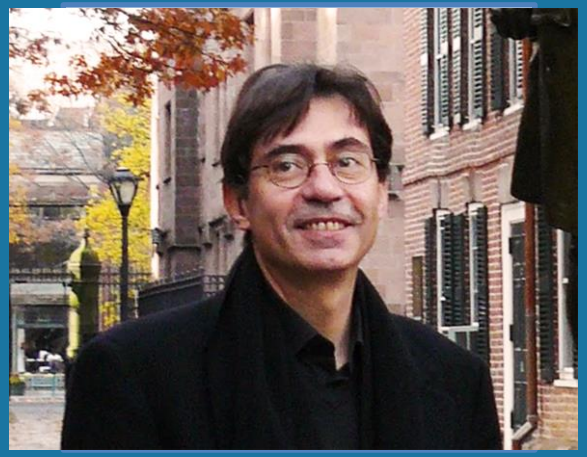
Welcome to

ERKNet/ERA Educational Webinars on Pediatric Nephrology & Rare Kidney Diseases

Disorders of renal calcium handling

WEBINAR

25/04/2023



Speaker: Pascal Houillier (Paris, France)

Moderator: Elena Levtchenko, Amsterdam

ERKNet
The European Rare Kidney Disease Reference Network

ERA
LEADING EUROPEAN NEPHROLOGY

Disorders of renal calcium handling

Pascal Houillier
Université Paris Cité

Case

- 4 year old boy
  - Seizures
  - Plasma calcium : 1.6 mmol/L
  - Plasma magnesium : normal
  - Plasma PTH : 15 pg/mL (« normal »)
  - eGFR « normal »
  - Urinary calcium « normal »

- Which one is the most likely diagnosis?
  - A. Hypoparathyroidism
  - B. Vitamin D-dependent rickets
  - C. Pseudohypoparathyroidism type 1

- Hypoparathyroidism
- Treatment: Alfacalcidol + calcium carbonate

- 22 years old
  - On alfacalcidol + calcium carbonate
  - Episodes of tetany
  - Plasma calcium : ~2.0 mmol/L
  - Plasma magnesium : normal
  - Urinary calcium : ~10 mmol/d
  - eGFR : 40 mL/min/1.73 m^2
  - Nephrocalcinosis
  - No renal salt-wasting syndrome

- Point mutation in the *CASR* gene: autosomal dominant hypocalcemia

- Treatment by rhPTH

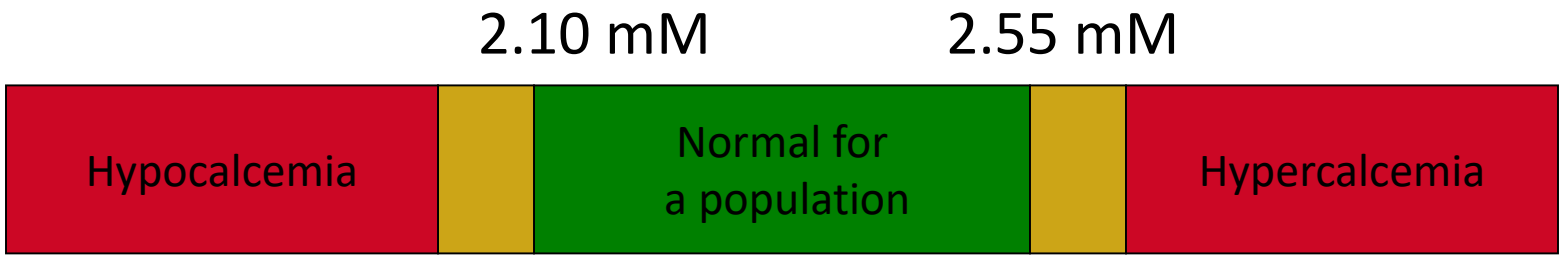
Outline

- To highlight the role of calcium reabsorption in the kidney in calcium homeostasis
- To describe the mechanisms and factors involved in calcium reabsorption in the kidney
- To describe the disorders of calcium reabsorption in the kidney

Serum calcium concentration

Adapted from Goldstein DA. Serum Calcium. In: Walker HK, Hall WD, Hurst JW, editors. Clinical Methods: The History, Physical, and Laboratory Examinations. 3rd edition. Boston: Butterworths; 1990.
Chapter 143. Available from: https://www.ncbi.nlm.nih.gov/books/NBK250/ Accessed April 2021.

