Transport rénal de magnésium :
Physiologie normale et anormale

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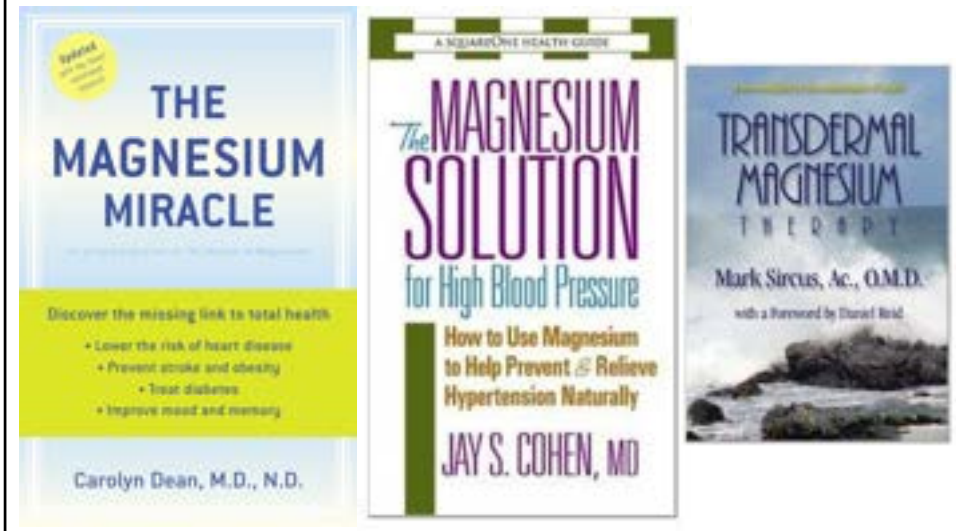

Sebastien L., 24 years old

- 2008: Traffic injury
- Multiple fractures
- Past history : cryptorchidia

- Plasma Mg = 0.42 mM

- What is Magnesium important for ?
- Where is Magnesium stored in the body ?
- How are Magnesium stores maintained ?
- What are the main causes of altered Magnesium metabolism ?

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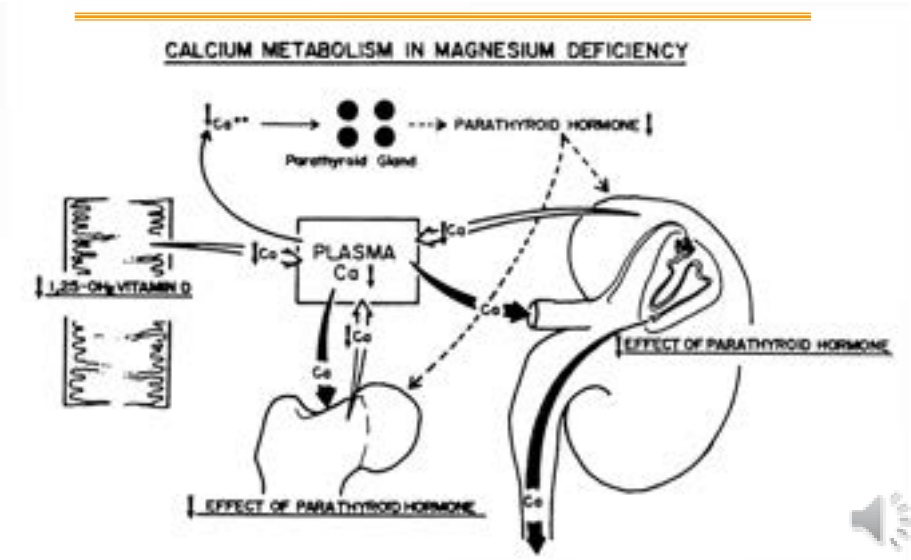
Many physiologic roles of magnesium

Enzyme substrate (ATPMg, GTPMg)
ATPase or GTPase (Na^+,K^+-ATPase, Ca^{++} ATPase,…)
Cyclases (adenylate cyclase, guanylate cyclase)
Kinases (hexokinase, creatine kinase, protein kinase)

