Hypermagnesemia
in gastrointestinal tract

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Overview

- Serum magnesium concentration

  $[Mg^{2+}] > 2.6$ mg/dL in adults

  – Renal failure OR Excessive intake of magnesium

- Typically asymptomatic unless $[Mg^{2+}] > 4.8$ mg/dL

Jahnen-Dechent W, Ketteler M. Magnesium basics. Clin Kidney J. 2012
Chang WT, Radin B, McCurdy MT. Calcium, magnesium, and phosphate abnormalities in the emergency department. Emerg Med Clin North Am. 2014 May

Overview

- Mechanisms of hypermagnesemia include:
  1. Excess intake via oral, rectal, or IV medications
  2. Decreased renal excretion renal failure
  3. Redistribution intra- to extracellular space with acidosis
  4. Release from cells (for example, due to tumor lysis syndrome)

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Clinical Sequelae of Magnesium Disturbances

	mg/dL	Manifestation
Severe hypomagnesemia	<1.2	Tetany, seizures, arrhythmias
Mild to moderate hypomagnesemia	1.2-1.8	Neuromuscular irritability, hypocalcemia, hypokalemia
Normal	1.8-2.5	Normal magnesium level
Hypermagnesaemia	2.5-4.8	Typically asymptomatic
Mild hypermagnesaemia	4.8-7.0	Lethargy, drowsiness, flushing, nausea and vomiting, diminished deep tendon reflexes
Moderate hypermagnesaemia	7.0-12	Somnolence, loss of deep tendon reflexes, hypotension, electrocardiographic changes (bradycardia)
Severe hypermagnesaemia	>12	Complete heart block, cardiac arrest, apnea, paralysis, coma

Jesse B. Hall, Gregory A. Schmidt, John P. Kress; Principles of Critical Care, 4th edition
Magnesium and cardiovascular complications of chronic kidney disease, Nat. Rev. Nephrol. 2015

Incidence/Prevalence

- Moderate-to-severe hypermagnesemia is rare in persons with normal renal function
- Hypermagnesemia reported to be common in hospitalized patients
  - 2.8% - 13.5% hospitalization patient
- Upper limit of [Mg^{2+}]: 2 - 2.6 mg/dL

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Chang WT, Radin B, McCurdy MT. Calcium, magnesium, and phosphate abnormalities in the emergency department. Emerg Med Clin North Am. 2014 May

Cause

1. Excess intake
   - Ingestion of magnesium
     - Magnesium-contain medication
       - Cathartics, antacids, laxatives, and dietary supplements
   - Magnesium-containing enemas
   - IV infusion for seizure prophylaxis in eclampsia

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Chang WT, Radin B, McCurdy MT. Calcium, magnesium, and phosphate abnormalities in the emergency department. Emerg Med Clin North Am. 2014 May

Cause

2. Decreased renal excretion
   - Renal insufficiency
   - Familial hypocalciuric hypercalcemia (CaSR inactivation)
3. Other causes (redistribution and release)
   - Redistribution from intra- to extracellular space with acidosis
   - Release from cells, such as in tumor lysis syndrome
   - Primary adrenal insufficiency
   - Hypothyroidism

Hypomagnesemia and hypermagnesemia. Rev Endocr Metab Disord. 2003 May
Magnesium basics. Clin Kidney J. 2012
Calcium, magnesium, and phosphate abnormalities in the emergency department. Emerg Med Clin North Am. 2014 May

Pathophysiology

- 2^{nd} intracellular cation
- Shares chemical properties with calcium but has distinct biologic properties and regulation
- $[Mg^{2+}]$ homeostasis depends:
  1. Intestine: uptake
  2. Bone: storage system
  3. Kidneys: $[Mg^{2+}]$ excretion

TRPM6 and TRPM7—Gatekeepers of human magnesium metabolism, Biochimica et Biophysica Acta, 2007
Intestinal Absorption and Factors Influencing Bioavailability of Magnesium, Current nurtition Food science, 2017

Pathophysiology

- [Mg^{2+}] required 3.0-4.5 mg/kg/day
  - Female: 310-320 mg/day
  - Male: 400-420 mg/day

    - Green vegetables, nuts, seeds, and unprocessed cereals
    - About 10% of daily intake comes from drinking water