Serum calcium concentration



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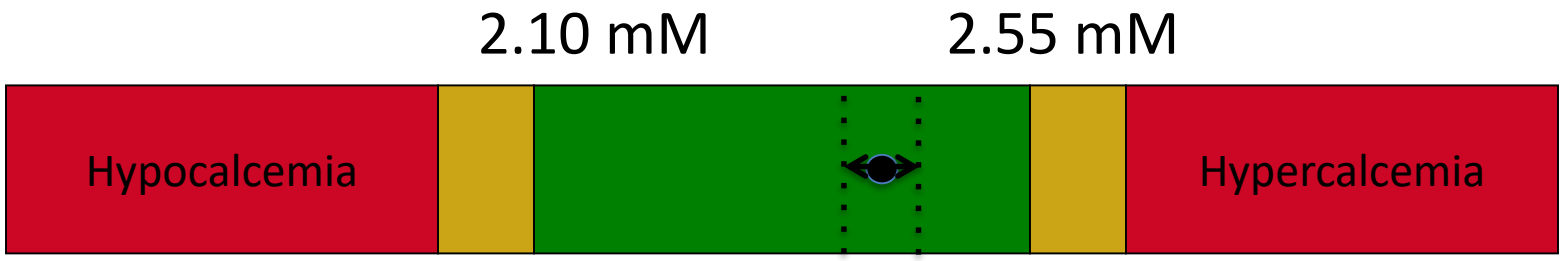
Serum calcium concentration



