information where Mg^{++} is absorbed and how important the absorption site is. These criteria have only be fulfilled in studies with ruminants. However, indirect conclusions can be made for man. Patients with a severe short bowel syndrome exhibited very low or even negative net absorption of Mg^{++} (52) resulting in hypomagnesemia (91). Studies of primary hypomagnesemia in man lead to the suggestion that "the abnormality in these patient is a defect in carrier-mediated transport of magnesium (in the small intestine) from low intraluminal concentrations of magnesium" (75).

3.3. Principles of epithelial transport

3.3.1. Transepithelial pathways

It is generally accepted that epithelia lining the gut have the capability of absorbing water, nutrients and electrolytes and serve as barriers between the lumen and the internal milieu of the body (79). The major structures of the functional barrier are the epithelial cells and the tight-junctional complex between these cells.

Two routes of movement of solutes have been described in epithelia. A paracellular pathway (shunt) between the cells consisting of tight junctions and the intercellular space. Magnitude and direction of flow of a solute through this pathway depends on the passive driving forces and the permeability of the shunt for the solute. The transcellular route includes uptake across the luminal and the extrusion across the basolateral membrane. Because hydrophilic compounds such as Mg^{++} permeate very poorly across (lipid) cell membranes of the enterocytes, transport proteins in the luminal and basolateral membrane of epithelial cells are necessary for transcellular transport (absorption) of Mg^{++}. Furthermore, Mg^{++} uptake across the luminal and extrusion across the basolateral membrane must be considered under the aspect of the underlying driving forces in order to distinguish between passive and active (primary or secondary) transport.

3.3.2. Transport proteins

Studies of the transcellular transport of hydrophilic solutes across two (lipid) membranes in series have very early led to the conclusion that these membranes must have the capability to increase the low permeability for solutes. This suggestion was first substantiated by the observation of Koefoed-Johnsen and Ussing in frog skin (51). These authors proposed that, for electrogenic Na transport in frog skin, there is a selective permeability for Na in the apical membrane ("outside surface"), which allows the diffusion of Na into the cell, as well as a mechanism for active transport in the basolateral membrane ("inner border"). This so called Koefoed-Johnsen Ussing model of transepithelial Na transport has been confirmed for many tissues (for review see 32) and is now generally accepted for transepithelial transport of electrolytes and nutrients. Research activities were then focussed on characterization of membrane components which permit the passage of hydrophilic solutes. These efforts led to the proposal and final verification of the existence of membrane proteins which serve as carriers, channels or pumps. The "selective permeability" of the apical membrane of frog skin mentioned above turn out to be a Na^+ channel which is now known to consist of a primary structure (15) with three homologous subunits (16). It is well established that the "active mechanism in the basolateral membrane" is represented by the Na,K-ATPase or Na pump which uses the energy from the hydrolysis of one molecule of ATP for the transport of three Na^+ ions out of the cell in exchange for the uptake of two K^+ ions. In addition the primary structures of the Na,K-ATPase including isozymes are known (9). Similar progress has been made in understanding transepithelial glucose transport (99) which finally lead to the differentiation between "primary" (sodium) and "secondary" (glucose) active transport.

Unfortunately, this rapid advancement of knowledge in epithelial solute transport does not or only to a small extent, apply to Mg^{++}. We are only at the beginning of the discussion of the possibility of involving membrane proteins as carriers or channels for Mg^{++} (see below).

3.3. Driving forces

The determination of intracellular Mg concentrations, $[Mg_i^{++}]$, in a variety of tissues or cells with dyes or microelectrodes has consistently shown that $[Mg_i^{++}]$ is within the range of 0.5 – 1.0 mM (14, 21, 94) and hence close to the extracellular concentrations. Since all cells exhibit an intracellular negative potential difference, $[Mg_i^{++}]$ is far below its Nernst equilibrium. Consequently, luminal Mg^{++} uptake (as an ion) driven by the electrochemical potential into an epithelial cell is passive, whereas basolateral extrusion of Mg^{++} out of the cell is an active transport. This simple approach for uptake and extrusion becomes more complicated if exchange or co-transport systems are involved (see below).

3.4. Magnesium transporting epithelia

Epithelia for transporting Mg^{++} are found in the gastrointestinal tract (4, 7, 47, 64,101) and in the kidney (21, 29, 80) of mammals and fish. Interest in the mechanisms of Mg^{++} transport across gastrointestinal epithelia stems from their ability to absorb or secrete Mg^{++}, thereby supporting whole body Mg^{++} balance.