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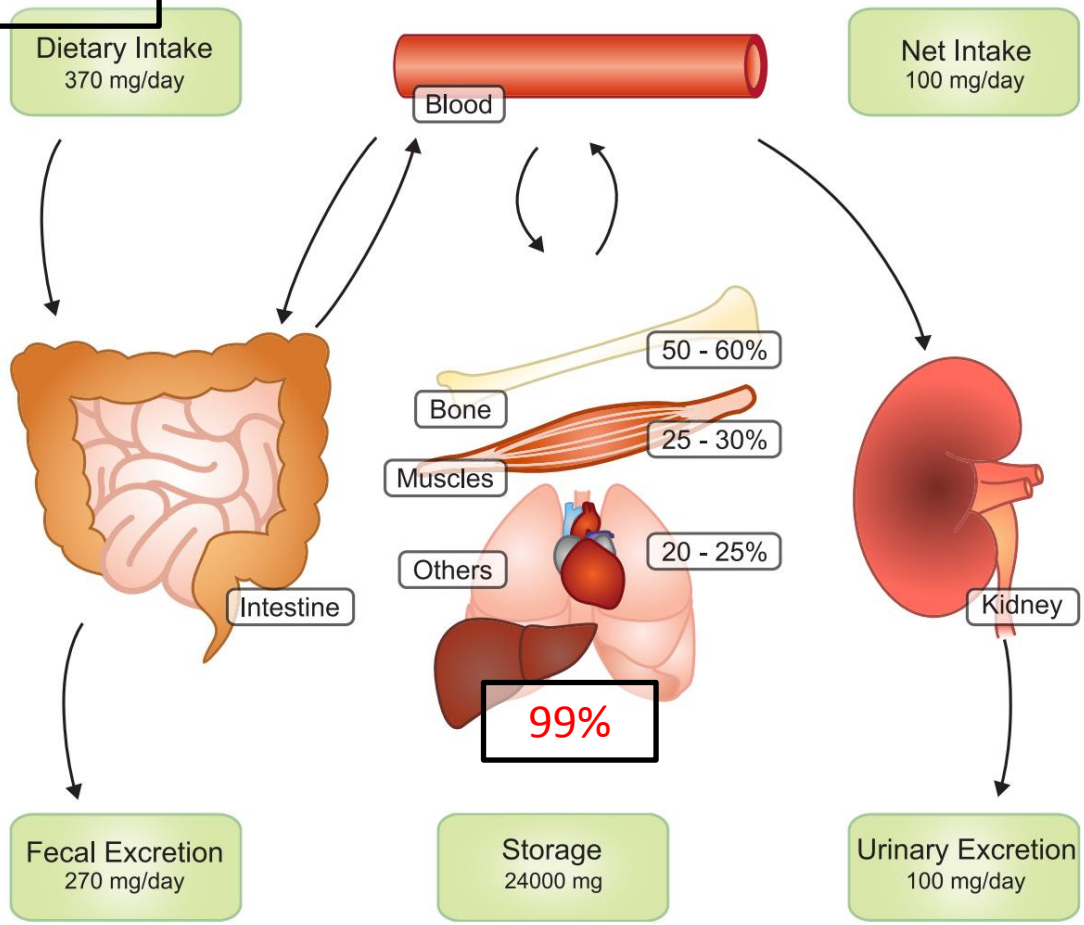
Pathophysiology

Distribution

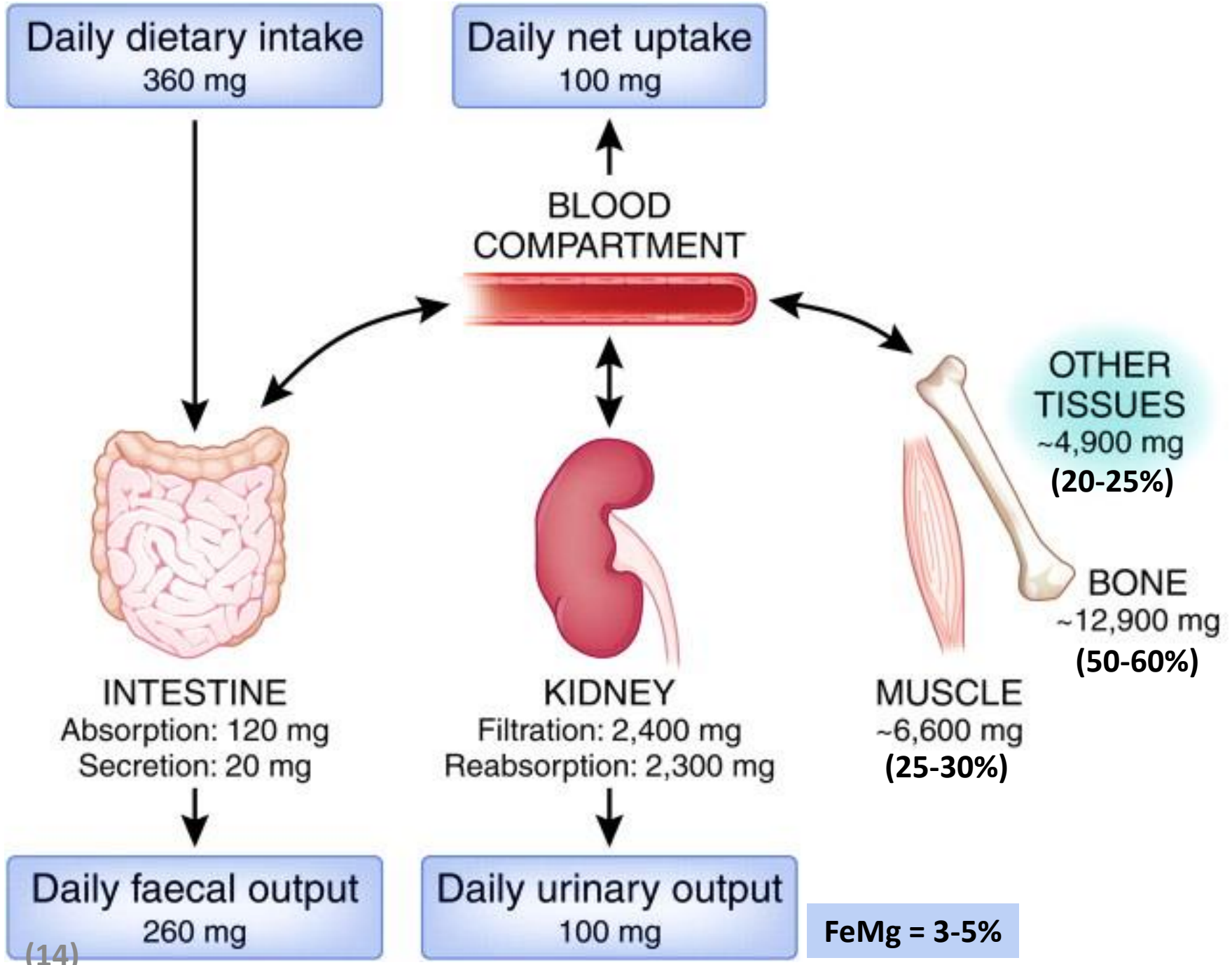


Magnesium in man: implications for health and disease, Physiol Rev. 2015

Pathophysiology

- Reported 85% of whole-body magnesium does not exchange or does so very slowly with an estimated half-life of 1,000 hours.