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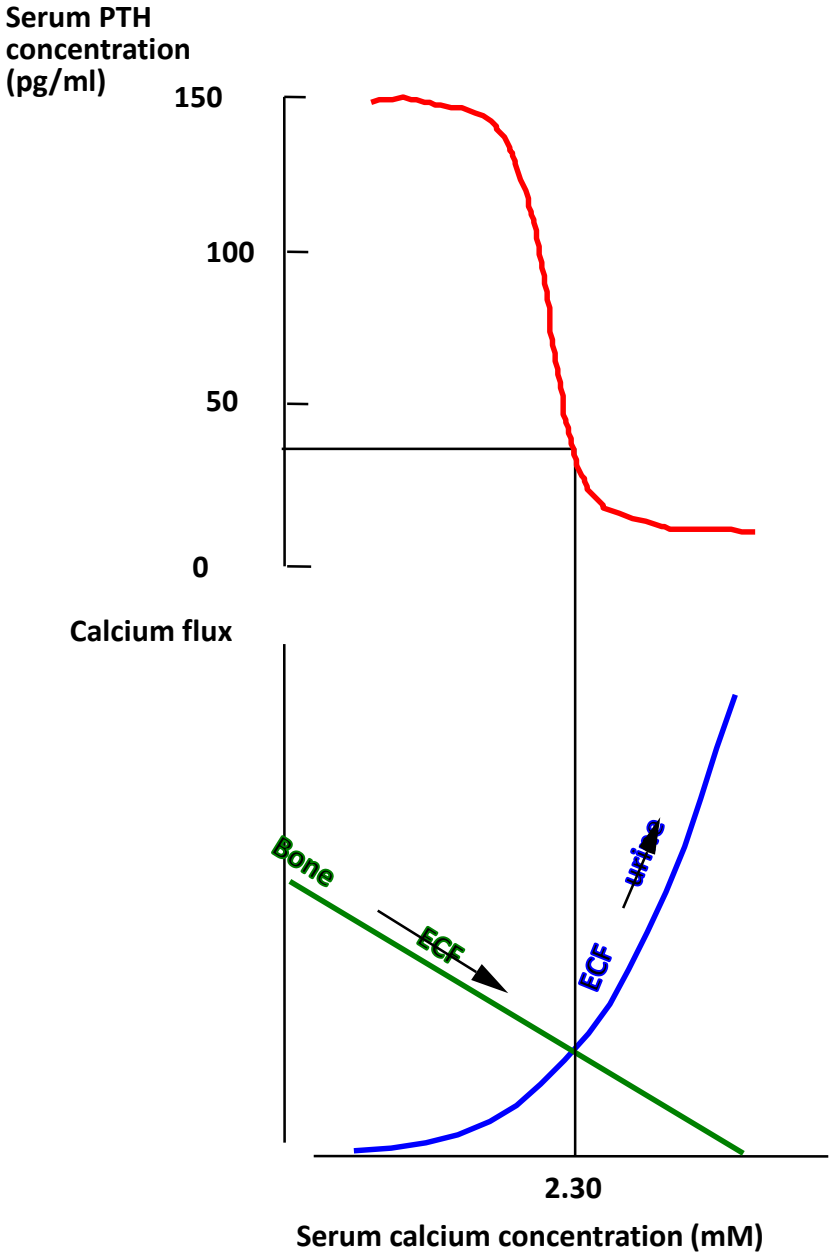
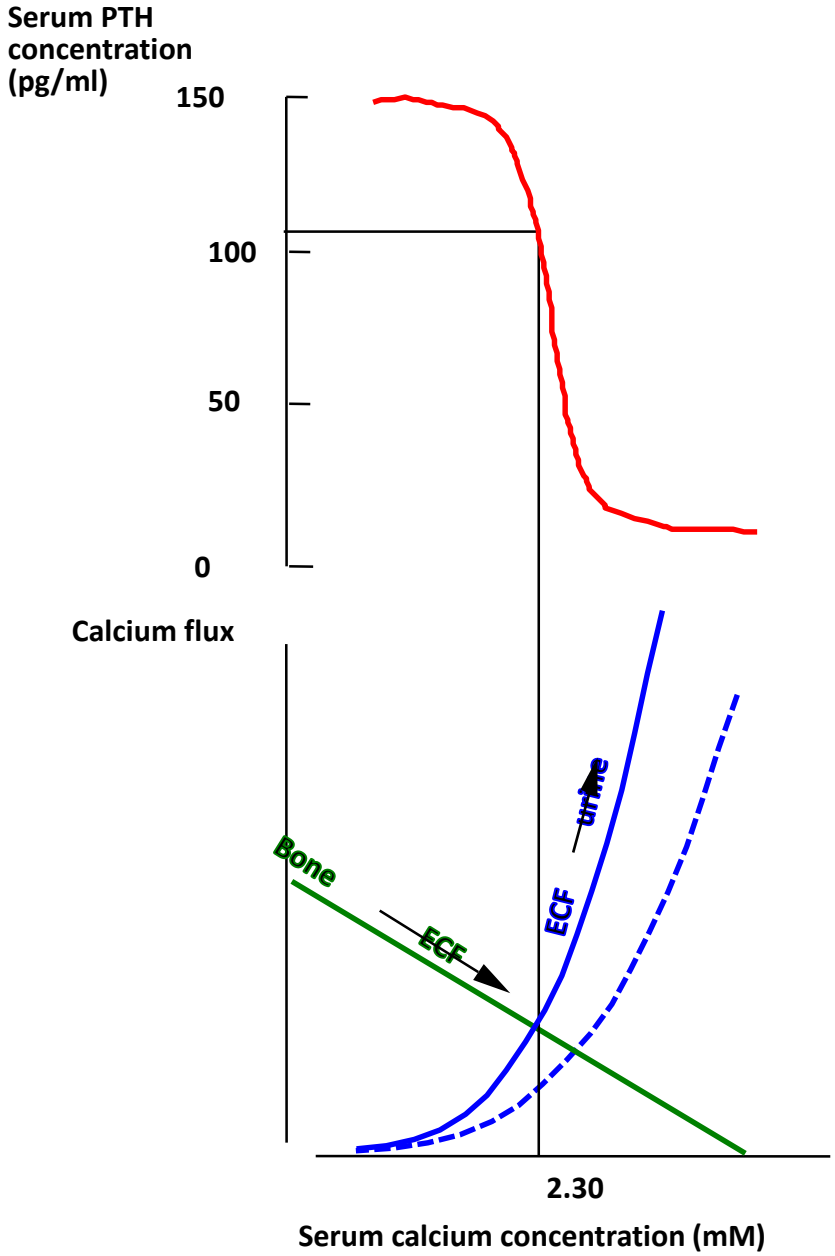
Chapter 143. Available from: https://www.ncbi.nlm.nih.gov/books/NBK250/ Accessed April 2021.

