The Macrominerals That Give us Grief
Ca, P, Mg

How they are absorbed, the problems that arise when they are not, and strategies to avoid these problems

Jesse Goff, DVM PhD
Ames, IA

1

Jesse Goff - Conflicts of Interest

Invented **Soychlor** anionic supplement – former advisor for the Landus Farmer's Cooperative on issues related to formulating diets with Soychlor.

Designed and Tested Solanum glaucophyllum boluses to help maintain normal blood Calcium in fresh cows, now marketed by Silberhorn Animal Health as Goff-Bol.

Owner of GlycoMyr- a company that makes a vitamin drench for baby pigs. Working to utilize plant sources of active vitamin D compounds for human inflammatory bowel disease

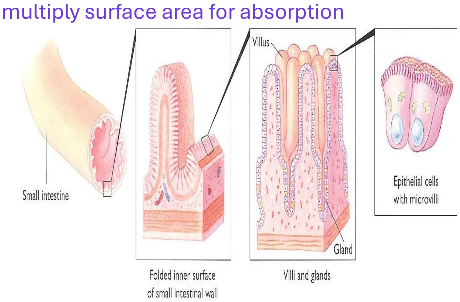
2

Anatomy of the Absorptive Epithelium of the GI Tract

3

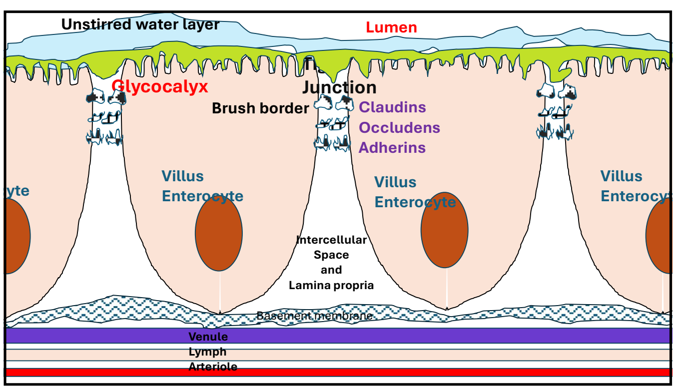
Intestine

Folds, villi, crypts and especially the microvilli (brush border) greatly multiply surface area for absorption



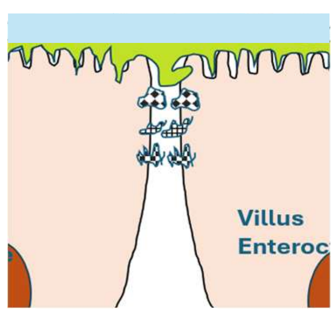
Sjaastad, Hove, Sand: Physiology of Domestic Animals

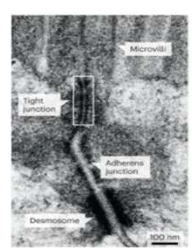
4



5

Tight Junctions are not completely tight





Horowitz et.al., Nature Reviews 2023

6

Tight Junctions and Intestinal Permeability

Resistance of intestine epithelia TIGHT JUNCTIONS to "leakage" ~ 6 ohms. (bladder wall resistance is 70,000 ohms!)

Absorption of minerals across the tight junctions between cells is called **PARACELLULAR ABSORPTION**.

Occurs ONLY if lumen IONIZED concentration of a mineral is many fold higher than on the interstitial side of the tight junction. **THEREFOR NOT THE MAJOR ABSORPTION PATHWAY FOR MOST MINERALS**

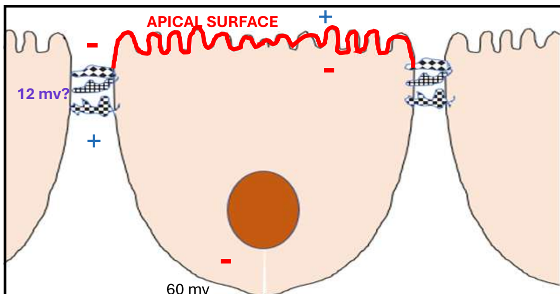
7

Transcellular absorption of Minerals

3 Components

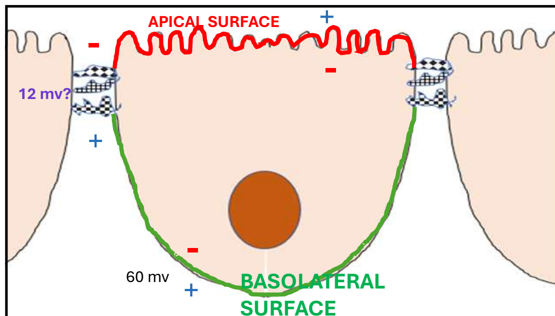
1. **Specific transporter / channel to allow charged, hydrophilic Mineral to cross lipid bilayer of apical membrane of enterocyte.**
2. **Carrier proteins to carry Mineral across interior of cell**
   - In the free ionized state minerals often act as free radicals or trigger reactions within the cell cytosol
3. **Another specific transporter / channel to move the mineral across the basolateral membrane and into the interstitial fluid and blood.**

8



Concentration Gradients

9



Concentration Gradients

10

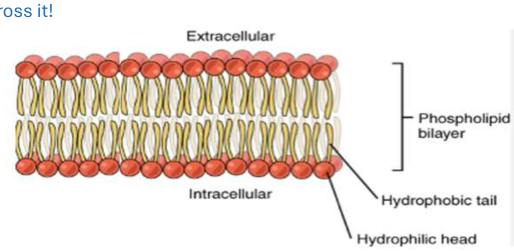
Transcellular absorption of Minerals

3 Components

1. **Specific transporter / channel to allow charged, hydrophilic Mineral to cross lipid bilayer of apical membrane of enterocyte.**
2. **Carrier proteins to carry Mineral across interior of cell**
   - In the free ionized state minerals often act as free radicals or trigger reactions within the cell cytosol
3. **Another specific transporter / channel to move the mineral across the basolateral membrane and into the interstitial fluid and blood.**

11

Phospholipid bilayer blocks passage of charged, hydrophilic minerals across it!



Macro and Trace Minerals are charged particles and NOT Lipid soluble

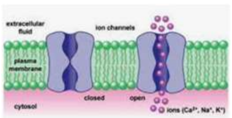
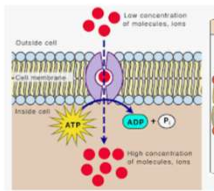
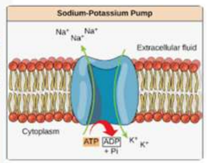
12

Ion Channel

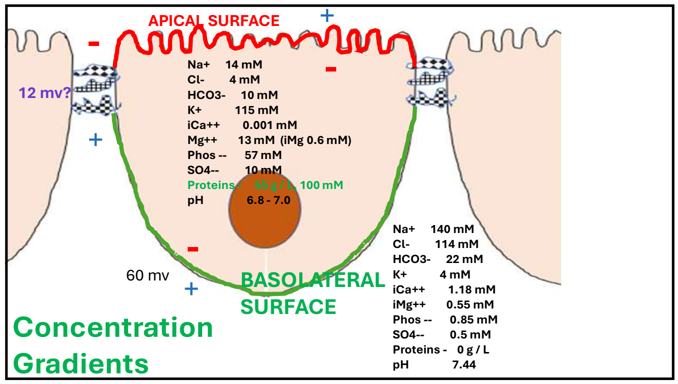
Allows passive diffusion down an electrical or concentration gradient