TRPM6 and TRPM7—Gatekeepers of human magnesium metabolism, Biochimica et Biophysica Acta, 2007



Regulation of magnesium balance: lessons learned from human genetic disease, Clin Kidney J. 2012

Pathophysiology - Kidney

- Mechanisms of Mg absorption in kidney
  - Maintaining magnesium homeostasis
  - Renal excretion: 0.5% - 70% of filtered load depending on magnesium balance
  - Filter 2,400 mg/day
    - 95% reabsorbed, and 3%-5% is excreted in urine
    - Proximal tube (10%)
    - Ascending loop of Henle (60%-70%)

Jahnen-Dechent W, Ketteler M. Magnesium basics. Clin Kidney J. 2012
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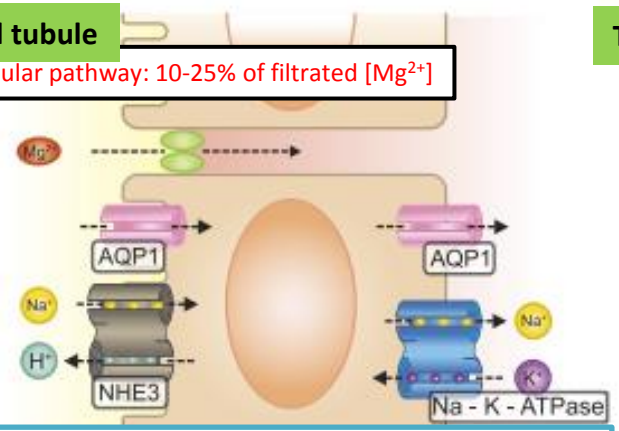
Proximal tubule

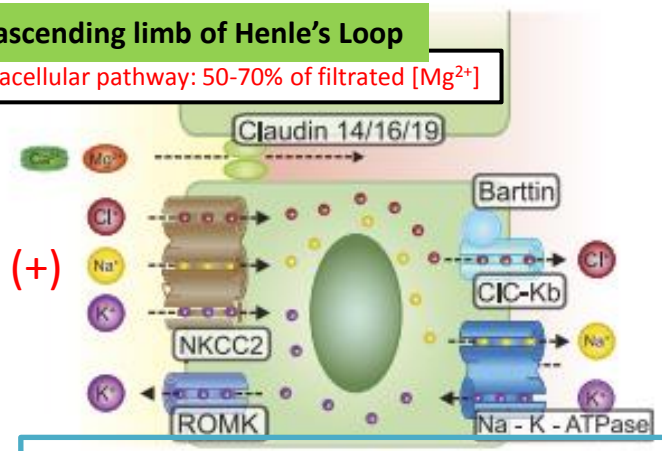
Paracellular pathway: 10-25% of filtrated [Mg^{2+}]



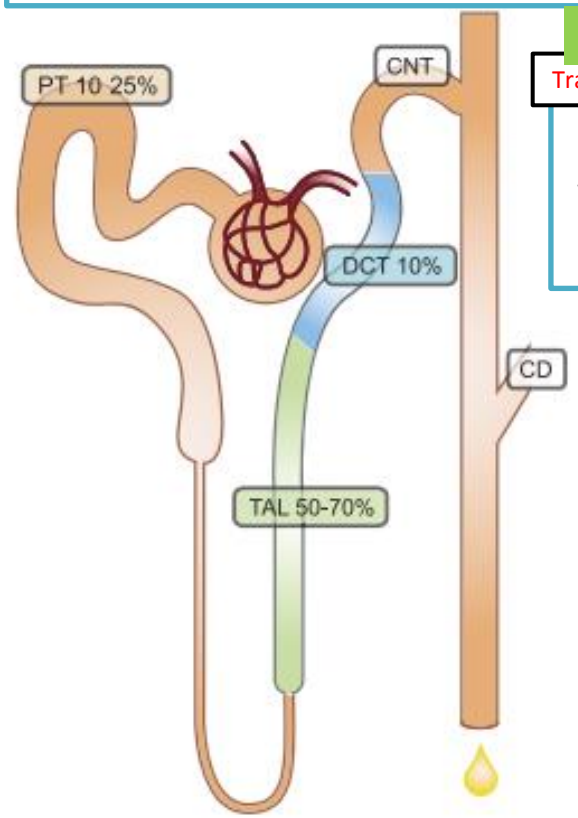
Gradient from Na^{+}/H^{+} and water

Thick ascending limb of Henle's Loop

Paracellular pathway: 50-70% of filtrated [Mg^{2+}]