The transepithelial mechanisms of Mg^{++} transport are even more complex than those across single membranes. These complexities arise because there are transcellular and paracellular pathways for Mg^{++} transport and because epithelial cells do not have homogeneous cell membranes. Instead, the apical membrane facing the external environment, e.g. the lumen of the gut, has functional properties different from the basolateral membrane facing the internal environment, the interstitial fluid.

The different segments of the gastrointestinal tract are characterized by different permeabilities to water and electrolytes. These marked differences are related to the properties of the paracellular or shunt pathway and therefore to the properties of tight junctions. Hence, net intestinal Mg^{++} absorption or secretion is not only determined by cellular mechanisms but also results from passive Mg^{++} flux across the paracellular shunt pathway, which could be the predominant pathway in leaky epithelia. Studies of net Mg^{++} transfer in leaky epithelia always raise the question of how much Mg^{++} is transported via the paracellular and how much via the transcellular routes.

3.4.1. Paracellular Mg^{++} transport

Passive Mg^{++} movement might be most effective in leaky epithelia of the gastrointestinal tract proximal segments (small intestine), where only a small fraction of the total tissue conductance can be attributed to transcellular ion flow across the mucosal and serosal membranes; the remainder (at least 85%) is a consequence of ion movements, mainly of Na^+, K^+ and Cl^-, through high

Table 1: Kinetic parameters for saturable Mg^{++} transport in the gastrointestinal tract

K_m (mM)	V_{max}	Tissue/ preparation	Species	Reference
1.64	1.79 nm · mg^{-1}· $5s^{-1}$	Ileum, BBMV	rabbit	47
12.3	-	isolated mucosa, jejunum	man	8
4.50	91 nm · cm^{-2} · min^{-1}	in vivo perfusion, jejunum	man	75
0.52	76 nm · cm^{-2} · min^{-1}	isolated mucosa; colon	rat	48
2.43	208.3 nm · cm^{-2}· h^{-1}	isolated mucosa; rumen	sheep	68

conductance, low resistance (120 Ω · cm^2) extracellular pathways (30). Actually, most results from *in vivo* and *in vitro* studies of Mg^{++} transport in duodenum, jejunum or ileum are interpreted to reflect passive Mg^{++} transport across the intercellular route, driven by electrochemical gradients (8) or solvent drag (4).

The parallel rise of net Mg^{2+} absorption with dietary Mg^{2+} content, as discussed above, is suggestive of absorption of Mg^{2+} predominantly by a passive diffusional process. This interpretation is in agreement with *in vitro* studies in which the transepithelial steady state Mg^{++} transport has been measured by the everted gut sac method (44, 83) or by using isolated epithelia (8). The serosal-mucosal (S/M) ratio for Mg^{++}, determined at different extracellular [Mg^{++}] from 0.1 to 3 mM, was not greater than 1 at any concentration studied. In contrast, active Ca^{2+} transport has been clearly demonstrated for the duodenum with a $^{45}Ca^{++}$ S/M ratio of 2.65 (44). Even at concentrations well below the K_m (Table 1), calculated for a saturable component of Mg^{2+} transport in the small intestine, Mg^{++} is not concentrated against a chemical gradient (44). These authors also examined the initial luminal uptake characteristics of Mg^{++} by the intact duodenal epithelium of rats at different ages and demonstrated that Mg^{++} uptake by the duodenum was entirely concentration dependent and fully described by a linear, nonsaturable component. This observation is confirmed by studies of Birch et al. (8) who found that the transepithelial transport of Mg^{++} increased linearly up to 200 mM Mg^{++} and was not influenced by metabolic inhibitors or ouabain, an ATPase inhibitor.

Unidirectional flux measurements of Mg^{++} *in vitro* in the absence of electrochemical gradients have shown that diffusive movement across the paracellular shunt also plays an important role in net Mg^{2+} transport in the descending rat colon (48). As expected for a merely diffusive process, Mg^{++} flux from serosa to mucosa was totally voltage dependent and increases linearly with the Mg^{++} concentration. 63% of the total mukosal to serosal (ms) Mg^{2+} flux measured across the short circuited epithelium was voltage-dependent and may represent paracellular passive diffusion. However, there was also a saturable, cellular mediated component.