Direct enzyme activation
Adenylate cyclase
Na^+,K^+,ATPase
Phospholipase C
Creatine kinase
Phosphofructokinase
5-Phosphoribosylpyrophosphate synthetase
Lipoprotein lipase

Influence Membrane Properties
Potassium transport
Calcium channel activity
Nerve conduction

Potential effect of Mg deficiency on calcium metabolism



Mg deficiency and potassium metabolism

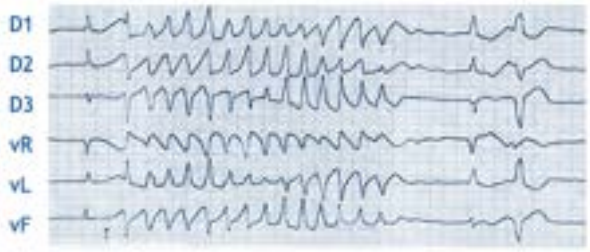
- 40-60 % of patients with hypomagnesemia have hypokalemia
(Wang R et al, JAMA, 1990)

- Of renal origin

- Due to removal of ATP inhibition of K channels in the kidney (ROMK)
(Huang SL et al, JASN, 2007)

Mg deficiency and heart

- Changes in ECG
  - Widening of QRS complex, peaking of T wave
  - Prolongation of the PR interval, further widening of the QRS complex, diminution of the T wave
- Ventricular arrhythmias



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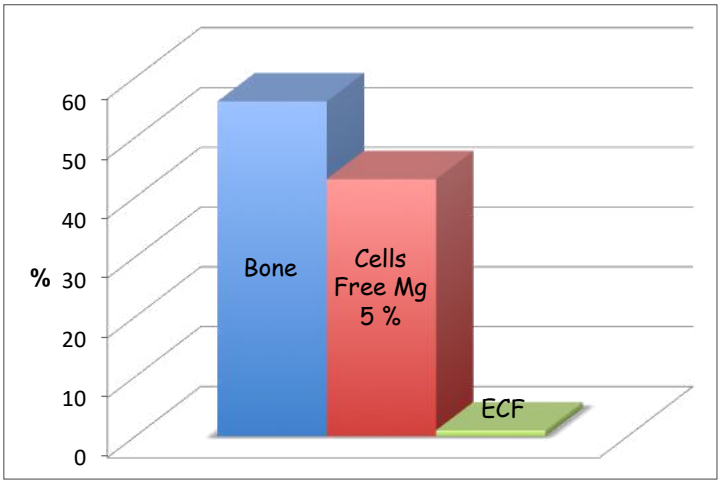
Magnesium stores in a normal adult



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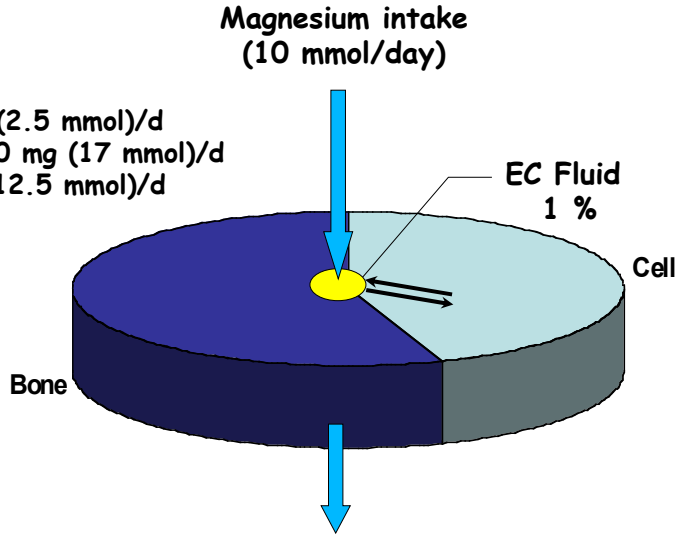
Magnesium balance in a normal adult

RDA:
- Infancy: 60 mg (2.5 mmol)/d
- Adolescence: 400 mg (17 mmol)/d
- Adult: 300 mg (12.5 mmol)/d