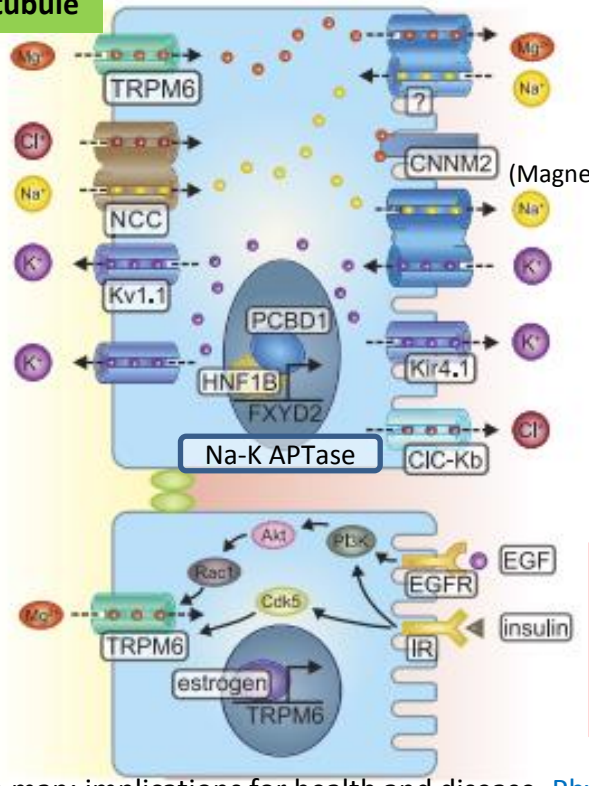
Epithelial voltage via NKCC2/ROMK



Distal convoluted tubule

Transcellular pathway

Epithelial voltage via NCC/Kv1.1

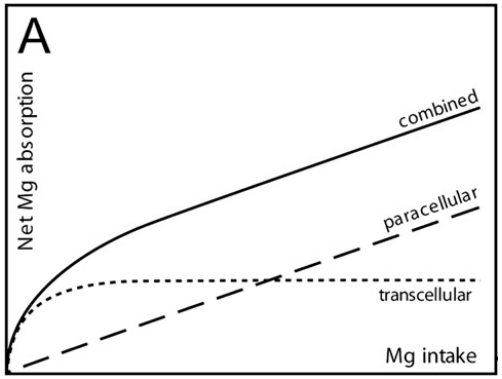


EGF
Insulin
Estrogen

Magnesium in man: implications for health and disease, Physiol Rev. 2015

Pathophysiology – GI tract

- Mechanisms of Mg absorption in intestine
  - Predominantly in small intestine (distal jejunum and ileum) via **paracellular pathway (80-90%)**
  - Smaller amounts are absorbed in the colon, mainly via a **transcellular pathway (10-20%)**
    - 24%-76% of dietary magnesium is absorbed
    - Absorption is determined by magnesium status



Regulation of magnesium balance: lessons learned from human genetic disease, Clin Kidney J. 2012
TRPM6 and TRPM7—Gatekeepers of human magnesium metabolism, Biochimica et Biophysica Acta, 2007
Intestinal Absorption and Factors Influencing Bioavailability of Magnesium, Current nurtition Food science, 2017

Mg Salts	Carbonate	Chloride	Citrate	Fumarate	Gluconate
Solubility	Nearly insoluble	High	Very good	Good	Moderate
Bioavailability	Extremely low	Good	Good	Good	Good
Delivery system	Tablets	Enteric coated tablets	Liquid tablets	Tablets	Tablets, liquid
Side effects	GI distress, diarrhea	GI distress, diarrhea	Laxative		GI distress, diarrhea

Bioavailability of US commercial magnesium preparations. Magnes. Res. 2001

Bioavailability and Pharmacokinetics of Magnesium Salts to Humans, Am J of therapeutic, 2001

Mg Salts	Glycinate	L-lactate	Oxide	K Mg citrate	DL-aspartate
Solubility	Good	Excellent	Extremely low	High solubility	Good
Bioavailability	Good	Excellent	Extremely low	Good	
Delivery system	Ingestion	Sustained release caplets	Tablets, capsule	Tablets	Tablets
Side effects		Minor GI disturbances	Emesis, diarrhea	No GI side effect	

Bioavailability of US commercial magnesium preparations. Magnes. Res. 2001
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Mg Salts	L-aspartate	Hydroxide	Salicylate	Sulfate	Aminoate
Solubility	Good		Freely soluble	Moderately soluble	
Bioavailability			80-100%		
Delivery system	Tablets	Tablets	Tablets	Iv solution	Tablets
Side effects		Occasional regurgitation and mild diarrhea			

Bioavailability of US commercial magnesium preparations. Magnes. Res. 2001

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Bioavailability of Mg preparation

- The complexity of [Mg^{2+}] absorption
  - **Direct method**: [Mg^{2+}] after oral administration
    - Insufficient to investigate: Rate and amount of [Mg^{2+}]
      - Rapid homeostasis: renal excretion + storage in compartment
  - **Indirect method**: faecal or urinary [Mg^{2+}] excretion after oral Mg2+ administration
    - Limitation: diet, long-term
  - **Isotopic method**: $^{25}Mg^{2+}$ and $^{26}Mg^{2+}$
    - highly abundant in nature; relative low sensitivity

Intestinal Absorption and Factors Influencing Bioavailability of Magnesium, Current nurtition Food science, 2017
Use of the stable isotopes technique to evaluate the bioavailability of a pharmaceutical form of magnesium in man. Pharm Res. 1998

Bioavailability of Mg preparation

- The bioavailability and intestinal absorption efficacy of orally ingested [Mg^{2+}] are influenced by **endogenous** and **exogenous** factors.