Behar (4) has pointed out that another mechanism of paracellular solute movement, the solvent drag effect, is of great importance in the regulation of intestinal Mg^{2+} transport. The author demonstrated that magnitude and direction of water movement have a marked influence on Mg^{++} transport in the rat ileum and colon. Net transfer took place almost exclusively in the presence of net water absorption. Since the rate of water absorption was a linear function of net solute transport, the influence of a given solute on net Mg^{++} absorption was proportional to its ability to generate passive water transport across the ileal and colonic epithelium. Mg^{++} transport was enhanced by the transport of sugars, urea and by osmotic pressure (hypotonic mannitol solutions). The effect of sugar was not dependent on the transport of the sugar or metabolic energy, but was constantly coupled to an increase in net water flow.

These data support the assumption that flow and direction of passive Mg^{++} transport through the paracelluar pathway is solely determined by electrochemical gradients or flow of water. However, these results do not mean that the passive Mg^{++} flux through the intercellular route is completely unregulated. There is a growing body of evidence that Mg^{++} absorption is related to luminal [Mg^{++}] in a curvilinear fashion (8, 10, 44, 75). As is discussed by some investigators (44, 49), these changes in the transport rate (changes in the slope of the curve) may reflect a progressive “tightening” of the junction complex induced by exposure to increasing [Mg^{++}], which could reduce solute transport through the paracellular pathway. The effect of luminal Mg^{++} exposure on changes in ultrastructure and functional permeability of the intestinal junction complex has been demonstrated by Tidball (96). Observations consistent with such an effect of Mg^{++} include the finding that Mg^{++} caused reversible changes in flux rates of paracellular markers as well as the morphology of the junction complex. Fluid and solute traffic through the intercellular route was increased in the absence of Mg^{++} and decreased in the presence of high Mg^{++} (10).

3.4.2. Transcellular Mg^{++} transport

Net movement of an ion in the absence of electrochemical gradients and its dependence on metabolic energy has been taken as evidence for the presence of an active, presumably cellular, mechanism. According to these criteria, Mg^{++} transport in the mucosal-serosal direction is partly cellular in the ileum and colon of the rat and in the forestomachs of ruminants, whereas Mg^{++} flux in the reverse direction is purely diffusive in all these tissues (47, 48, 67).

Transcellular intestinal Mg^{++} transport (or absorption) may be regarded as a three-step process, consisting of (1) entry into the epithelial cell from the lumen, (2) transit through the cytosol and (3) extrusion from the cell, across the basolateral membrane.

The entry of Mg^{++} into the intestinal cell across the brush border or apical membrane requires no metabolic energy, since Mg^{++} moves down a steep electrochemical gradient.

The concentration of Mg^{++} in the lumen is variable, but in the range of 0.5 – 2 mM in the fasting state and up to 45 mM following feeding (24). Although total cellular Mg^{2+} is relatively high (3 – 6 mM/mg wet weight; 3, 8), the intracellular free magnesium concentration, $[Mg^{++}]_i$ is maintained at 0.4 to 1 mM (89). In addition to this concentration difference, there is a significant negative potential difference from outside to inside the cell. The fact that Mg^{2+} entry is saturable at high levels of luminal Mg^{++} (10) suggests, besides possible regulation of the tightness of the junctional complex (49), the involvement of a Mg^{++} channel or carrier (75, 84); however there is very limited evidence for the existence of such transport proteins.

Small intestine: Behar (4) postulated for the rat ileum and colon passive diffusive Mg^{++} uptake into the epithelial cells because he found net tissue accumulation of Mg^{++} in parallel with intercellular transport by solvent drag. Birch et al. (8) also demonstrated net tissue accumulation of Mg^{++} in guinea pig and human ileum at mucosal Mg^{++} concentrations above 8 mM. Furthermore net Mg^{++} efflux from the serosal side of the isolated intestinal mucosa was much larger than mucosal efflux. This effect was abolished by the metabolic inhibitors dinitrophenol (DNP) and sodium fluoride (NaF). Milla et al. (75) used balanced and steady state perfusion techniques to study Mg^{++} transport in human small intestine. In normal children, they demonstrated a curvilinear relationship between rate of absorption at low luminal Mg^{++} (1,2, and 4 mM). A linear relationship was obtained at higher luminal Mg^{++} concentrations (6 and 10 mM). The authors suggest two separate transport systems for Mg^{++} absorption in the small intestine: a carrier mediated system which is saturated at low intraluminal Mg^{++}, and a simple diffusional process. The existence of a carrier-mediated transport is supported by the finding that a patient with primary hypomagnesemia showed net loss of Mg^{2+} to the lumen if luminal Mg^{++} was 1 or 2 mM, and hence in the saturable range of the uptake process. Jüttner and Ebel (47) used brush border membrane vesicles (BBMV) of rabbit ileum to study Mg^{++} transport with the aid of the fluorescence probe mag-fura-2. They are the first authors who showed that there was a saturable uptake of free Mg^{++} across the luminal membrane (K_m= 1.64 mM; V_{max}= 1.79 nm/mg protein/5 s). This Mg^{++} uptake was electrically silent and modulated by the anion gradient across the brush border membrane. An outward-directed anion gradient stimulated Mg^{++} influx and the Mg^{++} transport rate depended on anion permeability (SCN^- > Cl^- > SO_4^{2-}). These findings may reflect the fact that Mg^{++} uptake is mediated by a Mg^{++}/anion complex.

