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Magnesium endogenous loss as a function of plasma magnesium concentration rather than a constant allows better development of magnesium models in ruminants

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ABSTRACT

In the course of adapting an existing sheep model of magnesium metabolism for use with lactating dairy cattle it was found that the model failed to predict plasma magnesium concentrations in agreement with experimental data after scaling the model for animal size dependent parameters. An inspection of the model indicated that faecal endogenous Mg loss and Mg absorption from the hindgut were the model components requiring further development. Pooled data from Mg balance experiments were used to investigate the relationship between plasma Mg concentration, net faecal endogenous Mg loss and the apparent availability of magnesium. A mathematical relationship between Mg intake and faecal Mg output is presented. It was derived from the generalised non-linear case to allow for variability in both apparent absorption of Mg and faecal endogenous Mg loss. A balance trial simulation was carried out in which net faecal endogenous Mg was implemented as a linear function of plasma Mg concentration. The results of this simulation were in close agreement with the analysis of pooled balance trial data and suggest that net faecal endogenous Mg loss should be applied to the model as a function of plasma Mg concentration. In fact net faecal endogenous Mg loss is not useful in modelling since it is the net result of a true Mg secretion function being subject to reabsorption in distal regions of the tract. Post rumen magnesium exchanges are examined in the model by implementing net Mg exchanges in the small intestine and hindgut as separate secretion and absorption processes. The difficulties in isolating the true secretion and absorption functions in the hindgut are discussed in conjunction with an initial estimate of these functions. In the modified model the incorporation of a variable endogenous Mg secretion dependent on plasma magnesium concentration provides an additional mechanism for magnesium homeostasis which is sufficient to allow the model to scale between sheep and cattle.

Keywords: magnesium; ruminants; modelling

INTRODUCTION

In current work to scale a sheep model of magnesium metabolism (Robson *et al.,* 1997) for use with dairy cattle it was found that the model failed to predict urinary magnesium excretion and plasma magnesium concentrations in agreement with experimental data for cattle after simply scaling for animal size, predicting much too rapid a reduction in plasma Mg concentration. The urinary excretion of magnesium is controlled by a renal threshold which comes into effect when plasma magnesium concentrations fall below approximately 0.75 mmol/L (Rook *et al.*, 1958; ARC, 1980), providing an important control of magnesium homeostasis in the animal. Above the renal threshold, urinary magnesium excretion is of similar magnitude to the quantity of magnesium absorbed from the digestive tract (Robson *et al.*, 1997; Lavor, 1983), and is sensitive to changes in plasma magnesium concentration. This lack of agreement led to a rigorous inspection of the magnesium absorption and secretion fluxes operating in the model of Robson *et al.* (1997).

It was noted from studies of magnesium transport along the digestive tract in both sheep and cattle (Grace, 1983), that net secretion of magnesium into the small intestine and net absorption in distal regions, in addition to being approximately equal in magnitude, were of significant magnitude when compared with the quantity of magnesium absorbed from the rumen. The net secretion into the small intestine was observed to be in the range 0-11mg/kgBW/d (Grace, 1983; Ben-Ghedalia *et al.,* 1975). From this it was concluded by the authors that true secretion and absorption fluxes operating in the hindgut compartment of the model of Robson *et al.* (1997) had been underestimated and required review. A further observation, that net faecal endogenous loss may be dependent on plasma magnesium concentration (Allsop & Rook, 1979), provided the possibility of an additional mechanism for magnesium homeostasis that would be beneficial in the scaled model. A review of experimental data from the literature (ARC, 1980) showed a range of net faecal endogenous loss between 1-5mg/kgBW/d for both sheep and cattle.

MODEL DEVELOPMENT

Initially, an attempt was made to derive a relationship between plasma magnesium concentration and net faecal endogenous loss derived from pooled experimental data (ARC, 1980), by using linear regression of faecal Mg vs. Mg intake over discrete intervals, which were determined by the original experimental designs. The regression constant, previously considered to be an estimate of net faecal endogenous loss, was plotted as a function of the mean plasma magnesium concentration, calculated for each regression interval, fig 1. These data demonstrate non-linearity in the relationship between faecal magnesium and intake, and do not support a constant net faecal endogenous loss of 3mg/kgBW as recommended by ARC (1980). Further evidence that net faecal endogenous loss may be variable and dependant on plasma magnesium concentration exists in the results from experiment 1 of Allsop & Rook (1979) in which a linear relationship was derived between net faecal magnesium loss and plasma magnesium concentration (R^2=0.88,P<0.001); in this experiment, sheep were supplied close to zero dietary magnesium, with plasma magnesium concentration being maintained by intravenous infusion over a wide range of treatments. Consequently the faecal magnesium excretion measured in this experiment represents the net faecal endogenous loss under the experimental conditions.