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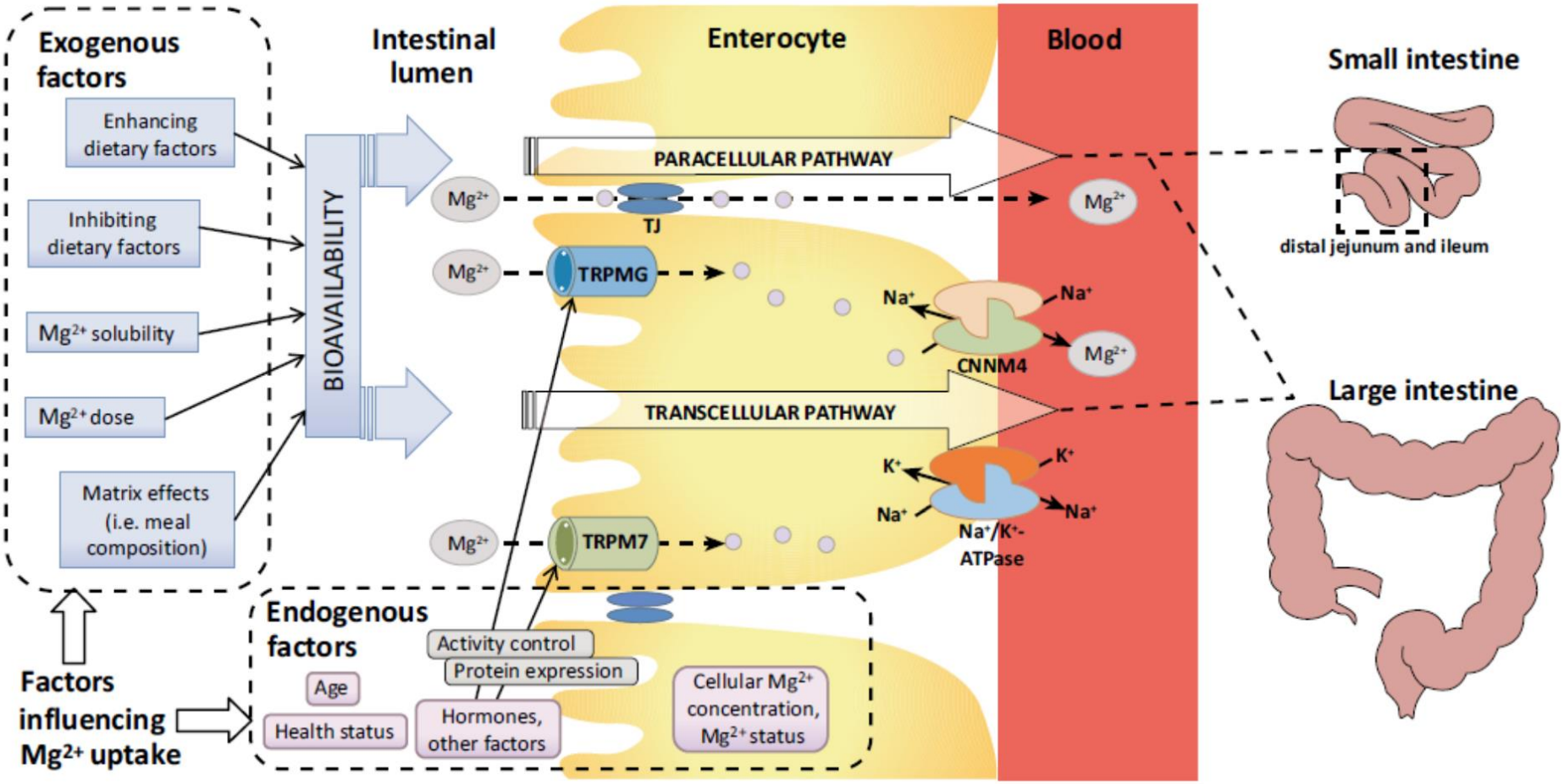
Pathophysiology



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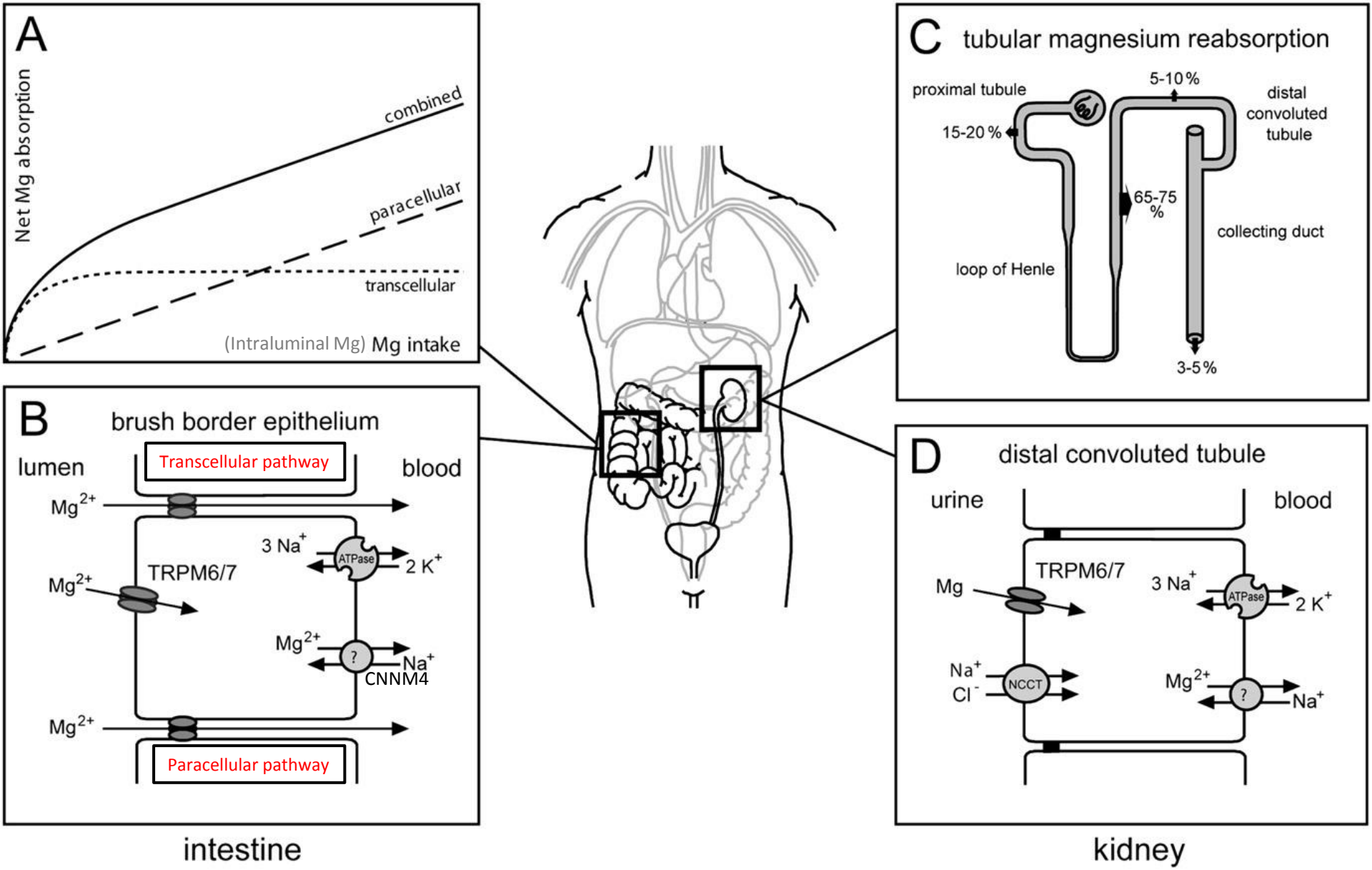