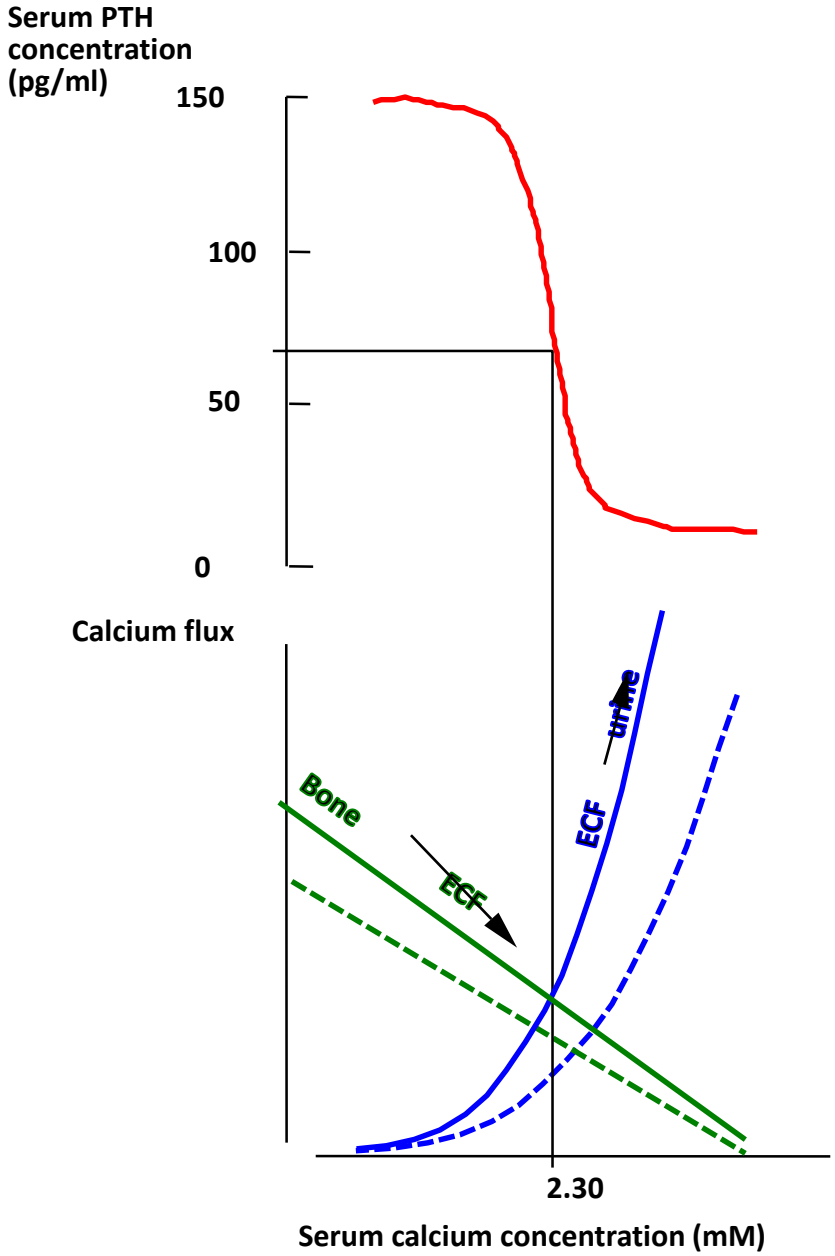
What maintains serum calcium concentration ?