Table 1 summarizes kinetic parameters of possible cellular transport systems. The obvious large variability my be explained by the variety of methods and species used. However, it should be kept in mind that *in vitro* total Mg^{++} uptake – with the exception of that calculated by Jüttner and Ebel (47) - was not corrected for Mg^{++} binding, and that in the *in vivo* perfusion experiments saturable Mg^{++} absorption may be due in part to a reduction of the tight junctional permeability.

Furthermore, it should be noted that cellular uptake and transcellular transport are not necessarily linked. It may be that the uptake mechanism observed in the brush border operates to maintain relatively constant Mg^{++} concentrations in cells of the epithelium. This view is supported by data from Birch et al. (8). These investigators showed that overall tissue Mg^{2+} concentration was maintained at a constant level, despite wide fluctuations in extracellular Mg^{2+}; only when $[Mg^{2+}]_o$ reached 50 mM were significant changes observed.

Mg^{++} transport in the colon: Karbach (48) demonstrated, across the descending colon of the rat, the existence of a voltage independent, cellular component of Mg^{++} transport in the mucosal-serosal direction. This cellular fraction of Mg^{++} transport accounted for only 37% of the J_{ms} Mg^{++} flux under short circuited conditions with a K_t of 0.52 ± 0.44 mM and V_{max} of 76.4 ± 34.9 nM/cm^2/hr. Short chain fatty acids (SCFA) stimulated Mg^{++} and K^+ absorption in the distal colon (61). Because it is known that SCFA stimulate Na^+ (caecum, proximal colon) and K^+ absorption (distal colon) in those segments of the large intestine, where Na^+/H^+ and K^+/H^+ exchanger exist in the apical membrane of the epithelium, it has been proposed that the stimulating effect of SCFA on mucosal to serosal Mg^{++} transport is mediated by activation of an Mg^{++}/H^+ exchanger.

It has been speculated (6) that the transcellular pathway plays only a minor role in net Mg^{2+} absorption under normal conditions, because solvent drag via the paracellular pathway dominates as long as net solute and water movement across the colonic epithelium proceeds from lumen to blood. In contrast, during diarrhea the colon secretes water and solutes. Under these conditions osmotic water and solvent drag of Mg^{++} through the paracellular pathway probably reverses, leading to Mg^{++} losses and clinically observed hypomagnesemia (24).

Basolateral efflux of Mg^{++}: At the present time no conclusive experimental data are available for the extrusion of Mg^{++} across the basolateral membrane. There is probably no - or only a very small - chemical gradient for Mg^{++} across this membrane. The significant uphill electrical gradient for the exit of a cation such as Mg^{++} would suggest the participation of a primary (Mg^{++} pump) or secondary (Mg^{++}/Na^+ exchange) active transport. Bijvelds et al. (7) concluded from there work on basolateral plasma membranes of fish (*tilapia*) enterocytes that an electrically neutral anion (Cl^-)-coupled Mg^{++} transport mechanism participates in Mg^{++} efflux.

Cellular mediated Mg^{2+} transport across rumen epithelium: In contrast to monogastric animals and humans who cover their Mg^{++} requirements by absorption from the intestine, ruminate animals (sheep, goat, cattle) absorb most of the required Mg^{++} from there forestomachs (34, 97). Net Mg^{++} absorption from rumen fluid has been shown by

Table 2. Mg^{++} fluxes across isolated rumen epithelium of sheep: Effects of high luminal $[K^+]$, changes in PD_t or of short chain fatty acids (SCFA) ($nM \cdot cm^{-2} \cdot h^{-1}$; mean ± S.E.M.)