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Pathophysiology

- In principle, [Mg^{2+}] uptake is higher
  - Multiple low doses > single, large dose
  - Mg salt: less relevant than is often thought.
    - Bioavailability: organic > inorganic Mg salts

Intestinal Absorption and Factors Influencing Bioavailability of Magnesium, Current nurtition Food science, 2017

Pathophysiology

- Effects on other electrolytes
  - Hypocalcemia
    - Inhibition of parathyroid hormone (PTH) by magnesium
    - [Ca^{2+}] and [PTH] fell after magnesium infusion in 7 pregnant women being treated to suppress labor
  - Hyperkalemia
    - [Mg^{2+}] blocking potassium channels in cortical collecting duct, resulting in reduced potassium clearance

The influence of hypermagnesemia on serum calcium and parathyroid hormone levels in human subjects, NEJM, 1984
Hypomagnesemia and hypermagnesemia, Rev Endocr Metab Disord. 2003

Making the diagnosis

- Correlations: clinical presentation and $[Mg^{2+}]$
  - $[Mg^{2+}] < 4.8$ mg/dL are usually asymptomatic
  - Deep tendon reflexes may be diminished with $[Mg^{2+}] > 6.1$ mg/dL

Hypermagnesemia in a constipated female, The Journal of Emergency Medicine, 2013
Jahnen-Dechent W, Ketteler M. Magnesium basics. Clin Kidney J. 2012
Calcium, magnesium, and phosphate abnormalities in the emergency department. Emerg Med Clin North Am. 2014 May

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Magnesium and cardiovascular complications of chronic kidney disease, Nat. Rev. Nephrol. 2015

Making the diagnosis

- Interpreting serum magnesium
  - The serum [Mg^{2+}]: not reflect total body status
  - Avoid hemolysis : RBC [Mg^{2+}] > serum [Mg^{2+}]
  - No clinically available "ionized" magnesium test to diagnose deficiency based on free magnesium

Moe SM. Disorders involving calcium, phosphorus, and magnesium. Prim Care. 2008 Jun
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Making the diagnosis

- Additional test: causes of alterations in calcium levels
  - parathyroid hormone
  - vitamin D
  - phosphate
  - muscle enzymes (to assess for rhabdomyolysis)
- urinary 24-hour magnesium collection

Moe SM. Disorders involving calcium, phosphorus, and magnesium. Prim Care. 2008 Jun
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Making the diagnosis

Electrocardiography

- In patient with unexplained bradycardia or tachycardia (not diagnostic)
  - prolonged PR, QRS, and QT intervals
  - complete heart block
  - atrial fibrillation and asystole

Disorders involving calcium, phosphorus, and magnesium. Prim Care. 2008 Jun
Magnesium basics. Clin Kidney J. 2012
Calcium, magnesium, and phosphate abnormalities in the emergency department. Emerg Med Clin North Am. 2014 May

Making the diagnosis

Additional test

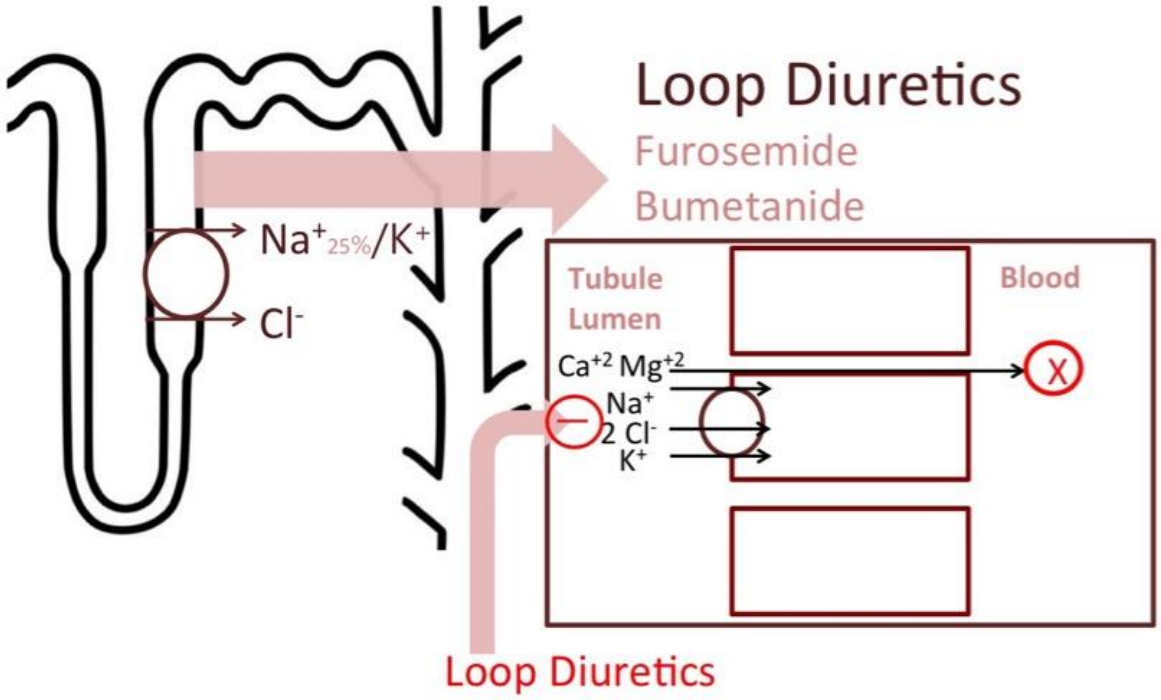
- Few case report showed
  - Abdominal computed tomography
    - Magnesium-containing bezoars
      - Magnesium oxide, aluminum and magnesium hydroxide