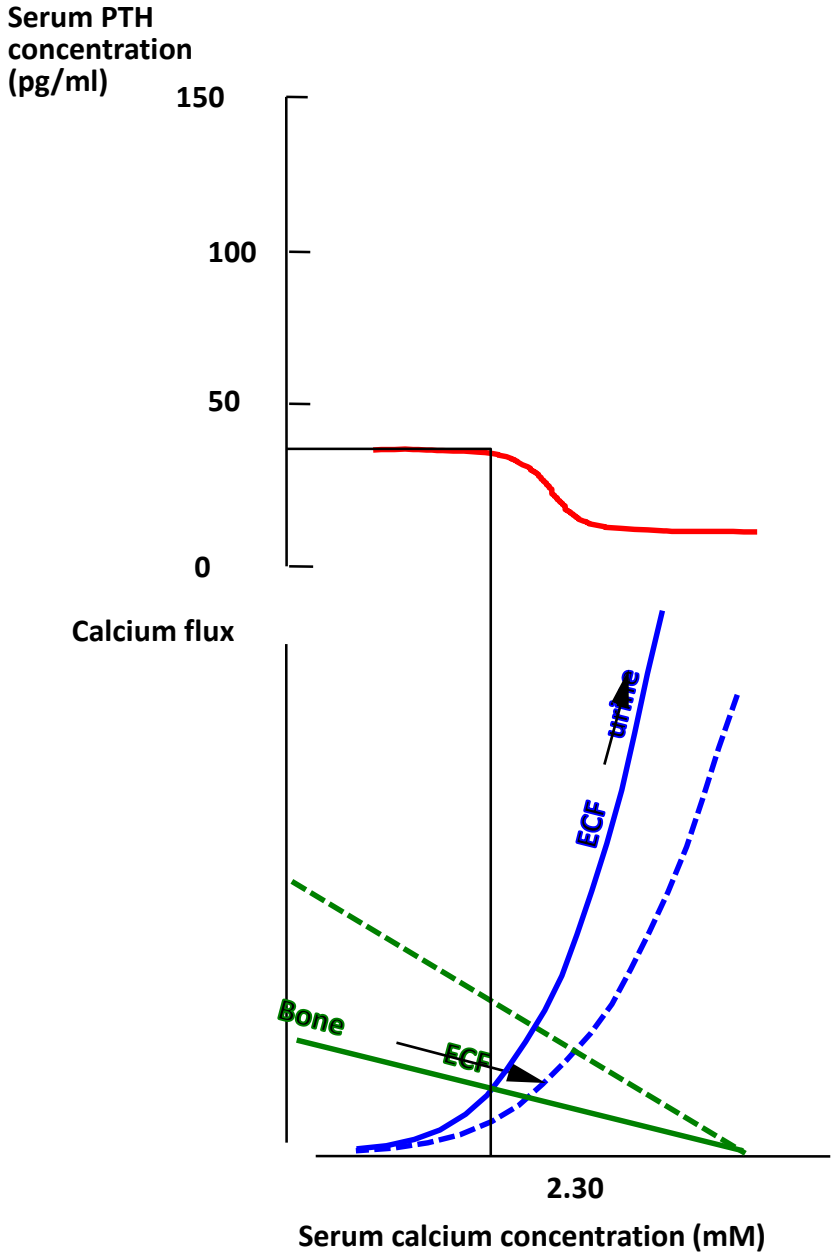
What maintains serum calcium concentration ?



What maintains serum calcium concentration ?