Group	PD_t	J^{Mg}_{ms}	J^{Mg}_{sm}	J^{Mg}_{net}	Reference
$[K^+]_e$ =70 mM[1]	25,1 ± 1,3	52,2 ± 6,5[a]	11,6 ± 1,4[a]	40,6 ± 5,9[a]	67
$[K^+]_e$ =70 mM[2]	0	76,1 ± 8,3[b]	8,0 ± 1,4[b]	68,1 ± 7,7[b]	
$[K^+]_e$ = 5 mM[1]	26,1 ± 1,6	47,4 ± 3,0[a]	12,2 ± 2,3[b]	35,2 ± 4,1[a]	
$[K^+]_e$ = 5 mM[2]	0	72,1 ± 8,8[b]	6,5 ± 1,7[b]	65,6 ± 9,0[b]	
Control[2] (SCFA)	0	82.3 ± 7.8[a]	3.2 ± 0.7	79.1 ± 7.8	54
SCFA free[2]	0	41.7 ± 4.6[b]	3.7 ± 0.5	37.9 ± 4.7	

a, b = different superscripts denote significant differences; 1: open circuit (70 mM K^+) or voltage clamp (5 mM K^+) 2: short circuit conditions

many authors and the data obtained revealed that Mg^{++} transport occurred against an electrochemical gradient (12, 17, 65). Because the intraruminal Mg^{++} concentration varies between 2 – 8 mM (86), the transepithelial chemical gradient permits passive Mg^{2+} absorption, but this chemical gradient is exceeded by the transepithelial potential difference (PD_t) 20 - 80 mV (blood side positive). Solvent drag, a simple means of overcoming the electrochemical gradient, has been shown to play no role in Mg^{++} transport across the rumen epithelium (31). *In vitro* studies with isolated rumen epithelium from sheep have lead to the conclusion that Mg^{++} transfer is mainly mediated by active transcellular Mg^{++} movement (64, 68). Net Mg^{++} transport across isolated sheets of sheep rumen mucosa shows some typical features common with other active transport processes: (a) uphill net absorption of Mg^{++} in the absence of a concentration gradient and against the electrical gradient across the epithelium; (b) reduction of net Mg^{++} transport (90%) by ouabain and therefore by inhibition of the Na^+-K^+-ATPase; (c) typical saturation kinetics (table 1); (d) inhibition by uncoupling oxidative phosphorylation (DNP); (e) sensitivity against temperature. Results from additional *in vitro* studies of the unidirectional Mg^{++} transport rates under controlled electrophysiological (open circuit, short circuit, voltage clamp) and chemical conditions confirmed the previously proposed mechanism of active transcellular Mg^{++} transport (55, 59, 67) and trans- and paracellular Mg^{++} flow has been distinguished in this epithelium (55). It has been shown that J^{Mg}_{sm} is paracellular, fully passive, and hence gradient-driven. Since J^{Mg}_{ms} also includes a passive movement which is equal to J^{Mg}_{sm} under short circuit conditions, J^{Mg}_{net} represents active and transcellular Mg^{++} transport. It can be seen from the data in Table 2 that J^{Mg}_{net} exceeds J^{Mg}_{sm} 10 – 20 fold, which indicates that transcellular and active Mg^{2+} transport is the predominant pathway for Mg^{2+} absorption across the rumen epithelium. The mechanisms of this cellular Mg^{2+} transport – luminal uptake and basolateral extrusion – could not be derived from these studies. Significant progress has been made in understanding luminal Mg^{++} uptake when ruminal Mg^{++} transport was studied at elevated ruminal K^+ concentrations.