Hypermagnesemia in a constipated female, The Journal of Emergency Medicine, 2013
Antacid bezoar in a newborn. Pediatrics, 1979
Hypermagnesemia and intestinal perforation following antacid administration in a premature infant. Pediatrics, 1990

Management

- Most cases of sufficiently treated by
  - Discontinuing magnesium-containing supplements
  - Volume replacement with IV saline
- Loop diuretics: enhance magnesium excretion
  - Prevent volume overload from volume repletion
  - Monitor [Ca^{2+}], because increased calcium excretion

Moe SM. Disorders involving calcium, phosphorus, and magnesium. Prim Care. 2008 Jun
Jahnen-Dechent W, Ketteler M. Magnesium basics. Clin Kidney J. 2012
Chang WT, Radin B, McCurdy MT. Calcium, magnesium, and phosphate abnormalities in the emergency department. Emerg Med Clin North Am. 2014 May

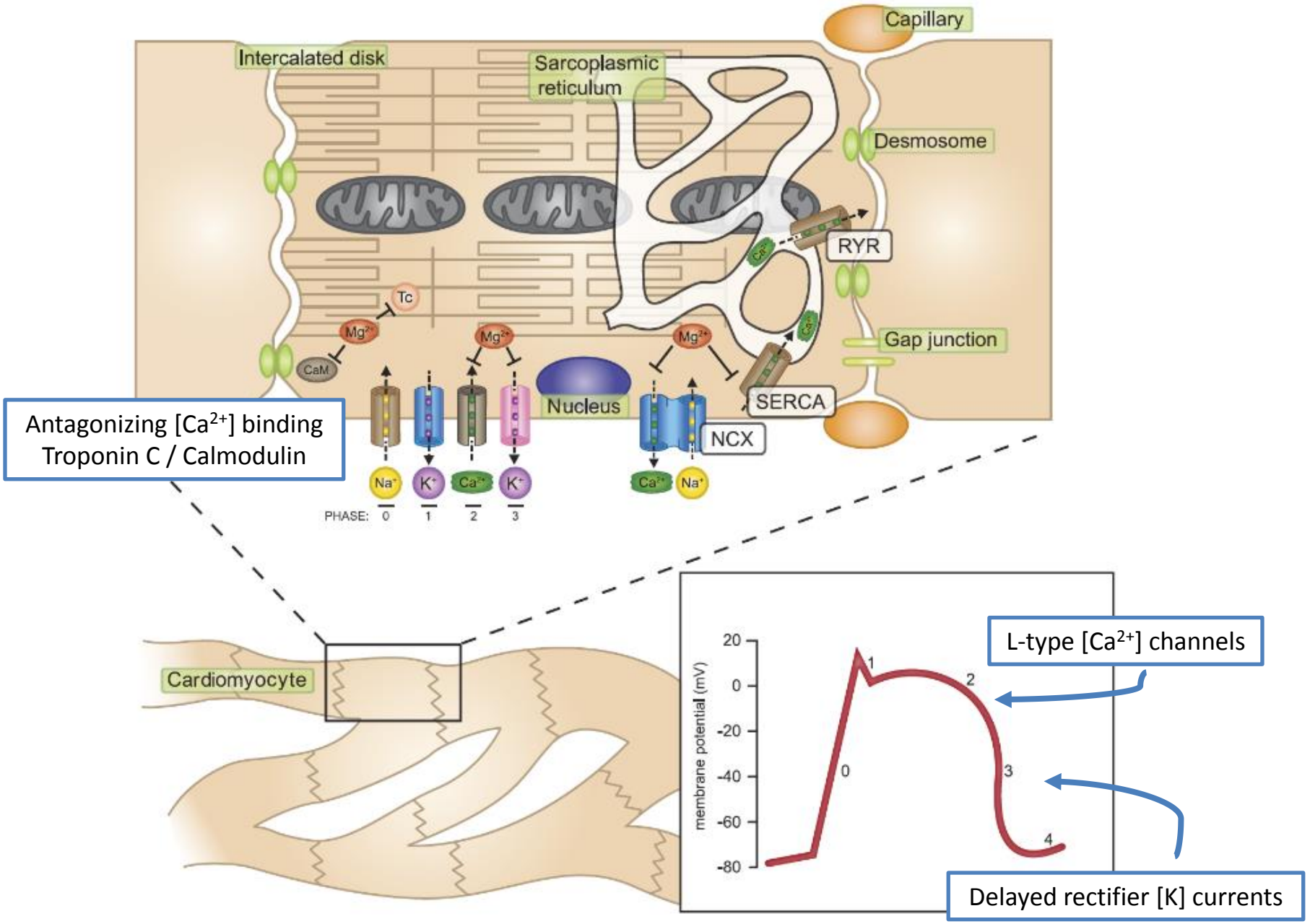


Reduced paracellular [Mg^{2+}] reabsorption

Management

- Cardiac dysfunction or hypotension and respiratory depression, additionally
  - Calcium to counteract effects of magnesium
    - [Mg^{2+}] interfere with synaptic transmission by blocking calcium channels; formulations used include
      - Elemental calcium 100-200 mg IV over 5-10 minutes
      - Calcium chloride 10% solution 5-10 mL (500-1,000 mg) IV
      - Calcium gluconate 1 g IV over 3 minutes

Excess magnesium. Pharmacol Rev. 1977
Magnesium basics. Clin Kidney J. 2012
Chang WT, Radin B, McCurdy MT. Calcium, magnesium, and phosphate abnormalities in the emergency department. Emerg Med Clin North Am. 2014 May