In summary, the constant in the regression of faecal magnesium vs. magnesium intake can no longer be considered to be an estimate of net faecal endogenous loss,

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FIGURE 1: Constant terms in discrete regression of faecal Mg output vs Mg intake from experimentald ata used by ARC (1980) tocalculate Mg endogenous loss, as a function of plasma magnesium concentration

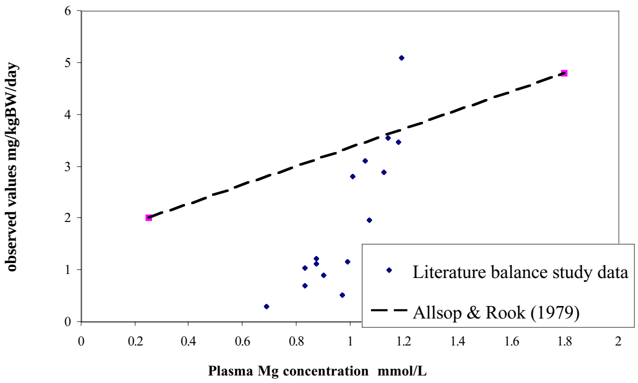
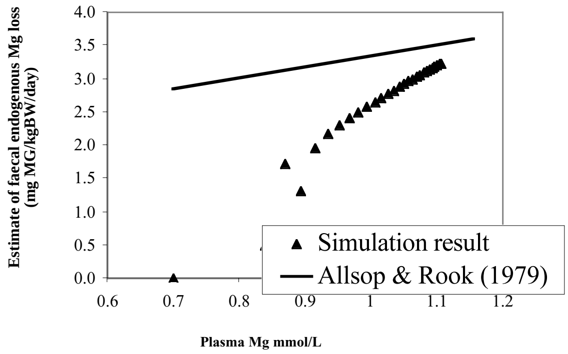


FIGURE 2: Simulation of Mg endogenous loss estimates by linear regression, on the assumption of constant Mg availability (0.25), and daily net faecal endogenous loss dependant on plasma magnesium concentration (Mgp), of (1.6+1.7/mmol Mg_p)mg Mg/kg BW



as shown by the following mathematical derivation.

A non-linear function, which describes the data in fig 1 was derived from the general form of the linear regression equation

$$g(x) = y - x\,\frac{\delta y}{dx}$$

Defining:

F = faecal magnesiuim
I = dietary magnesium intake
FE = faecal endogenous Mg loss
AA = apparent absorption Mg
UA = (1-AA) unabosrbed fraction of dietary Mg intake

$$F = FE + I{\cdot}UA$$

Applying the definitions to the nonlinear regression equation gives;

$$g(I) = F - I{\cdot}\frac{\delta F}{\delta I}$$

which after substitution yields

$$g(I) = (FE + I{\cdot}UA) - I\;\frac{\delta[FE + I{\cdot}UA]}{\delta I}$$

separating the partial derivatives simplifies to

$$g(I) = FE - I\left[\frac{\delta FE}{\delta I} + I\,\frac{\delta UA}{\delta I}\right]$$

This function demonstrates that variability in both endogenous loss and/or apparent availability are important factors in determining the results from fig 1 and may help explain a large source of the error noted in previous experiments (Field ,1962) to determine endogenous loss. The equation is of little value in determining the degree to which each of the variable terms is responsible for the observed effect. For this reason a simulation of a balance trial experiment was carried out in which apparent availability was assumed to be constant at 25%, utilising a net endogenous loss function based on plasma magnesium concentration derived from the results of Allsop & Rook (1979). The results of discrete interval regression were calculated from the simulation data (fig 2)

As net faecal endogenous loss is the result of the true secretion and absorption fluxes either an increase in the true absorption of magnesium or a decrease in the true secretion of magnesium could be responsible for the observed decrease in net endogenous loss. Studies of magnesium transport in the digestive tract using ^{28}Mg (Field, 1961) and indigestible markers reviewed by Laporté *et al.* (2001), show that the true secretion of magnesium into the small intestine is typically 3-4 times the net secretion of magnesium at that site.