Ion Pumps and Ion exchangers

Energy is required to move an ion against an electrical or concentration gradient
Generally requires energy of ATP or co-transport with an ion that is moving down its electrical and concentration gradient

13



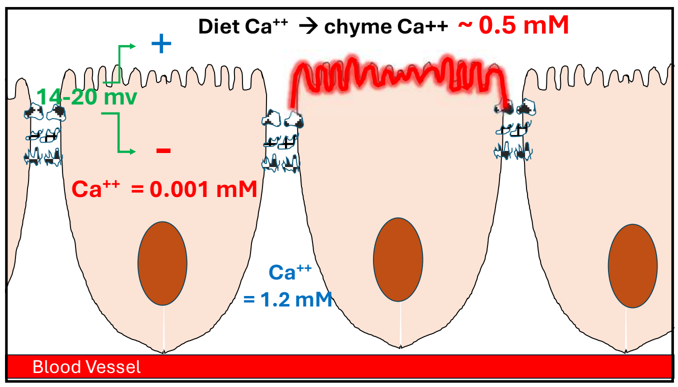
14

Electrical and Chemical Gradients must be overcome to move a mineral across an intestinal cell and into the blood.

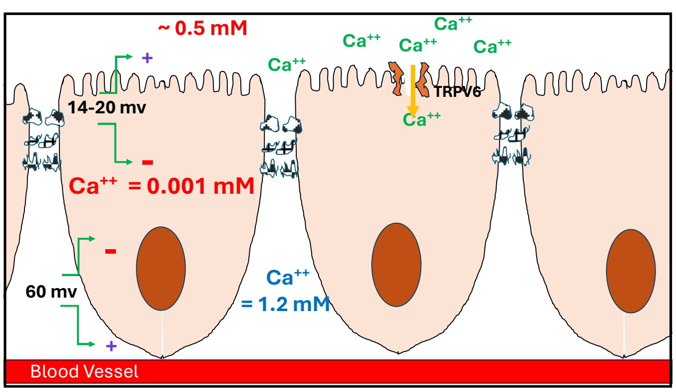
Example - CALCIUM

Ca has a +2 charge when in solution in water or is "ionized". Only ionized Ca is eligible for absorption

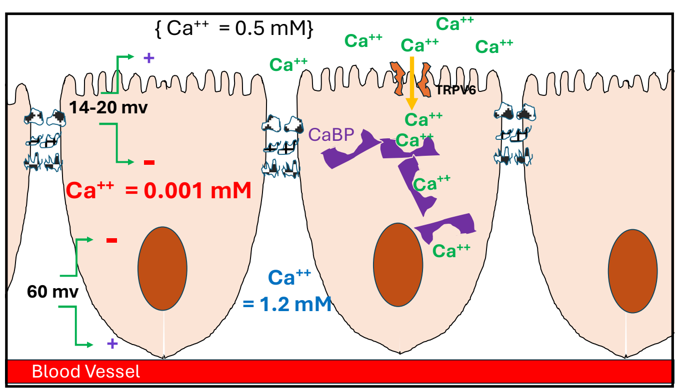
15



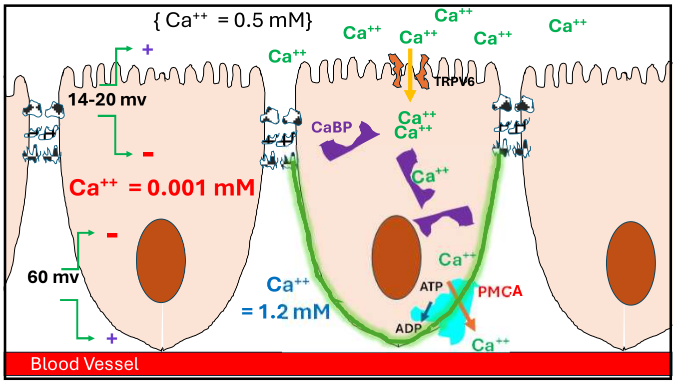
16



17



18



19

In Ruminants and Many Monogastric Animals

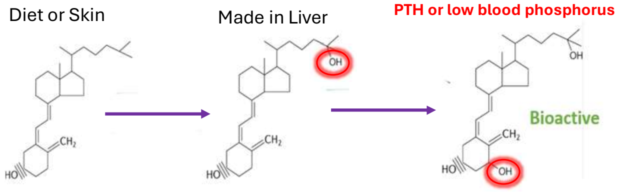
Calcium and Phosphorus (as phosphate HPO_4^{-2}) absorption across cells is **tightly controlled**

The bioactive form of vitamin D, 1,25-dihydroxyvitamin D, controls the production of Ca and Phosphorus absorbing proteins by the intestinal epithelial cells

20

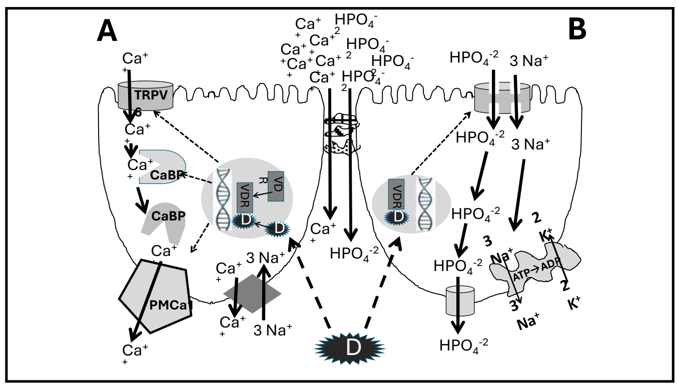
Vitamin D3 | 25-HydroxyVitamin D3 | 1,25-DihydroxyVitamin D3

Diet or Skin | Made in Liver | **Made in Kidney if turned on by PTH or low blood phosphorus**



Only 1,25-DihydroxyVitamin D is able to act on intestinal cells to stimulate production of proteins needed for Transcellular Calcium and phosphorus absorption.

21



22

23

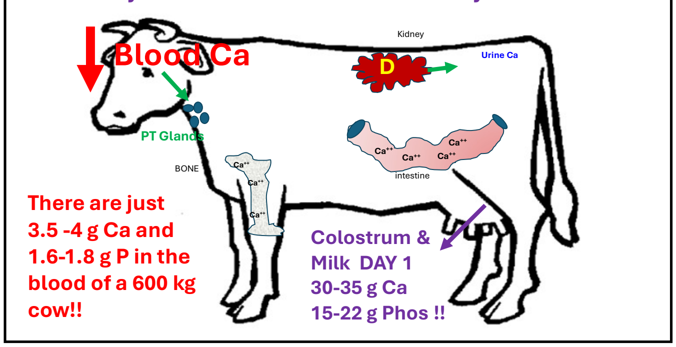
Milk and Colostrum Macrominerals

Mineral	Milk at 40 liters/day g mineral /Liter (g / day typical)	Colostrum 7 liters /day Transition milk 10 liters/day Colostrum g/Liter	Transition milk g/Liter	Total g/day 1
Calcium	1.1 (44 g day)	2.4	1.7	33.8 g
Phosphorus	0.9 (36 g/day)	1.3 *	1	19.1 g
Magnesium	0.12 (4.8 g /day)	0.35	0.2	4.5 g
Sodium	0.6 (24 g /day)	0.9	0.7	13.3 g
Potassium	1.5 (60 g /day)	1.45	1.5	25.2 g
Chloride	1.1 (44 g / day)	1.2	1.2	20.4 g

Adapted from Valldecabres and Silva-del-Rio, 2022: Westhoff et al., 2024

24

Why does blood Ca fall in almost every cow??