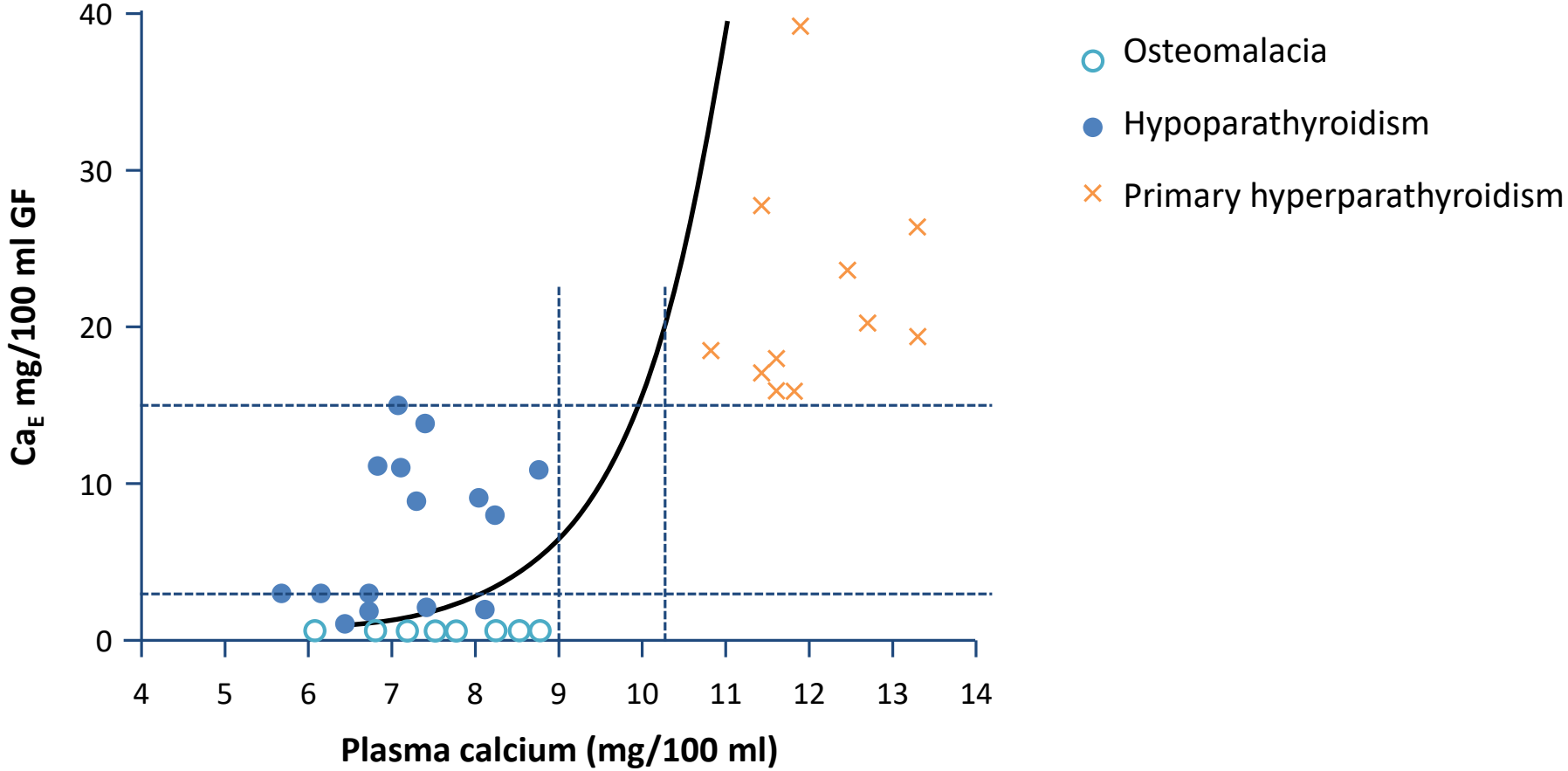
What maintains serum calcium concentration ?



- Which definition of hypercalciuria is correct, in adults?
  - A. > 6.25 mmol/day for a woman and > 7.5 mmol/day for a man
  - B. > 10 mmol/day, for both women and men
  - C. > 5 mmol/day for a woman and > 6 mmol/day for a man