The model of Robson *et al.* (1997) lacks state variables at the site of secretion into the small intestine. However, since secretion occurs in bile, pancreatic juice and duodenal secretions in which the magnesium concentration is closely related to plasma magnesium concentration (Storry, 1961), it was assumed the net secretion into the small intestine could be implemented as a function of plasma magnesium concentration to test the response of the modified model.

RESULTS AND DISCUSSION

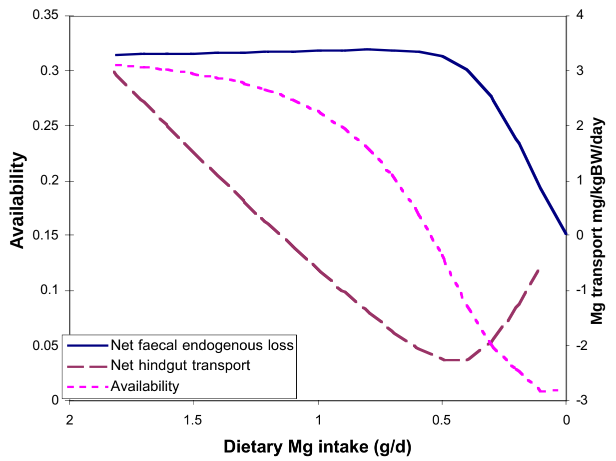
In the following modified model, which is based on a 40-kg sheep, the hindgut secretion flux is considered to represent the net secretion into the small intestine, and the absorption flux the net absorption from lower down the digestive tract. The hindgut liquid phase and solid phase magnesium pools are considered to be at the site of net absorption and determine the magnesium concentration in digesta which drive the passive absorption process at that site. The hindgut secretion flux (UPlHg) was set at 8 mg Mg/kgBW/mmol Mg_p/d which at a plasma magnesium concentration of 1 mmol/l gives a net secretion into the small intestine of 0.32g/d for a 40 kg sheep, similar to experimental observations for sheep of this weight range (Grace, 1983). The constant term kHgPl controlling the rate of passive absorption was adjusted to give an absorption flux (UHgPl) equal to the secretion flux UPlHg at a magnesium intake of 1.2 g/d, resulting in zero net magnesium transport in the hindgut. This led to a value of 0.15 being chosen for kHgPl.

At a true secretion rate of 8 mg/kgBW/mmol Mg_p /d the model predicts a linear increase in net hindgut magnesium absorption with increasing dietary intake above 1 g/d as observed by McClean *et al.* (1984), however the rate of increase was approximately double the experimental result. Reducing the net secretion to 4 mg/kgBW/mmol/d and readjusting kHgPl to give zero net magnesium transport at an intake of 1.2 g/d (kHgPl=0.08), halves the net magnesium transport in the model at higher magnesium intakes so that the model predicts magnesium absorption from both the rumen and hindgut in agreement with data in the literature.

Availability of magnesium has been calculated from the model by adding the net absorption from the rumen and hindgut compartments and dividing by intake. Net endogenous faecal loss is calculated by estimating the ratio of endogenous:unabsorbed magnesium entering the hindgut magnesium pool. When the model is in equilibrium, and assuming that both endogenously secreted and unabsorbed dietary magnesium in the liquid phase are absorbed with equal preference, net faecal endogenous magnesium can be calculated from this ratio and the total faecal magnesium output. The net endogenous secretion from the rumen pool is calculated by the same method and contributes to the estimate of endogenous magnesium entering the small intestine.

The model has been run over a range of dietary magnesium intakes (Fig 3.)

FIGURE 3: Model estimates for: Mg availability, net faecal endogenous Mg loss and net Mg transport in the hindgut over a range of Mg intakes. 40kg sheep, 4mg Mg/kgBW/mmol Mg_p/day true secretion.