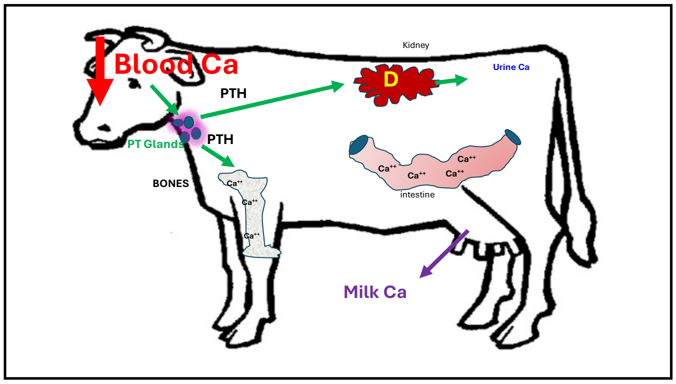


25

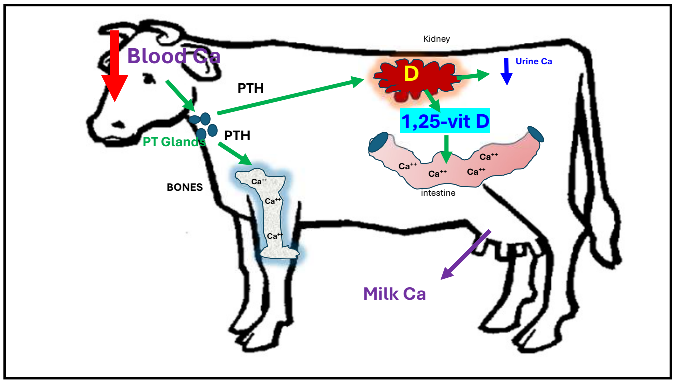
Why don't all cows get milk fever????

Calcium Homeostasis!

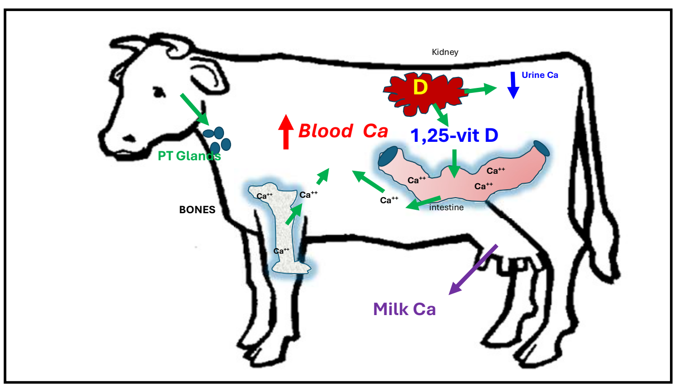
26



27



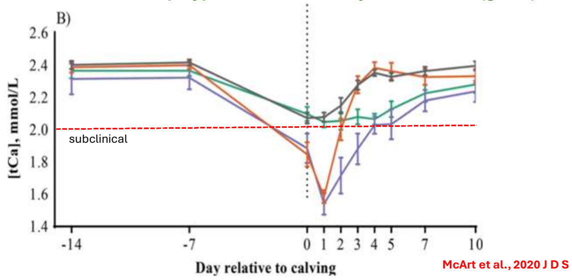
28



29

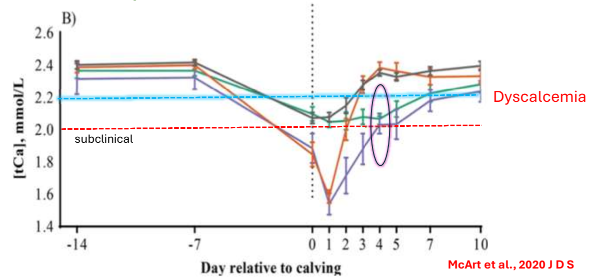
30

Some cows do not develop any subclinical hypocalcemia (black).
Transient hypocalcemia (red) associated with higher milk production.
Persistent hypocalcemia (purple) associated with higher cull rate.
Delayed -A few cows develop hypocalcemia after day 2 of lactation (green).



31

Dyscalcemia = cows with blood Ca below 8.8 mg/dl (2.2 mM) on day 4.
- reduced DM intake, rumination, fertility
- 1.7 to 5.3 times more likely to be culled or dead
- reduced milk production



32

Parity	Ca nadir	% cows with Ca nadir < 8.0	% SCH at 2 DIM	% Dyscalcemia Ca < 8.8 4 DIM
2	7.96 ± 0.12 ^{a}	41 ± 6 ^{c} (122/298)	20 ± 3 ^{b} (54/272)	**27 ± 5 ^{b} (61/227)**
3	7.48 ± 0.16 ^{b}	63 ± 6 ^{b} (123/195)	27 ± 4 ^{b} (48/176)	41 ± 6 ^{a} (68/165)
≥ 4	6.80 ± 0.16 ^{c}	87 ± 4 ^{a} (145/167)	45 ± 0.4 ^{a} (60/134)	41 ± 6 ^{a} (58/142)

Goff et al, Frontiers Veterinary Science 2025

Old Cows have more subclinical hypocalcemia (Ca below 8 mg/dl) and More Dyscalcemia (Ca below 8.8 on day 4)

33

34

Why doesn't Ca Homeostasis work in all cows???

OLD AGE: Cow stops growing by end of 2nd lactation!
Bones are slow to release Ca, heifers don't get milk fever!

Renal production of 1,25-dihydroxyvitamin D slows.
- **lower # of receptors for 1,25-dihydroxyvitamin D in intestine of older cows**

Failure to produce 1,25-dihydroxyvitamin D quickly enough and in an adequate amount is a major factor contributing to hypocalcemia and Milk Fever

35

ALL CLOSE-UP DIETS SHOULD FOLLOW THESE 3 PRINCIPLES

Keep Diet Potassium as low as possible
a. Avoid alfalfa and rye/ brome type grass hays or haylages (2.2-4% K)
b. Use Prairie hays and clean wheat straw (0.8 – 1.4% K)
c. Use some corn silage (0.9-1.3% K)

Keep Diet Phosphorus as low as possible
a. **Avoid Canola meal (1.05% P), DDG (0.8% P) and Brewers grains (0.65% P)**

Provide Adequate Magnesium – Mg needed for PTH secretion and action on target tissues
a. **> 0.4% Mg for prepartum and early postpartum diets**
b. **Use Readily soluble Mg source**

36

1. **Close-up Diets High in potassium cause alkalosis of blood and urine**

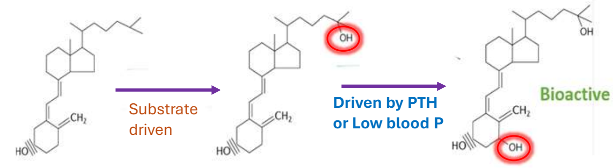
Changes shape of receptor for parathyroid hormone so it does NOT RECOGNIZE PTH as well .