Balance of magnesium – Intestinal absorption

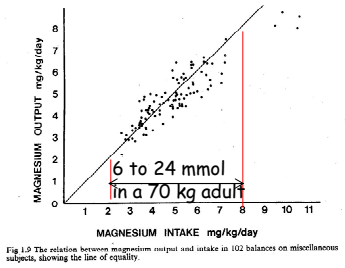
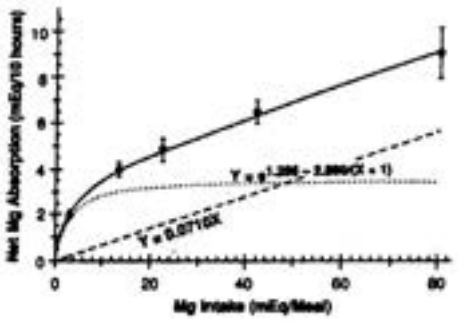


Fig 1.9 The relation between magnesium output and intake in 102 balances on miscellaneous subjects, showing the line of equality.

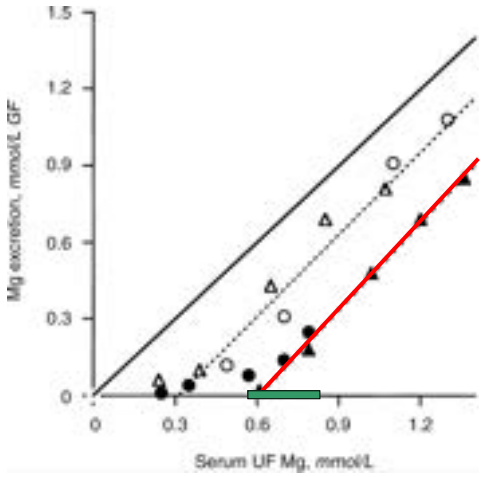
BEC Nordin, 1976



Fine et al., J Clin Invest. 1991

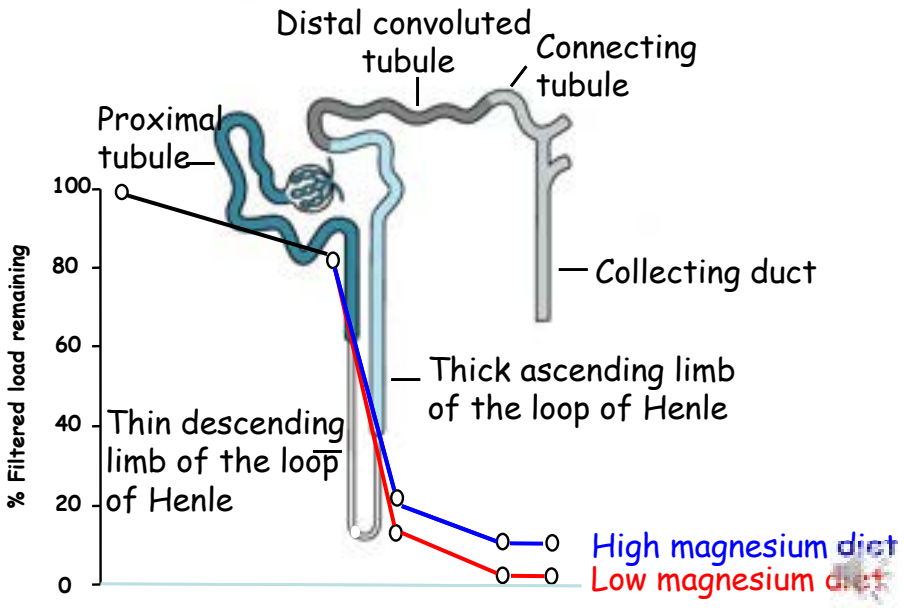
What maintains serum magnesium concentration ?