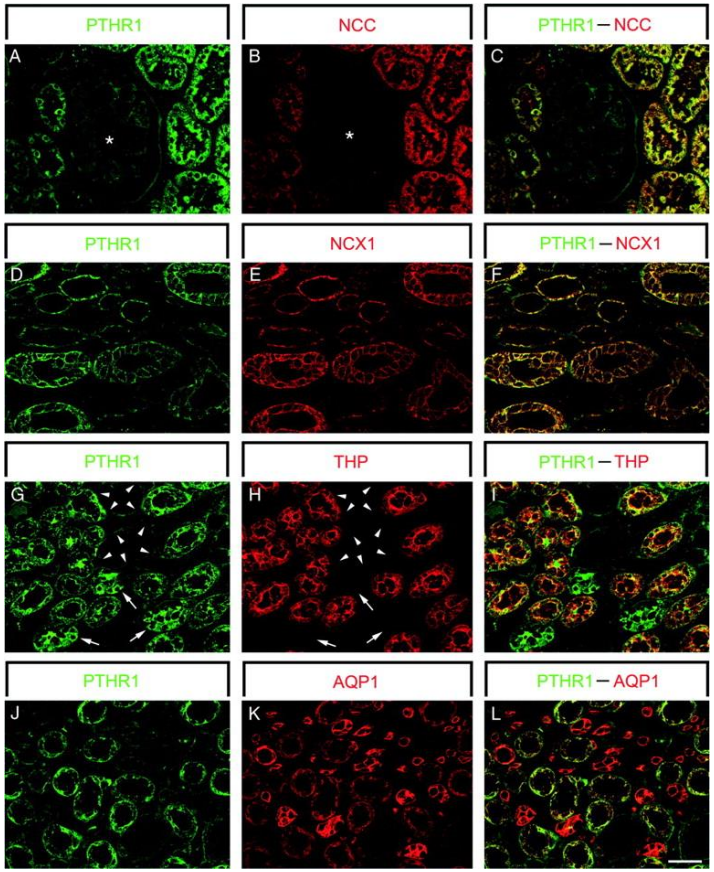
- On steady state, a high value of 24-hr urinary calcium excretion tells you that
  - A. renal tubular calcium reabsorption is lower than normal
  - B. more calcium is entering the extracellular fluid from bone and/or intestine

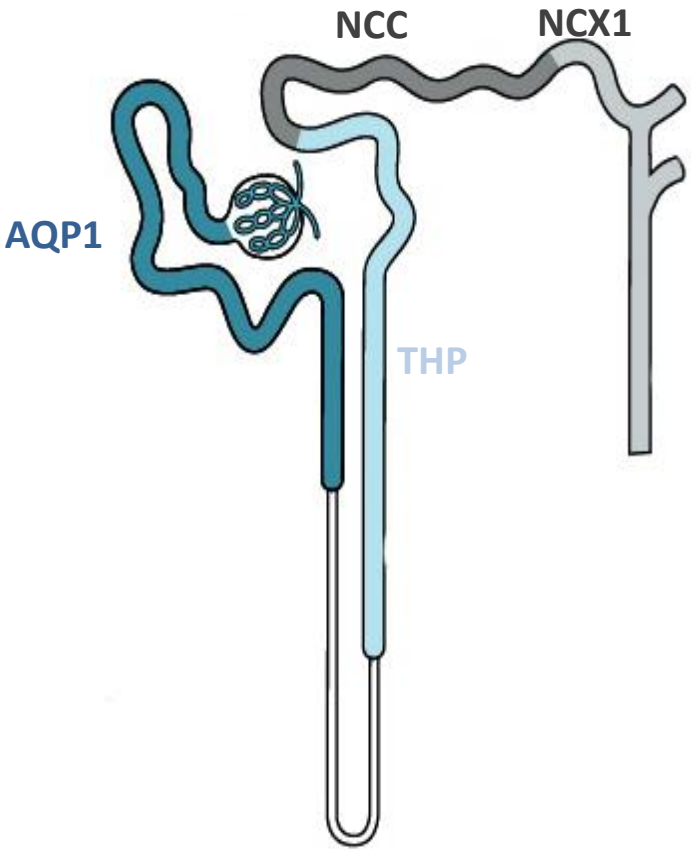
Renal tubular handling of calcium in patients with hyper or hypoparathyroidism



Adapted from Nordin BEC. Calcium, Phosphate and Magnesium Metabolism: Clinical Physiology and Diagnostic Procedures. Edinburgh. Churchill Livingstone, 1976. Fig 5.13.