Bone and kidney surrounded by lots of PTH, but bone fails to release Ca and kidney fails to produce 1,25-dihydroxyvitamin D.

37

Vitamin D3 | 25-HydroxyVitamin D3 | 1,25-DihydroxyVitamin D3

Diet or Skin | Made in Liver | Made in Kidney



Only 1,25-DihydroxyVitamin D is able to act on intestinal cells to stimulate production of proteins needed for Transcellular Calcium and phosphorus absorption.

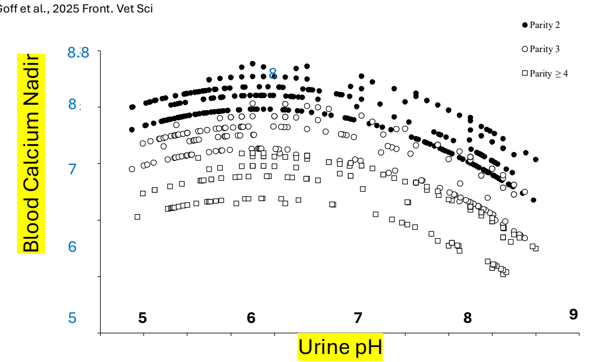
38

1. **Diets High in potassium cause alkalosis→ bone & kidney PTH resistance**

Anionic diets ↓ alkalinity of blood allowing parathyroid hormone to work on the kidney and increase synthesis of 1,25-dihydroxyvitamin D!

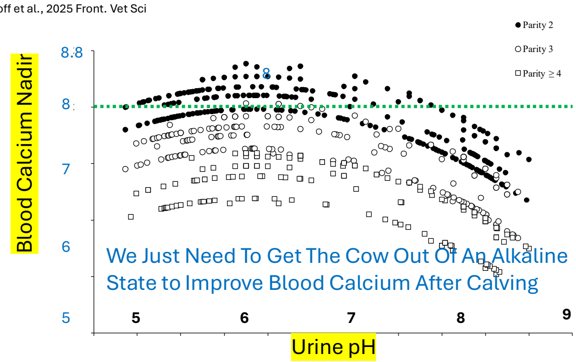
39

Goff et al., 2025 Front. Vet Sci



40

Goff et al., 2025 Front. Vet Sci



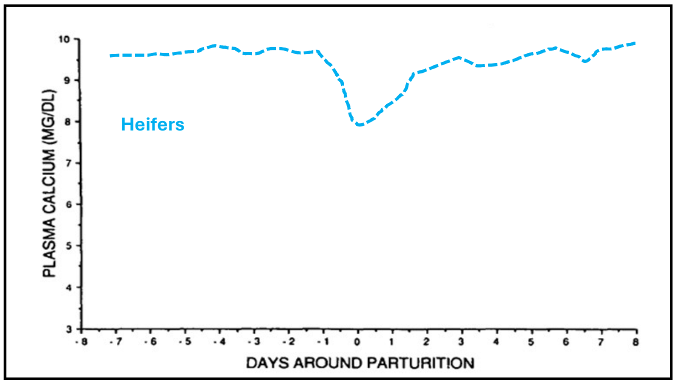
41

Blood Ca and blood 1,25-vit D concentrations as heifers and cows go thru the onset of lactation.

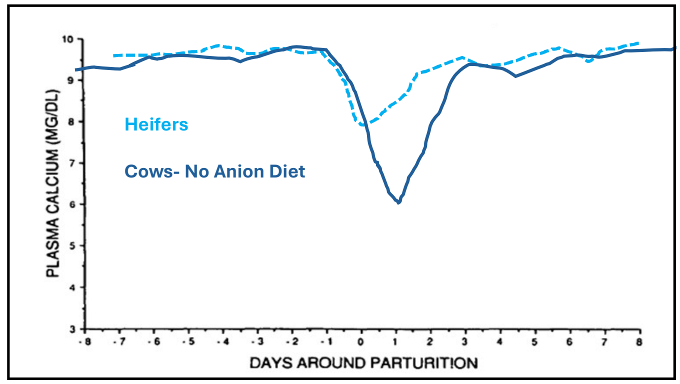
Data from Horst et al, 1977; Goff et al., 1989; Gaynor et al., 1989; Goff and Horst, 1997;

Older cows struggle to produce adequate amounts of 1,25-dihydroxyvitamin D quickly enough to prevent hypocalcemia