Normal range of plasma magnesium concentration in humans : 0.7 - 1.0 mM (ultrafilterable magnesium = 0.55 - 0.80 mM)

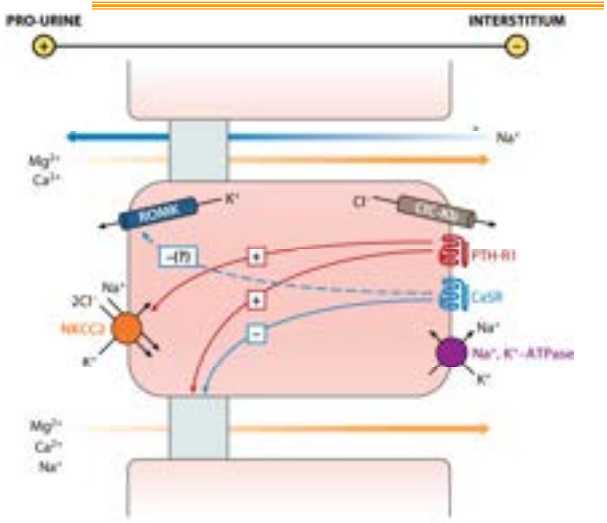


Blanchard et al., Kidney Int. 2002

Segmental handling of Mg



Model of transport in the cortical thick ascending limb (TAL)



Houillier P. 2014.
Annu. Rev. Physiol. 76:411–30

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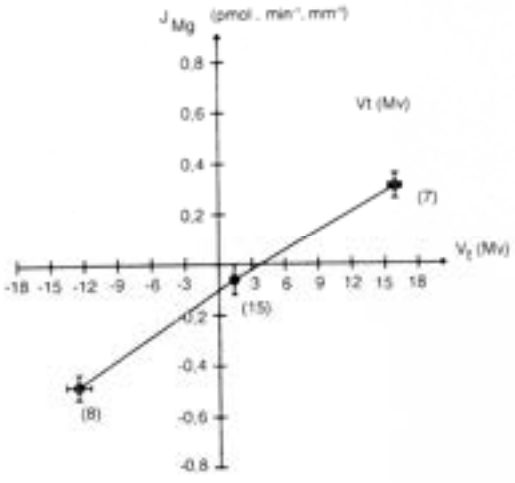
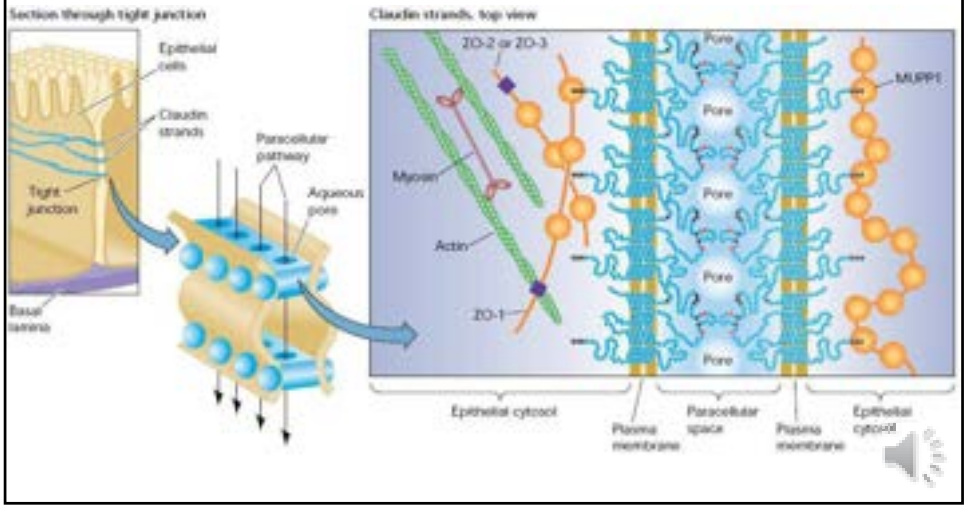
Net magnesium absorption is proportional to transepithelial voltage in the TAL