For many decades it has been well known that adult cattle and sheep are suffering from hypomagnesemia and possibly tetany when they are fed on lush grass in spring that is high in K^+ and low in Mg^{++}. High dietary K^+ intake and, consequently, high ruminal K^+ concentrations decrease the apparent digestibility of Mg^{++} in ruminants (28, 34, 86, 98) because of impaired Mg^{++} absorption from the forestomachs (34, 98). Many *in vivo* and *in vitro* experiments have been performed to determine the mechanisms of this impaired Mg^{++} absorption (17, 65) and have shown that the reduced net Mg^{++} transport at high ruminal K^+ concentrations is closely correlated with electrophysiological changes within the rumen epithelium. a) There is a positive correlation between the (log) K^+ concentration of the ruminal fluid and the transepithelial potential difference (PD_t) (23, 45, 92; see Table 3). The elevated PD_t (blood side positive) at higher luminal K^+ concentrations causes a small passive backflow of Mg^{2+} (J^{Mg}_{sm}) most likely through the paracellular pathway (17, 55,67). b) The transcellular component of Mg^{++} transport, J^{Mg}_{ms} is significantly reduced by high ruminal K^+ concentrations (55, 67). c) Increasing mucosal K^+ concentrations causes a reversible, concentration-dependent depolarization of the potential across the apical membrane of the rumen epithelium (PD_a), which is accompanied by a decrease of the unidirectional mucosa to serosa transcellular Mg^{++} flux (55) and decrease of intracelluar Mg^{++} (88, 89). d) The K-dependent alterations of PD_t and PD_a and Mg^{++} fluxes can be ultimately simulated by means of a simple voltage clamp, which indicates that the electrophysiological changes are the cause of altered Mg^{++} fluxes and not K^+ (67; see Table 2). These observations led to a preliminary model of luminal uptake of Mg^{++} in the rumen epithelium (55, 67) which suggests that Mg^{2+} enters the apical membrane by a PD-dependent, PD-sensitive or - because K^+ influences PD_a - K^+-sensitive transport mechanism via a conductance or a carrier. The predominant driving force for this Mg^{++} uptake is probably PD_a and to a lesser extent the chemical gradient between the luminal and cytosolic Mg^{++} concentrations.

The hypothesis of a PD-dependent Mg^{++} uptake is supported by some recent data obtained from

Table 3. Effect of increasing K^+ concentrations in the rumen of sheep on PD_t and J^{Mg}_{net}

[K^+] and [Na^+] in the luminal buffer		**J^{Mg}_{net}**	**PD_t**	**Reference**
K^+ (mM)	Na^+ (mM)	($\mu M \cdot l^{-1} \bullet min^{-1}$)	(mV)	
30	90	2.12 ± 0.70	18.9 ± 0.9	17
90	30	0.03 ± 0.04*	42.1 ± 1.4	
30	120	3.93 ± 1.17	26.0 ± 6.3	65
75	75	2.40 ± 1.03*	39.5 ± 5.1	

* = significant differences

measurements with isolated ruminal epithelial cells (88, 89). With the aid of the fluorescence probe Mag-fura-2, the free intracellular Mg^{2+} concentration ($[Mg^{2+}]_i$) in isolated ruminal epithelial cells (REC) was measured under basal conditions and after alterations of the transmembrane voltage (E_m). Basal $[Mg^{2+}]_i$ of REC measured in solutions containing normal extracellular $[Mg^{2+}]$ of 1.0 mM to 5.0 mM was between 0.8 ± 0.1 mM and 1.2 ± 0.1 mM. An increase of extracellular $[K^+]$ led to membrane depolarization, as was shown in REC by whole cell patch clamp recordings, and was accompanied by reduction of $[Mg^{2+}]_i$. Exposure to quinidine, a blocker of K^+ channels, also reduced $[Mg^{2+}]_i$ significantly by approximately 17% (50 µM quinidine) or 29 % (100 µM quinidine). On the other hand, hyperpolarization produced by K^+-diffusion ($K_i > K_o$) in the presence of valinomycin (a K^+-ionophor) and 2 mM Mg^{2+}, induced a rapid 15% increase in $[Mg^{2+}]_i$ compared to control measurements ($K_i = K_o$).

Studies with isolated REC are in agreement with *in vivo* and *in vitro* observations and are consistent with the hypothesis that luminal Mg^{++} uptake is driven by an electrochemical gradient via a channel or carrier.