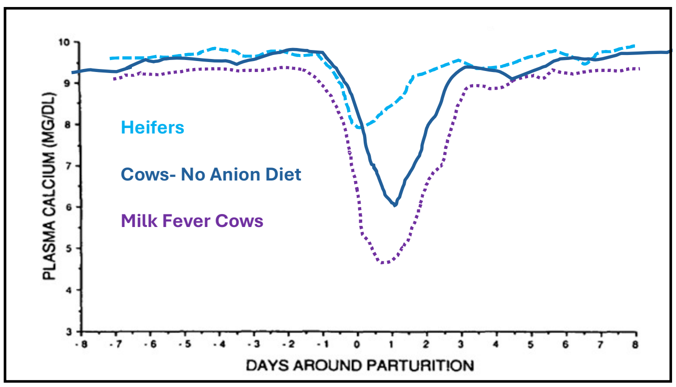
42



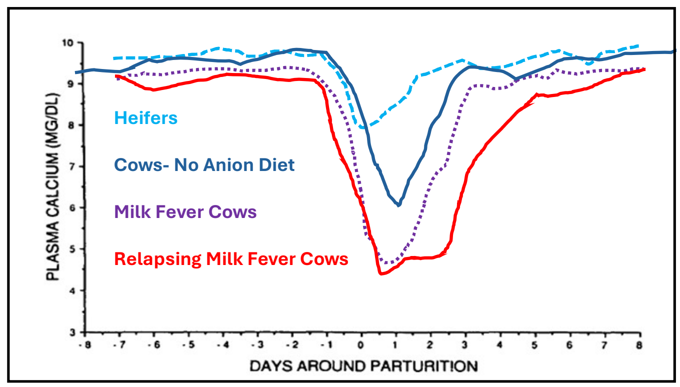
43



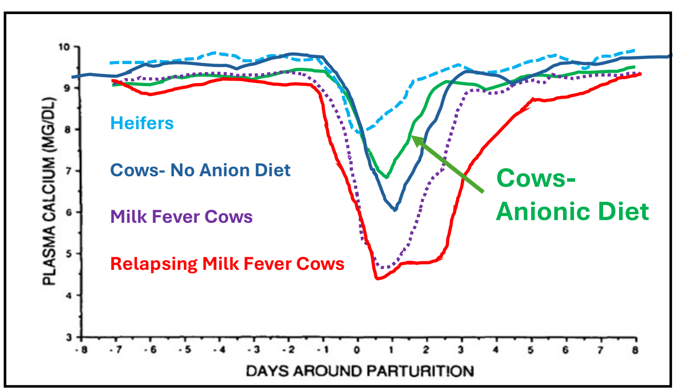
44



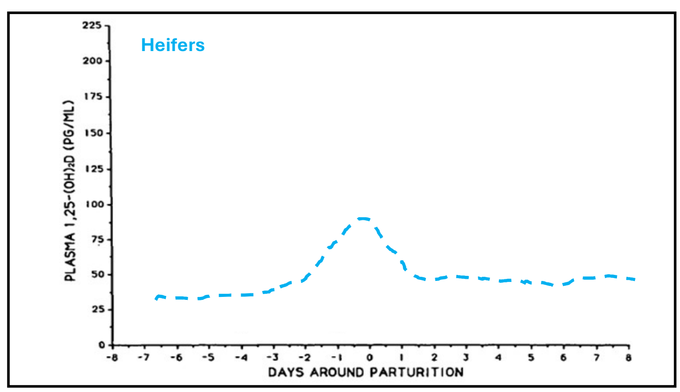
45



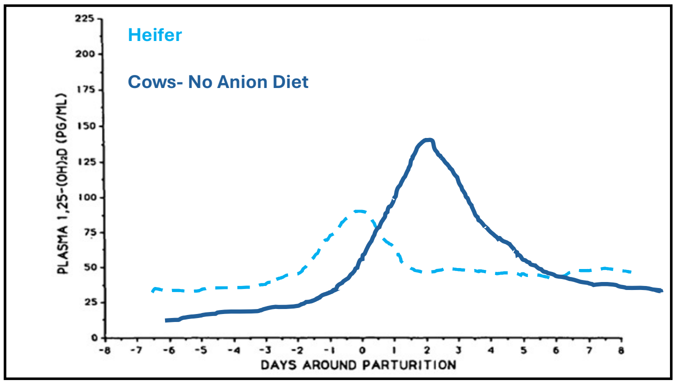
46



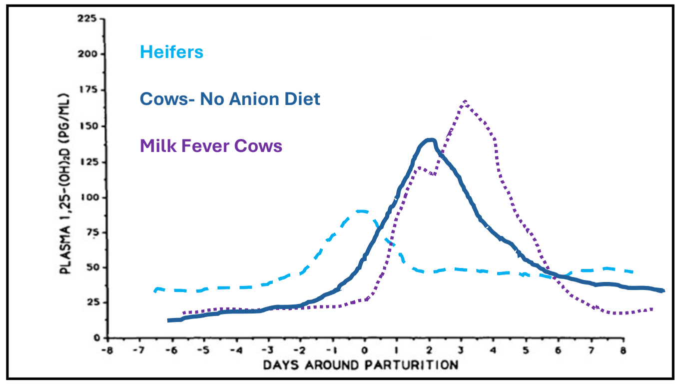
47



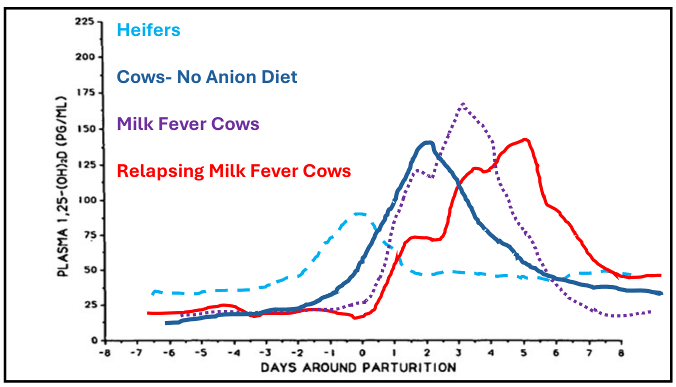
48



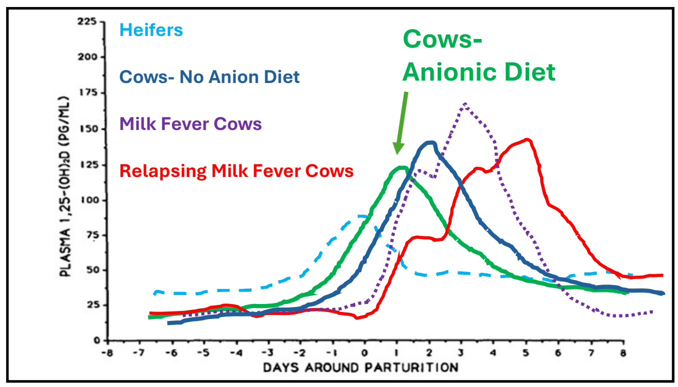
49



50



51



52

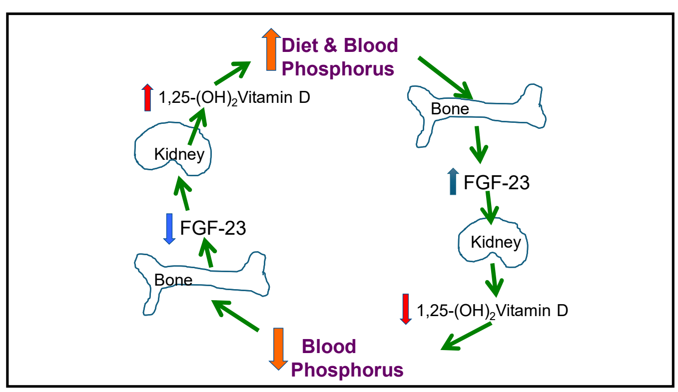
1. Diets High in potassium causing alkalosis→ bone & kidney PTH resistance

   Anionic diets ↓alkalinity of blood allowing parathyroid hormone to work!

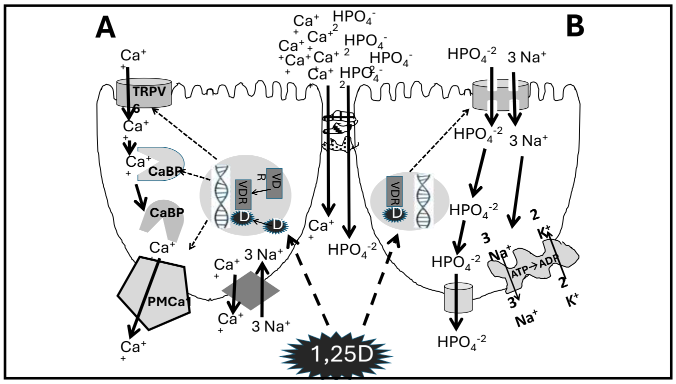
2. Diets High in phosphorus block enzyme producing 1,25 (OH)2 vitamin D in kidney via FGF23 made by bone cells.

Phosphorus Homeostasis

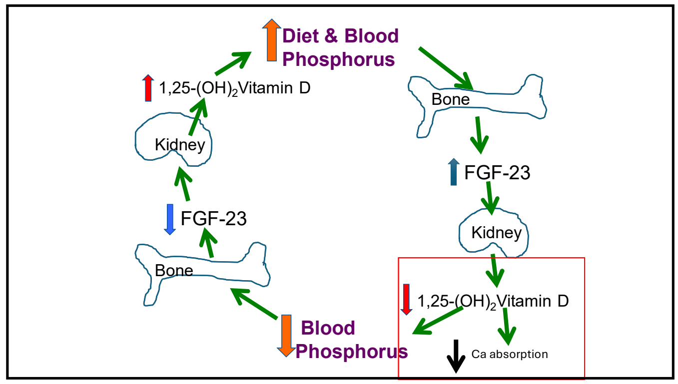
53



54



55



56

1. Diets High in potassium causing alkalosis→ bone & kidney PTH resistance
   Anionic diets ↓ alkalinity of blood allowing parathyroid hormone to work!