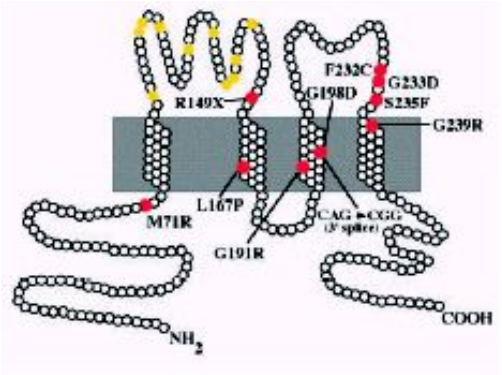


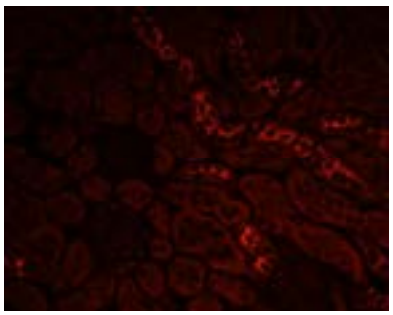
Sharegi and Agus, J. Clin. Invest., 1982

The important of the 'tight junction'



Paracellin –1/Claudin 16

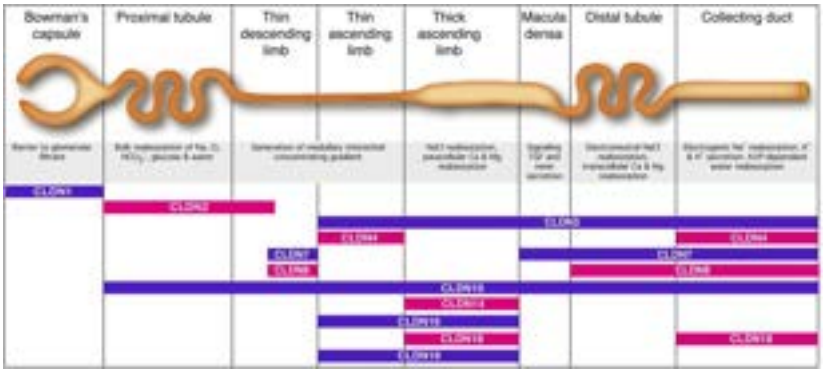




Unpublished data

D. Simon et al Science 1999;285:103-106

Localization of claudins along the adult mammalian renal tubule.