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Management

- For patients with severe renal dysfunction and/or severe hypermagnesemia, consider dialysis

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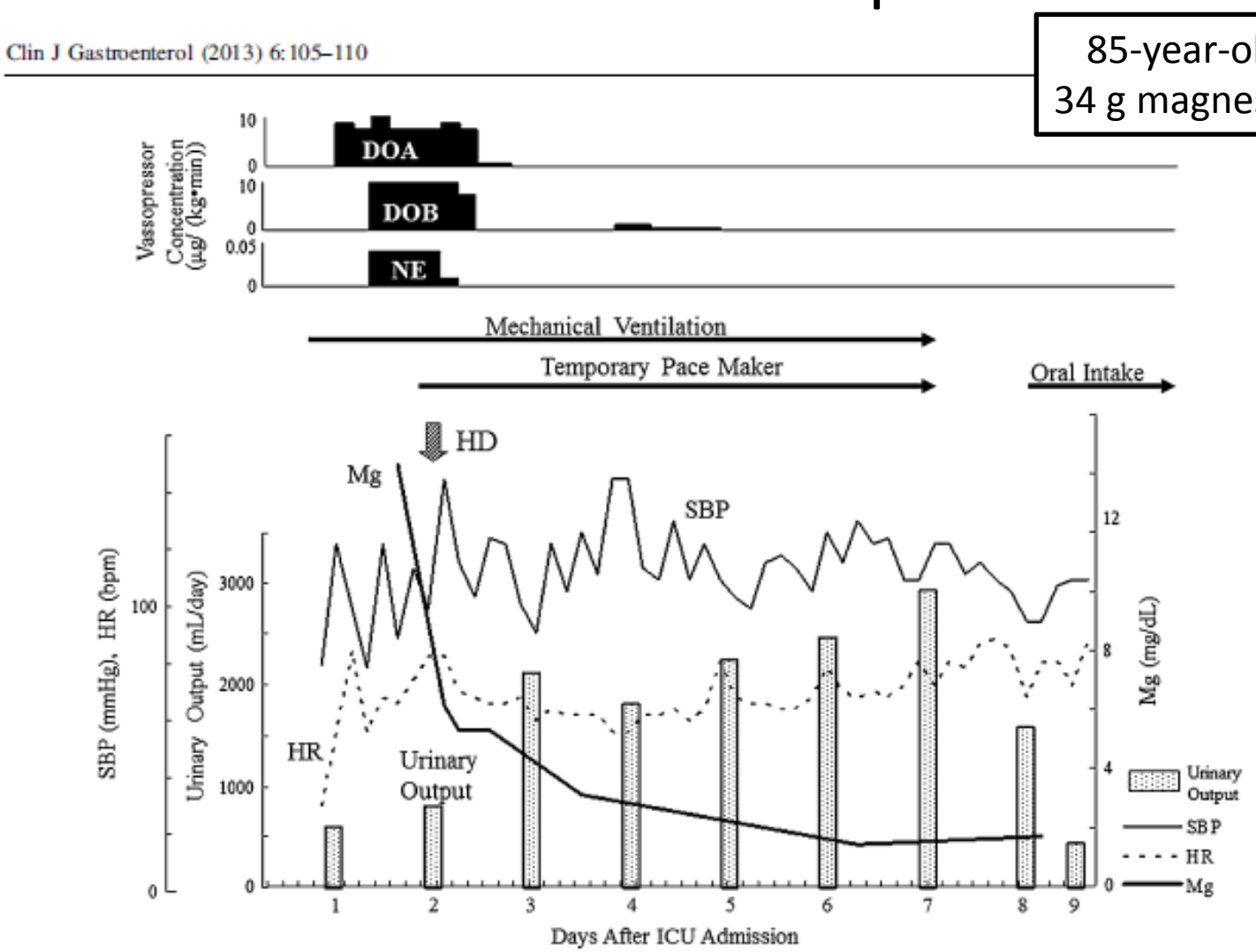
Chang WT, Radin B, McCurdy MT. Calcium, magnesium, and phosphate abnormalities in the emergency department. Emerg Med Clin North Am. 2014 May

Mg product develop hypermagnesemia in normal renal function patient.

85-year-old woman
34 g magnesium citrate



Fatal hypermagnesemia induced by preoperative colon preparation in an elderly woman, Clin J Gastroenterol, 2013

Management – case experience

- Regularly measured serum magnesium in
  - Geriatric patients
  - Administered magnesium oxide for prolonged periods

厚生労働省
Ministry of Health, Labour and Welfare

The Japanese Ministry of Health, Labour and Welfare. Revision of Precautions Magnesium Oxide. 2015

Prognosis and prevention

- With adequate renal function typically recover and normalize magnesium levels once supply of magnesium has been stopped.

- Reduced prescription magnesium-containing antacids or cathartics to patients with renal insufficiency.

Hypomagnesemia and hypermagnesemia, Rev Endocr Metab Disord. 2003

	Fleet Phospho-Soda	Bow-klean Powder	GI Klean Powder
	Sodium phosphate	Magnesium oxide, Sodium picosulfate, citric acid anhydrous	Sodium sulfate, sodium bicarbonate
清腸乾淨度	76.6-78.8%	72.5%	65.7-77.6%
自費價格	336元	578元	352元
Side effect	13.6-32.2% Renal toxicity, hyperphosphatemia, hypo-K/Ca	4.3-26.7% Hypermagnesemia Hypo-Na/K	10.4-33.1%
Benefit	Cheapest + cleanest		No renal adverse event
Disadvantage	Renal toxicity	Electrolyte imbalance	
Contraindication	Renal insufficiency	Renal insufficiency	
	Intestinal obstruction, intestinal perforation		


感謝您的指導與聆聽