2. Prepartum Diets High in phosphorus block enzyme producing 1,25 (OH)2 vitamin D in kidney via FGF23.
   Avoid Canola meal (1.05% P) and DDG (0.85% P)

   Zeolite or Binder diets ↓ blood Phos, eliminating the inhibition of conversion of 25-OHD to 1.25(OH)2 vitamin D

57

1. Diets High in potassium causing alkalosis→ bone & kidney PTH resistance
   Anionic diets ↓ alkalinity of blood allowing parathyroid hormone to work!

2. Diets High in phosphorus block enzyme producing 1,25 (OH)2 vitamin D in kidney via FGF23.
   Zeolite or Binder diets ↓ blood Phos, eliminating the inhibition of conversion of 25-OHD to 1.25(OH)2 vitamin D

3. Pre and Post Calving diets Low in magnesium- inhibits secretion and action of PTH
   Add soluble Mg to diet! Get to 0.4% Mg diets

58

Magnesium Metabolism

Diet Mg can only be absorbed across the rumen wall.

Only ionized (soluble) Mg can be absorbed.

59

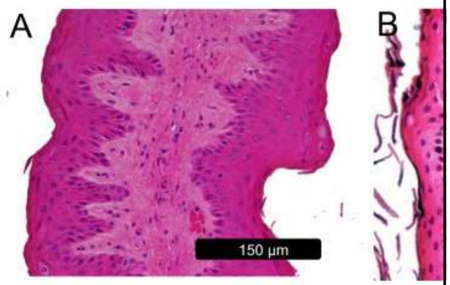
How Can Magnesium cross the Rumen wall???

60

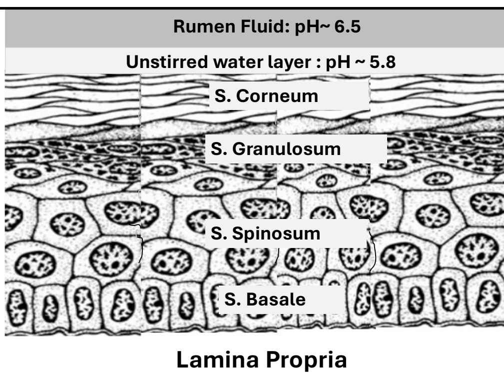
Rumen Papillae have stratified squamous epithelium presenting greater resistance to absorption.

61

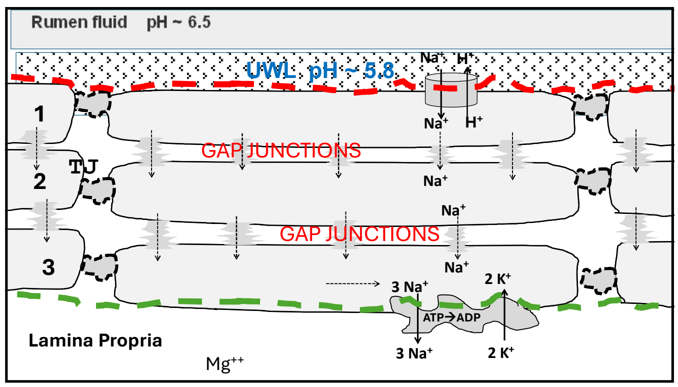
Multiple cell layers for a mineral to cross in the rumen



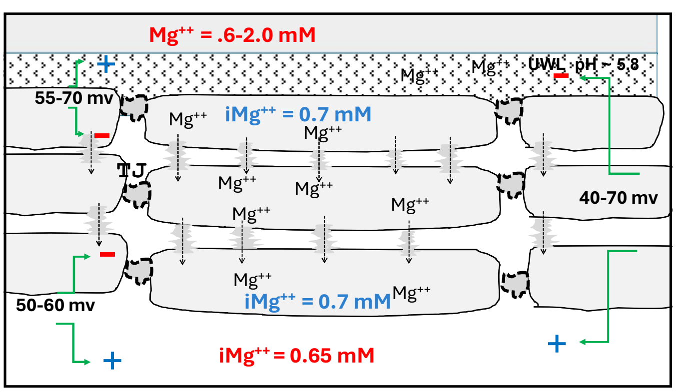
62



63



64

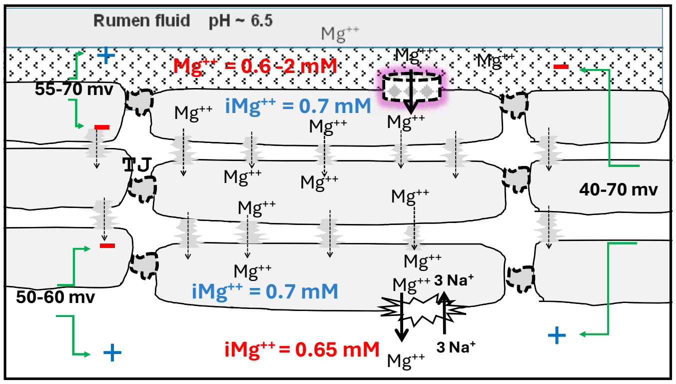


65

Magnesium Ion Crosses Apical membrane via TRPM7 channels (divalent cation channel)

The main driving force is the electrical potential difference across the apical cell membrane which is - 55 to – 70 mv, inside negative

66



67

High K diets inhibit transport of Mg ions thru TRPM7 channel

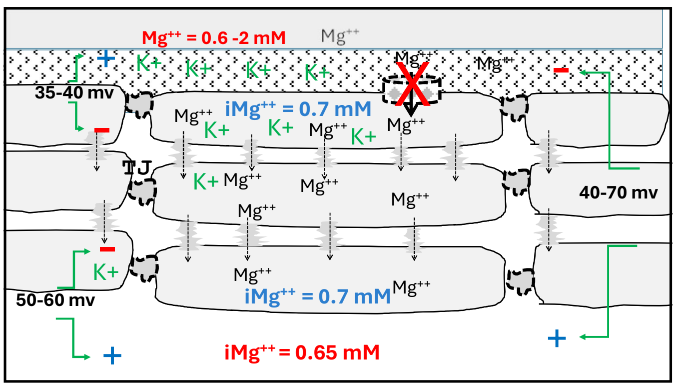
High potassium outside cell increases K+ leaking into cell (cell membranes are K leaky)

This causes potential difference across the apical membrane to be reduced

The driving force pushing Mg thru the TRPM7 channel is reduced!!!

Mg++ ion when diet Mg is low can no longer be transported by this mechanism

68



69

Weiss (2004) calculated an average apparent digestibility for diet Mg, from all sources, of 24% when diet K was 1% (close to the K requirement for a dry cow) when diet Mg between 0.2 and 0.36%.

AND apparent digestibility of Mg was reduced by 7.5% for every 1% increase in diet K.

Tebbe, Wyatt, & Weiss (2018)- demonstrated bioavailability of MgO was considerably lower than NRC 2001 suggested

CORRECTED IN THE 2021 NASEM!!!!