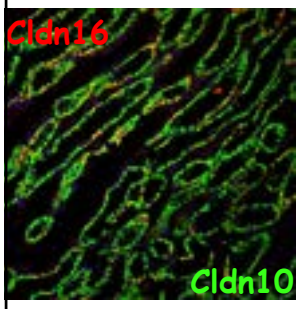


Alan S.L. Yu JASN 2015;26:11-19

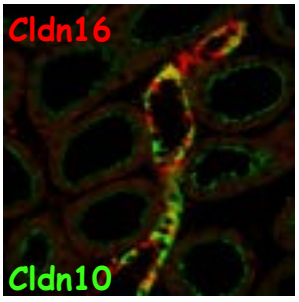
JASN

Exclusion réciproque de l'expression des claudines

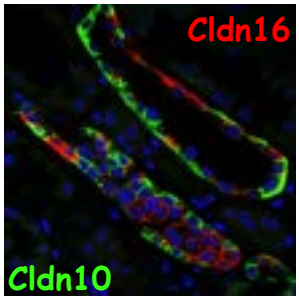
Rat



Rat

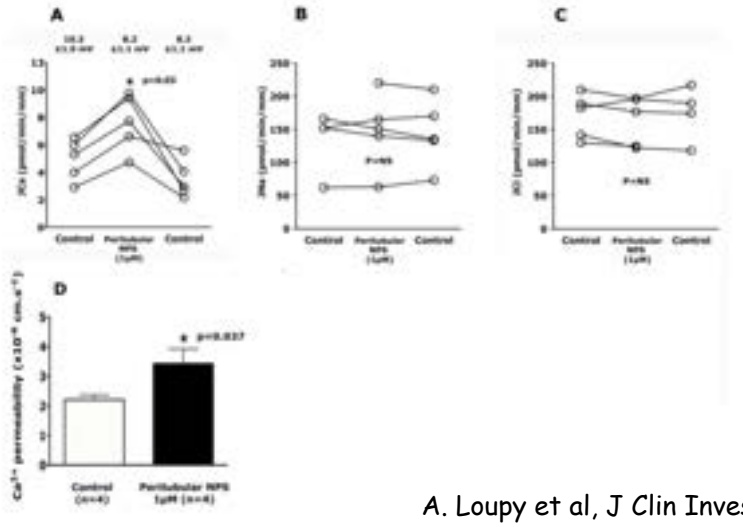


Humain



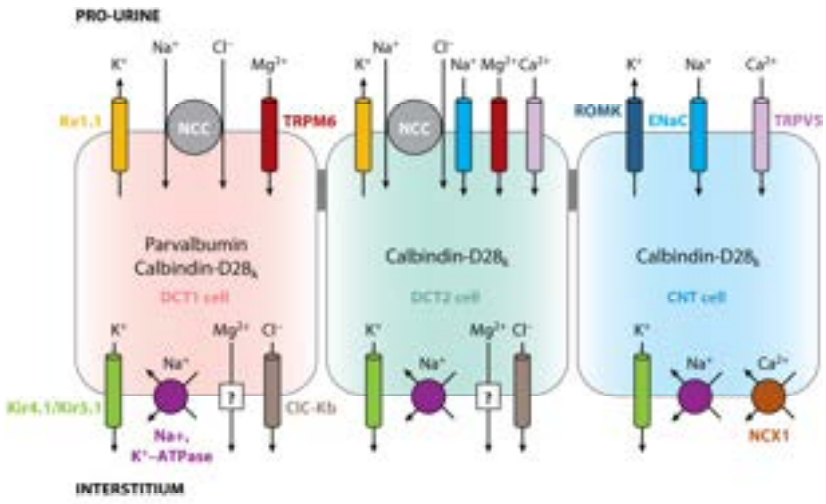
d'après Caroline Prot-Bertoye et al. AJP Renal, 2021

The permeability of the paracellular pathway is controlled



A. Loupy et al, J Clin Invest, 2012

Model of transport in the **distal tubule**



Houillier P. 2014.
Annu. Rev. Physiol. 76:411–30

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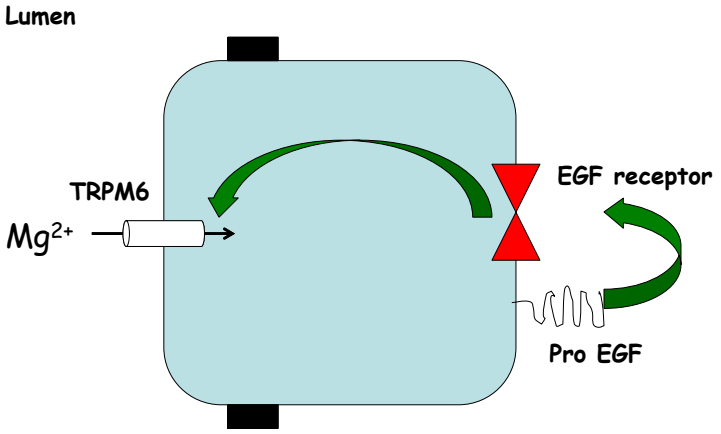
EGF receptor activation is required for Mg absorption in the DCT



Hypomagnesemia and chemotherapy

- Platinum salt. Incidence > 30 %
- Anti EGF-R antibody (cetuximab, panitumumab) : RR = 5.83 (Petrelli et al, Expert Opin Drug Saf, 2012)
- Incidence :
  - Decrease in blood magnesium : > 90 %
  - Severe hypomagnesemia: 6-23 %

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Mg depletion and hypomagnesemia

- Hypomagnesemia usually means magnesium depletion
- Magnesium depletion might be more common than hypomagnesemia
- Magnesium tolerance test

(Ryzen E. et al, Magnesium, 1985)