However, a second PD-independent uptake mechanism has been demonstrated in the rumen epithelium of sheep. This PD-independent uptake is dependent on luminal short chain fatty acids (SCFA), CO_2/HCO_3^-, and Cl^-, and may result in part from apical $Mg^{++}/2H^+$ exchange (54, 56, 58). The existence of an $Mg^{++}/2H^+$ exchange as a second PD-independent Mg^{++} uptake mechanism has been derived indirectly from several observations. Feeding high levels of readily fermentable carbohydrates to ruminants increased Mg^{++} absorption (31, 33). Such a diet leads to an alteration of microbial activity and composition in the rumen contents. Among other variables, the concentration of SCFA and CO_2/HCO_3^- are increased; these are the major end-products of microbial fermentation of carbohydrates in the forestomachs and they stimulate net Mg^{++} absorption in vivo (69) and in vitro (54, 56, 58). The in vitro experiments with isolated sheep rumen epithelium revealed that this increase in net Mg^{2+} absorption is due entirely to a stimulation of the mucosal-to-serosal Mg^{++} flux (J^{Mg}_{ms}), which is specifically reduced by removal of SCFA, CO_2/HCO_3^- and Cl^- from the luminal fluid (58). Because the stimulating effect of SCFA on J^{Mg}_{ms} depends on their lipid solubility (acetate < propionate < butyrate) and because the carbonic anhydrase inhibitor ethoxyzolamide reduces J^{Mg}_{ms} in SCFA-free buffer, it has been suggested that the PD-independent stimulation of ruminal Mg^{++} transport depends upon permeant anions that supply substrates for $Mg^{++}/2H^+$ and Cl^-/HCO_3^- exchange mechanisms in the apical membrane of ruminal epithelium (56, 58). SCFA are the predominant anions in the ruminal fluid and are readily absorbed by the stratified epithelium of the rumen (13). Therefore it was hypothesized that the supply of H^+ for the exchange may come in part from intracellular dissociation of SCFA that were absorbed in their non-ionized form by diffusion (13), and from the intracellular hydration of CO_2 produced in the lumen by microbial fermentation and in mucosa by SCFA catabolism. With such a model, the effect of Cl^- withdrawal could be explained by a reduction of the Cl^-/HCO_3^- exchange activity that is present in the ruminal epithelium (18, 66). However, it should be emphasized that these conclusions are indirect and other possibilities, e. g., cotransport of Mg^{++} with anions such as Cl^- or HCO_3^-, not can be ruled out.

Basolateral efflux: Only a few data are available regarding basolateral Mg^{++} efflux in ruminal epithelium. The significant uphill electrochemical gradient (PD_b = 50 – 70 mV, extracellular positive) for the basolateral extrusion of Mg^{++}, suggests the participation of an energy-dependent mechanism. Because inhibition of Na^+-K^+-ATPase by ouabain reduces net movement of Mg^{++} by 90 % (68), a Na-linked mechanism has been suggested utilizing the electrochemical gradient of Na^+ (generated by Na^+-K^+-ATPase) for Mg^{++} extrusion via a Na^+/Mg^{++} exchange. Some evidence for such a mechanism comes from *in vitro* experiments using short-circuited isolated sheep rumen mucosa (57), in which low serosal Na^+ concentrations led to a significant reduction in J^{Mg}_{ms} without affecting J^{Mg}_{sm}. Recent studies with isolated REC support the assumption of a Na^+/Mg^{++} exchange, because an increase of $[Mg^{++}]_i$ was observed after reversing the transmembrane Na^+ gradient. This PD-independent rise in $[Mg^{++}]_i$ was imipramine-sensitive and was accompanied by a decrease of $[Na^+]_i$ (90). These results are consistent with the suggestion of a Na^+/Mg^{++} exchange which has been proposed as the regulator of $[Mg^{++}]_i$ in a variety of other cells (22, 26, 27, 37, 38, 39, 41, 42, 60).

In Figure 1 a tentative model of ruminal Mg^{++} transport is depicted. In contrast to other epithelia of the intestine, the passive and paracellular Mg^{++} permeability of the rumen epithelium is low and Mg^{++} absorption is mainly mediated by a transcellular process.

PD-dependent influx: Mg^{++} influx into the cytosol across the apical membrane is probably a passive process