70

A 2nd Mg transporter exists at Apical Surface

2Cl- / Mg++ Co-Transporter

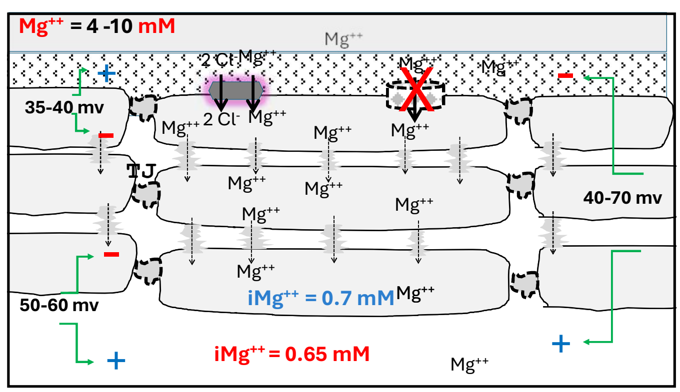
Uses energy of Chloride diffusing into an area of lower concentration and Mg moving into an area of relative negativity to drive Mg from rumen fluid into the cells

But this mechanism requires much higher concentrations of Mg ions be present in the rumen fluid to work!!!

Pre-calving and post-calving diets with 0.4% Mg generally ensures this pathway will work

-mid-lactation milk fever!!

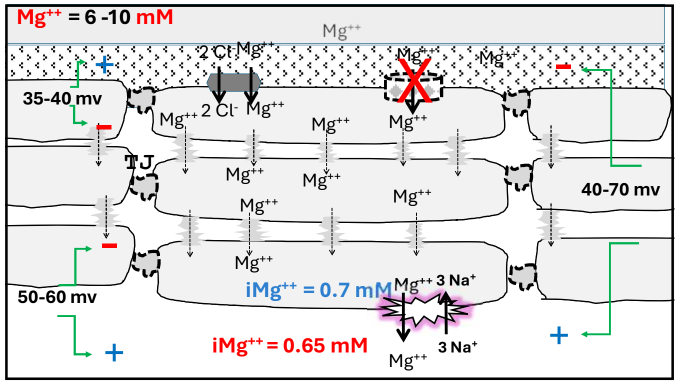
71



72

Finally , the magnesium must be pumped across the basolateral side, AGAINST its electrical gradient, by a Mg++/ 3 Na+ Exchanger

73



74

Magnesium – ONLY ABSORBED ACROSS RUMEN WALL

Pre-calving

- using $MgSO_4$ or $MgCl_2$ as "anions" also supplies readily available, soluble Mg.

-The better anion supplements on the market include Mg in this form to remove Mg worries pre-calving.

-Zeolite diets – beware that the zeolite binds magnesium!!!

Post-calving is the bigger issue!!!!!!
Magnesium Oxide – supplies Mg and acts as rumen alkalinizer.

MgO must become soluble to be available for absorption by rumen wall!!!!

75

Testing Magnesium Oxide Availability

Weigh out 3 g MgO into large vessel.

Add 40 ml of 5% acetic acid (white vinegar) slowly!!

Cap container and shake well and let sit 30 minutes. Check the pH.

Vinegar will be pH 2.6-2.8!

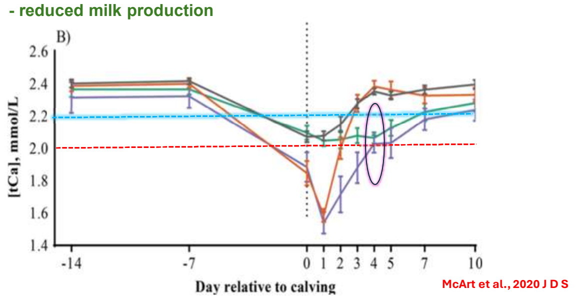
The best MgO will bring the pH up to 8.2.

The worst to just 3.8.

pH is a log scale so this represents >10,000 fold difference in buffering action.

76

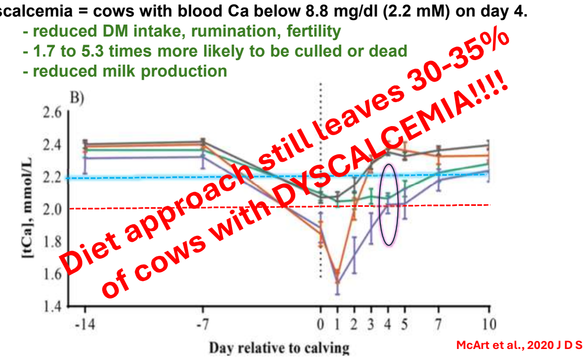
Dyscalcemia = cows with blood Ca below 8.8 mg/dl (2.2 mM) on day 4.
- **reduced DM intake, rumination, fertility**
- **1.7 to 5.3 times more likely to be culled or dead**
- **reduced milk production**



McArt et al., 2020 J D S

77

Dyscalcemia = cows with blood Ca below 8.8 mg/dl (2.2 mM) on day 4.
- **reduced DM intake, rumination, fertility**
- **1.7 to 5.3 times more likely to be culled or dead**
- **reduced milk production**



McArt et al., 2020 J D S

78

Oral Calcium Boluses

Typically each bolus supplies 30-45 g Ca in a highly soluble form, often as calcium chloride, to permit passive vitamin D independent absorption of Ca into the blood

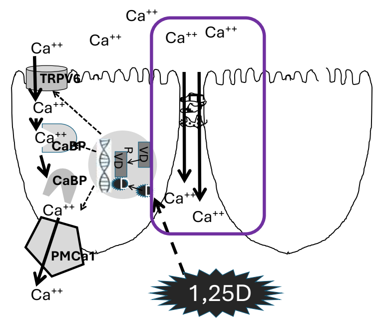
- effect lasts JUST 3-6 hrs

Convenient, easy to use – give to multiparous cows at calving and often again 12-24 hours later

85% of dairies with less than 125 cows use Ca boluses

60% of dairies that feed an anionic diet use Ca boluses.

79



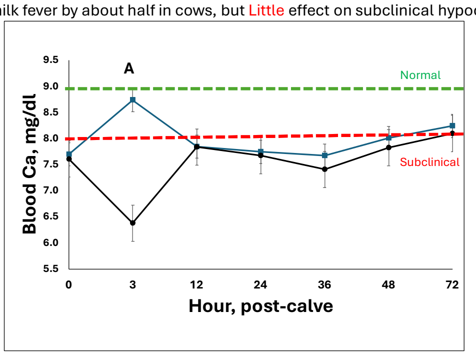
VITAMIN D INDEPENDENT **PARACELLULAR** CALCIUM ABSORPTION

Very Inefficient

Only ~ 4 g Ca from a 50 g Ca bolus gets into the blood!!!

80

Reduce milk fever by about half in cows, but Little effect on subclinical hypocalcemia



81

Paracellular Ca Absorption

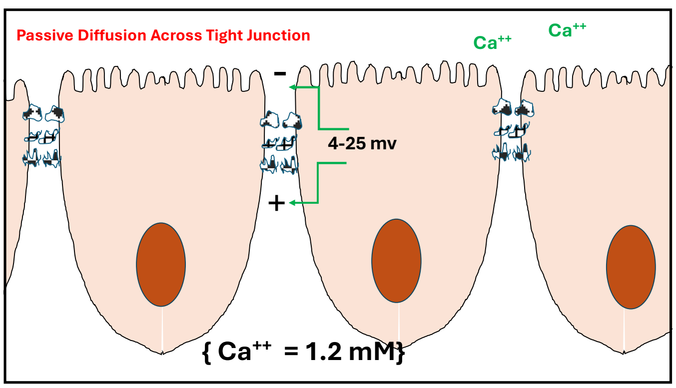
Ionized Ca concentration in interstitial fluids is ~ 1 mM .