Mg-losing disorders

- Gastrointestinal disorders
  - Urinary Mg < 1 mmol/d
  - Nasogastric suction/vomiting
  - Diarrhea
  - Malabsorption syndromes
  - Extensive bowel resection
  - Malnutrition
  - Acute haemorrhagic pancreatitis
  - gHKA inhibitors (PPI)
  - Hypomagnesaemia with secondary hypocalcaemia
- Renal disorders
  - Urinary Mg > 1 mmol/d

gHKA inhibitors (PPI)

- Blood magnesium at presentation
- 0.37 ± 0.27 mmol/L
- Urinary magnesium at presentation
- 0.49 ± 0.42 mmol/24 h

JPF Bai, Mol. Pharmaceutics, 2012

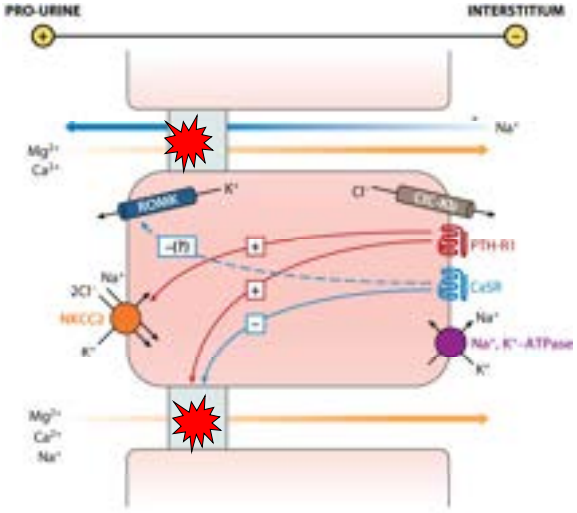
Acquired Mg-losing disorders of renal origin

- They are common
- Osmotic diuresis
- Hypercalcaemia
- Drugs
  - Diuretics, Aminoglycosides, Cisplatin, Cyclosporin/FK506, EGF receptor inhibitors…
- Alcohol
- Metabolic acidosis

Hereditary renal Mg-losing disorders

- Isolated Mg-losing disorders
- Mg- and Ca-losing tubular disorders

Familial **hypomagnesaemia** with hypercalciuria and nephrocalcinosis



Houillier P. 2014.
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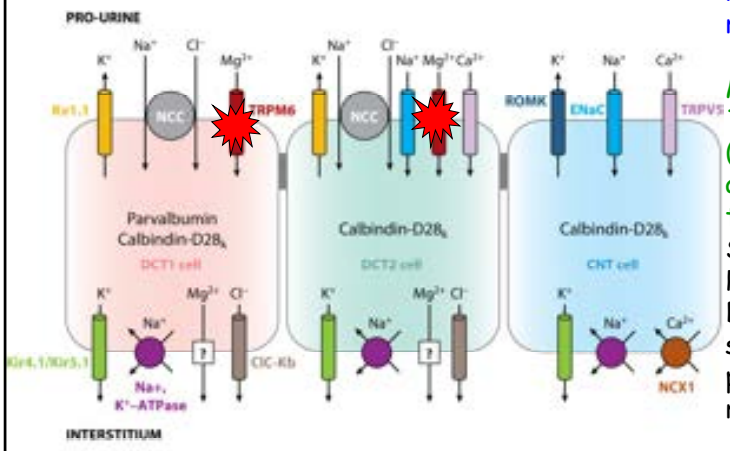
Autosomal recessive

Claudin 16 or Claudin 19 loss-of-function mutations

Nephrocalcinosis

Renal failure

Hypomagnesaemia with secondary hypocalciuria



Houillier P. 2014.
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Autosomal recessive

Mutation in the *TRPM6* gene (mixed intestinal and renal transport defect)