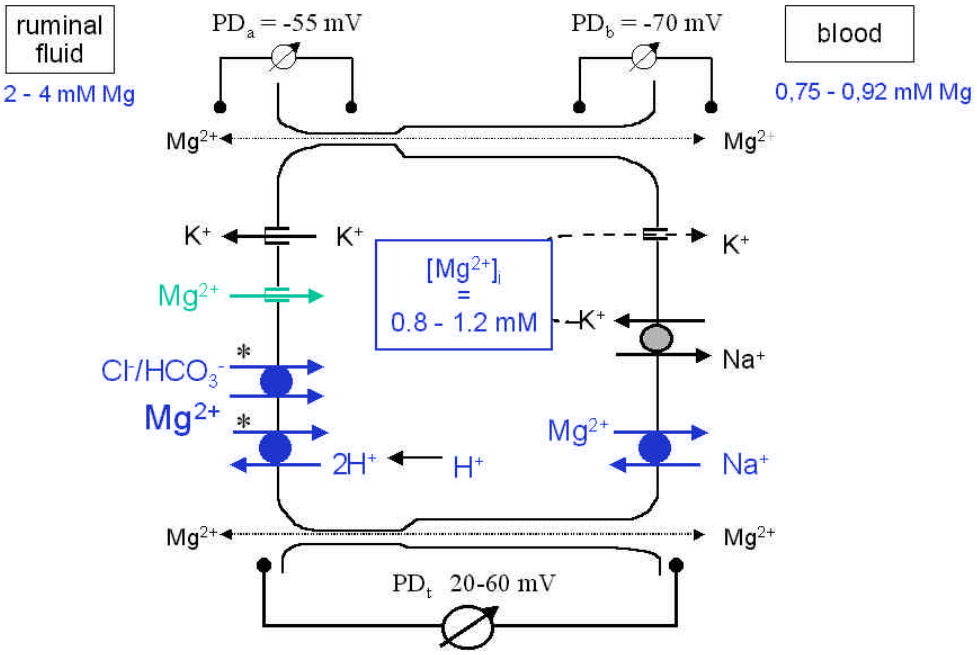

Figure 1. Tentative model of ruminal Mg^{++} transport in sheep. * $Mg^{++}/2H^+$ exchange or coupled transport with anions (Cl^- or HCO_3^-). For details see text.

using the electrochemical gradient across the apical membrane. PD_a of the rumen epithelium varies between -40 and -70 mV under short-circuit conditions, which serves as a strong driving force for the uptake of a divalent cation, such as Mg^{++}. Assuming an $[Mg^{++}]_i$ of 1 mM, a PD_a of approximately –55 mV would permit Mg^{2+} uptake at all luminal Mg^{2+} concentrations greater than 0.03 mM. With a typical intraruminal $[Mg^{++}]$ of 2.5 mM and an intracellular $[Mg^{++}]_i$ of 1 mM, the transmembrane chemical gradient is equivalent to -12 mV (Nernst equation). This is much lower than PD_a and accounts for only 22 % of the electrochemical driving force ($\Delta\mu_{Mg}$) across the luminal membrane. All our results have supported the assumption that PD_a acts as the principal driving force for Mg^{++} uptake in epithelial cells. The transport pathways mediating this influx have not been identified but could be the Mg^{++} channel or carrier.

PD-independent influx: The second Mg^{++} uptake mechanism is electrically silent and depends on luminal anions ($SCFA^-$, CO_2/HCO_3^- and Cl^-). It is assumed that it could result from $Mg^{++}/2H^+$ exchange or from co-transport of Mg^{++} with anions.

Basolateral extrusion: Extrusion of Mg^{++} is an "uphill" transport and is probably coupled to the electrochemical gradient of Na^+. There is some evidence for the existence of a Na^+/Mg^{++} exchange mechanism using the inwardly directed Na^+ gradient to promote Mg^{++} efflux.

4. PERSPECTIVES

The first steps for a better understanding of epithelial transport of Mg^{++} in the gut have been made. Since general principles of epithelial transport have been established for many years for a variety of solutes, the transfer of this knowledge for Mg^{++} transport has considerably advanced information on epithelial passage of Mg^{++}. A reliable approach has been supposed for estimating the driving forces of Mg^{++} uptake and basolateral extrusion. Future research should be directed to characterising the proteins which are involved in transfer of Mg^{++} across membranes. These studies should include verification of the suggested transfer mechanisms (co-transport, exchange system), purification and isolation of the proteins (channel, carrier) and finally identification of their molecular structures. Furthermore, the possible regulation of epithelial Mg^{++} transport is not well understood. What are the mechanisms which adapt luminal Mg^{++} uptake to basolateral extrusion? Because the driving forces across the apical membrane are very high, regulation of Mg^{++} uptake appears to be an obligation in avoiding unphysiological increases of $[Mg^{++}]_i$. The well known saturation of the Mg^{++} transport mechanisms in some epithelia supports the assumption of regulated uptake, and suggests that luminal uptake is the rate limiting step in epithelial transport as has been shown for Na^+ (99). "Self-inhibition" (modulation of channel activity by the apical Na^+ concentration) or "feedback inhibition" (downregulation due to Na^+ transport across the luminal membrane) are discussed as possible mechanisms for saturation of luminal Na uptake. Corresponding information is not available for epithelial Mg^{++} transport.

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Send correspondence to: Dr Monika Schweigel, Holger Martens, Department of Veterinary-Physiology, Oertzenweg 19b, 14163 Berlin, Germany, Tel.: +49 30 8386 2611, Fax: +49 30 8386 2610, E-mail: shweigel@vetmed.fu-berlin.de

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