To overcome the electrical potential stopping Ca++ from going across the tight junction requires a minimum of 4 mM Ca++ on luminal side of tight junction to get Ca++ to move to interstitial space.

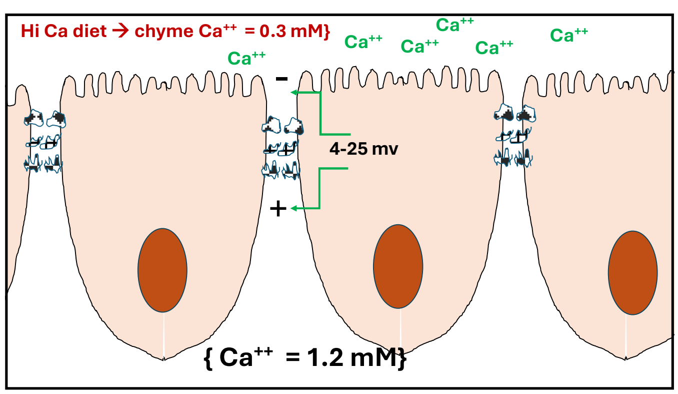
This can be achieved in calves fed milk (high Ca and very soluble) and in cows it is felt that with high Ca diets a portion (10-30%) of the Ca leaving the abomasum can be absorbed paracellularly in upper small intestine.

Ca Boluses- in localized areas of rumen the concentration of Ca++ will be high enough to push Ca++ across tight junctions for several hours

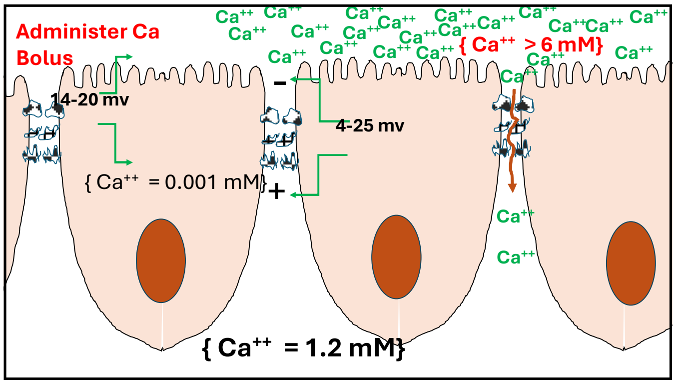
82



83



84



85

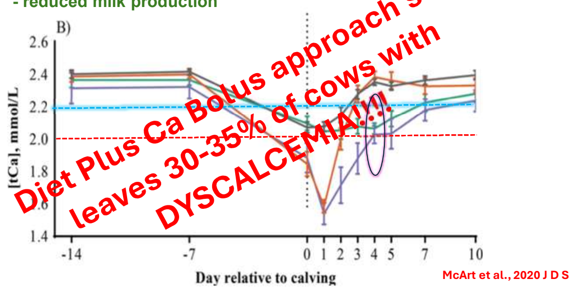
Ca salts suitable for incorporation into boluses for rapid elevation of blood Ca must be highly soluble at rumen pH

Solubility Within the Rumen (pH 6-7) at 39 Celsius

Calcium chloride = 104 g/ 100 ml water
Calcium propionate = 38 g /100 ml water
Calcium carbonate = 0.0007 g / 100 ml water
Calcium sulfate = 0.4 g/ 100 ml water
Calcium lactate = 9.4 g /100 ml water
Calcium acetate = 33 g / 100 ml water
Calcium gluconate = 5 g/100 ml water

86

Dyscalcemia = cows with blood Ca below 8.8 mg/dl (2.2 mM) on day 4.
- reduced DM intake, rumination, fertility
- 1.7 to 5.3 times more likely to be culled or dead
- reduced milk production

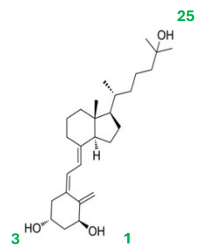


McArt et al., 2020 J D S

87

Solanum glaucophyllum

Plant that produces glycosides of 1,25-$(OH)_2$vitamin D_3.



Where OH on carbons 1,3 or 25 are replaced by 1-8 glucose molecules.

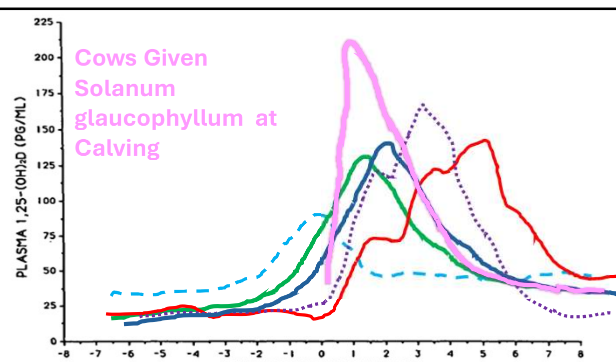
Glucose cleaved off in rumen liberating active form of vitamin D!!!

88

Since failure to produce 1,25-dihydroxyvitamin D is a cause of Milk fever and hypocalcemia:

Can we utilize S. glaucophyllum to supply a natural bioactive form of vitamin D and help maintain more normal blood calcium concentrations in early days of lactation??

89



90

New Zealand - 2 farms , one fed MgSO4, (urine pH 7.3) and one fed no anions at all
Cuttance et.al.,

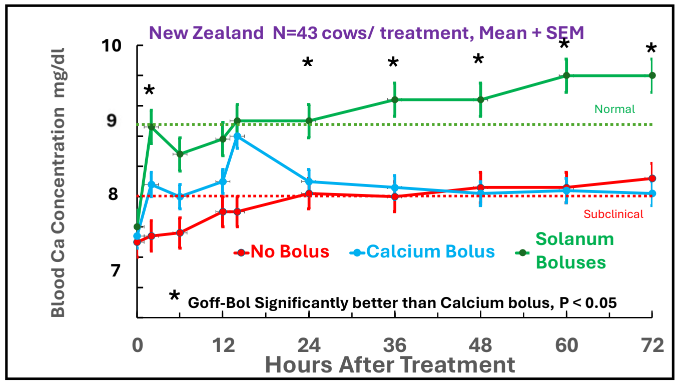
Treatments - 43 cows/ treatment by Parity

1. **Two Solanum Boluses given at Time 0**
2. **Two Calcium boluses, one at time 0 and one at 12 hours**
3. **No Boluses**

Blood sampled just before, and then 2, 6, 12, 14, 24, 36, 48, 60 and 72 hours after bolus administration (**at either 7 AM or 7 PM**)

8 mg/dl = **cutpoint for subclinical hypocalcemia**
8.8 mg/dl = cutpoint for Dyscalcemia

91



92

Keys to reducing hypocalcemia and dyscalcemia in fresh cow

ACTIVATE TRANSCELLULAR CALCIUM TRANSPORT QUICKLY AFTER CALVING

Keep diet K and P low and diet soluble Mg elevated

Ensure the cow's GI tract is turned on by 1,25-dihydroxyvitamin D quickly

93