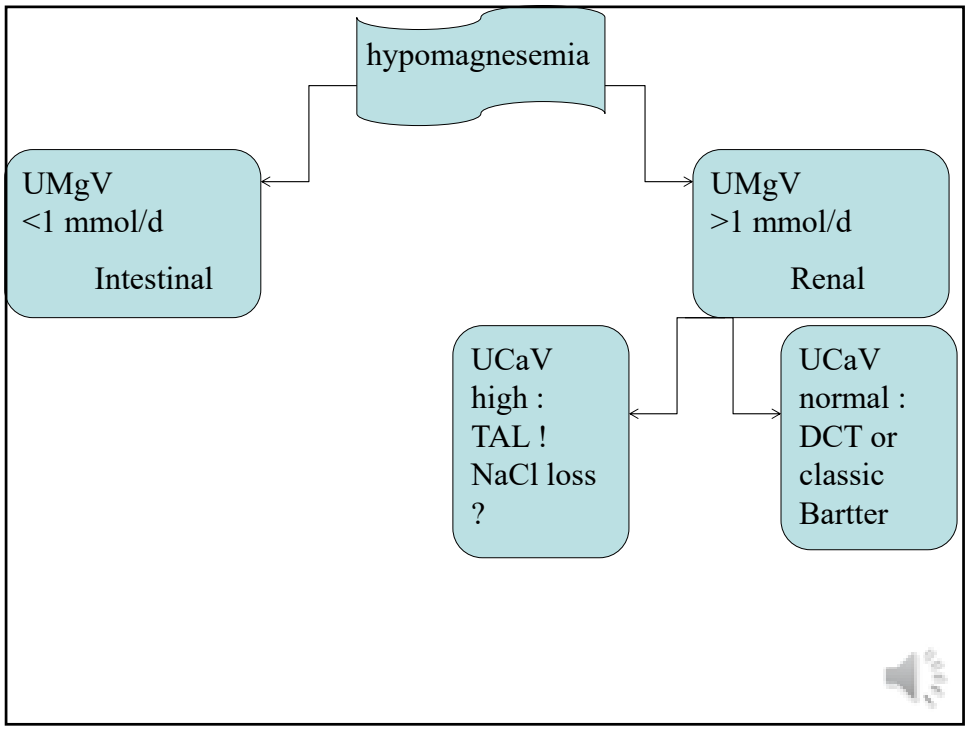
Seizures

Hypocalcaemia

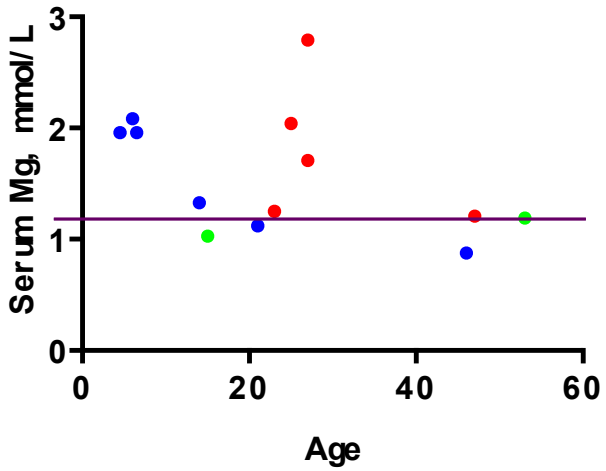
Defect in PTH secretion and peripheral resistance to PTH

No nephrocalcinosis

No renal stone



Hypermagnesemia in the HELIX syndrome (Claudin 10b mutation)



S. Hadj-Rabia et al, Genet Med, 2017

Sebastien L., 24 years old

- Plasma Mg = 0.42 mM
- Urinary Mg = 4 mmol/d
- Renal US : cysts (bilateral)
- UCaV = 4 mmol/d
- No renal NaCl loss
- No diabetes mellitus (yet)
- TCF2 : deletion of exon 2

Conclusion

- Renal tubular Mg reabsorption plays a prominent role in the maintenance of plasma Mg concentration
- Magnesium losing disorders are common
- The mechanisms underlying these disorders demonstrate a surprising variety
- Monogenic diseases help us to understand the functions of these transport or regulatory proteins

Message personnel

- Si vous êtes intéressé-e par un travail de recherche (M2 ou autre) dans le domaine des transports ioniques, contactez moi

- pascal.houillier@inserm.fr