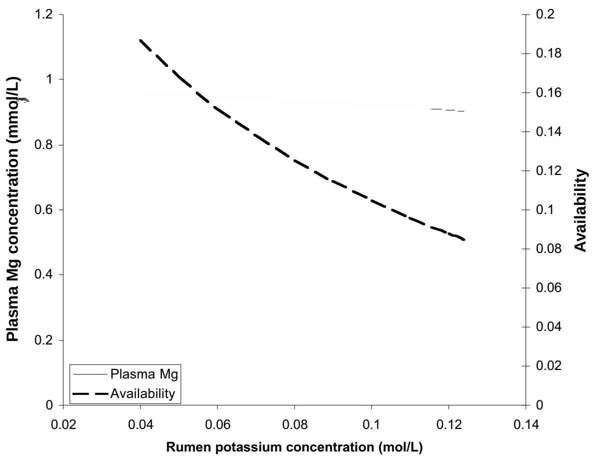


At magnesium intakes above 0.8 g/d the plasma magnesium concentration is relatively constant in the range 0.9-1.1 mmol/l, consequently the net secretion is also relatively constant in this range. The decrease in net magnesium absorption from the hindgut at low dietary magnesium intake is due mainly to lower concentrations of magnesium in the hindgut The increase in net absorption of magnesium which occurs at very low Mg intakes is due to both decreased secretion of magnesium at low plasma magnesium concentrations and to an increase in the magnesium concentration gradient between plasma and hindgut digesta.

Endogenous loss. At normal to high magnesium intakes the endogenously secreted magnesium is approximately 30% of the hindgut magnesium pool. Initially the ratio of endogenous:unabsorbed magnesium, magnesium pool size and magnesium absorption in the hindgut combine so that net endogenous magnesium loss is approximately constant. As dietary magnesium intake decreases the ratio of endogenous:unabsorbed magnesium increases, consequently more endogenously secreted magnesium is reabsorbed and net endogenous loss decreases. The factors which determine the quantity of net magnesium secretion in the small intestine have yet to be determined. In the current model it is the net secretion into the small intestine which determines the net endogenous loss in the critical magnesium intake range. This net secretion has been observed over a range of 0-11 mg/kgBW/d in experiments with cannulated animals.

Effect of potassium. The original model utilises rumen potassium concentration to determine the transepithelial potential difference, which is a determining factor in the rate of active absorption in the rumen. It has been thought that the hindgut may provide some degree of compensatory magnesium absorption when absorption of magnesium is depressed in the rumen by high potassium concentrations. In the modified model (Fig 4) there is an increase in the quantity of magnesium flowing from the rumen into the hindgut but although there is an increase in net absorption from the hindgut due to a small increase in the concentration of magnesium in the hindgut, this is insufficient to compensate for the decrease in magnesium absorption from the rumen.

FIGURE 4: Model predictions of plasma magnesium concentration and magnesium availability over a range of rumen potassium concentrations. 40kg sheep, dietary magnesium intake 0.8g/d



At dietary magnesium intakes over 1.5-2 g/d the higher concentrations of magnesium in the hindgut allow sufficient absorption of magnesium in the hindgut to overcome the effect of potassium on magnesium absorption from the rumen. Dalley *et al.* (1997) observed that potassium infused into the rumen decreased the plasma magnesium concentration over a range of dietary magnesium intakes from 1-3 g/d. It is estimated from the model state variables that saturation of magnesium absorption in the hindgut at a digesta magnesium concentration of 7-10 mmol/L would be sufficient to prevent complete compensatory absorption at high magnesium intakes providing closer agreement with experimental data.

Scaling to cattle. After revising the sheep model the three model parameters that determine animal scale in the model; live weight, total rumen volume and rumen liquid volume were scaled up for cattle. Absorption from the rumen scaled in agreement with experimental data, secretion and absorption in the hindgut were greater in the scaled model than experimental data. However adjustment for differences in the water content in the hindgut between sheep and cattle (Hecker & Grovum, 1975), decreases the hindgut magnesium concentration and brings the hindgut absorption into agreement with experimental data for cattle (Rogers & van't Klooster, 1969).

Conclusions. The incorporation of plasma Mg concentration dependant Mg secretion into the small intestine with absorption in distal regions of the digestive tract allows improved modelling of Mg transport in the hindgut. The modified model responds to changes in potassium concentration in the rumen and dietary magnesium intake in general agreement with data from the literature (Dalley *et al*., 1997).

Compensatory absorption of magnesium from the hindgut can occur in the model when magnesium absorption from the rumen is reduced by high rumen potassium concentrations, however the model predicts that low absorption rates of magnesium from the hindgut at low digesta magnesium concentrations are a limiting factor for absorption from this site. The model is scalable over a wider range of animal live weights than the previous sheep model and may be used for dairy cattle after adjustment for the differences in hindgut water content between sheep and cattle.

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