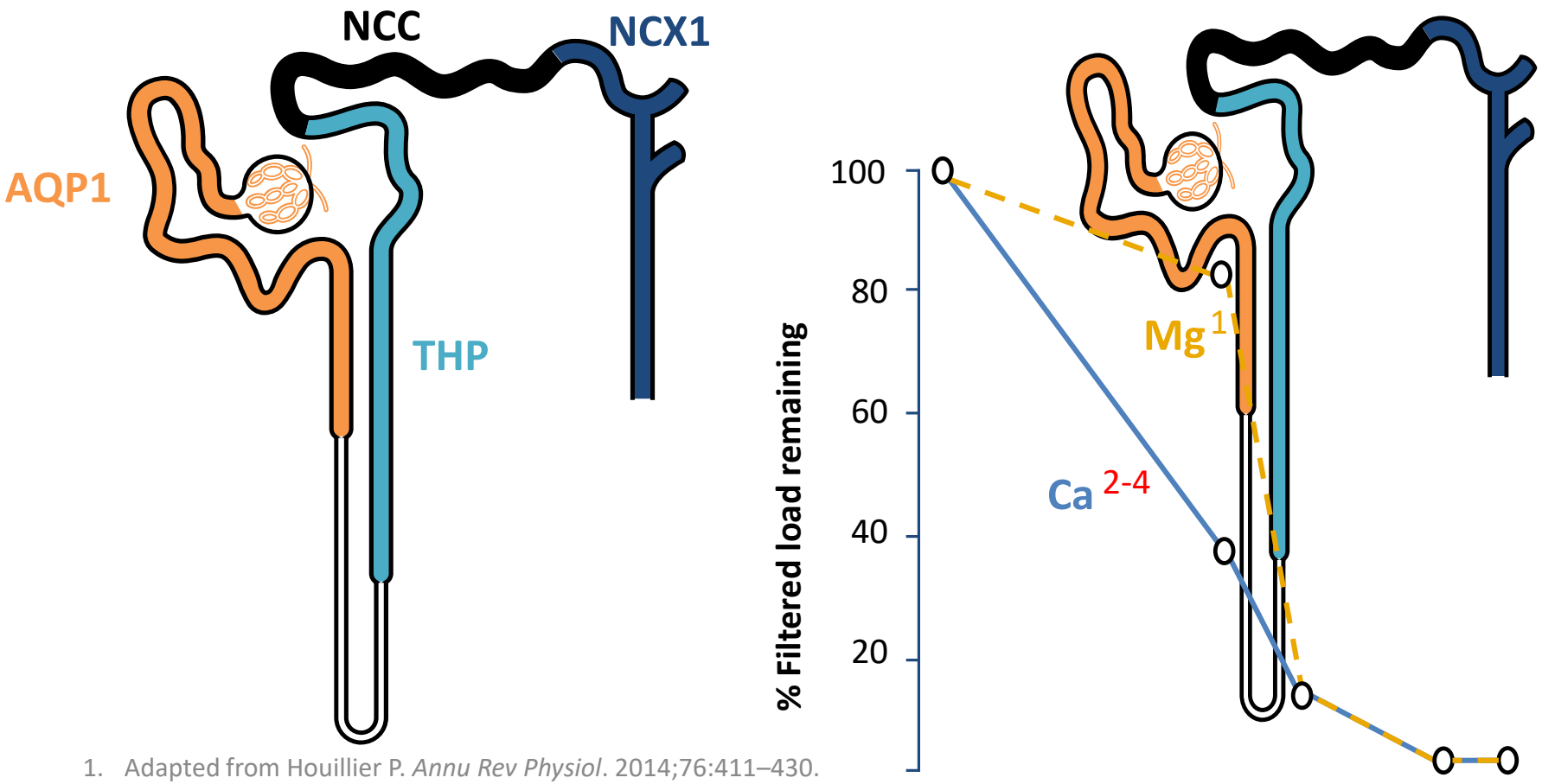
Expression of PTH receptor PTH1R along human kidney tubule





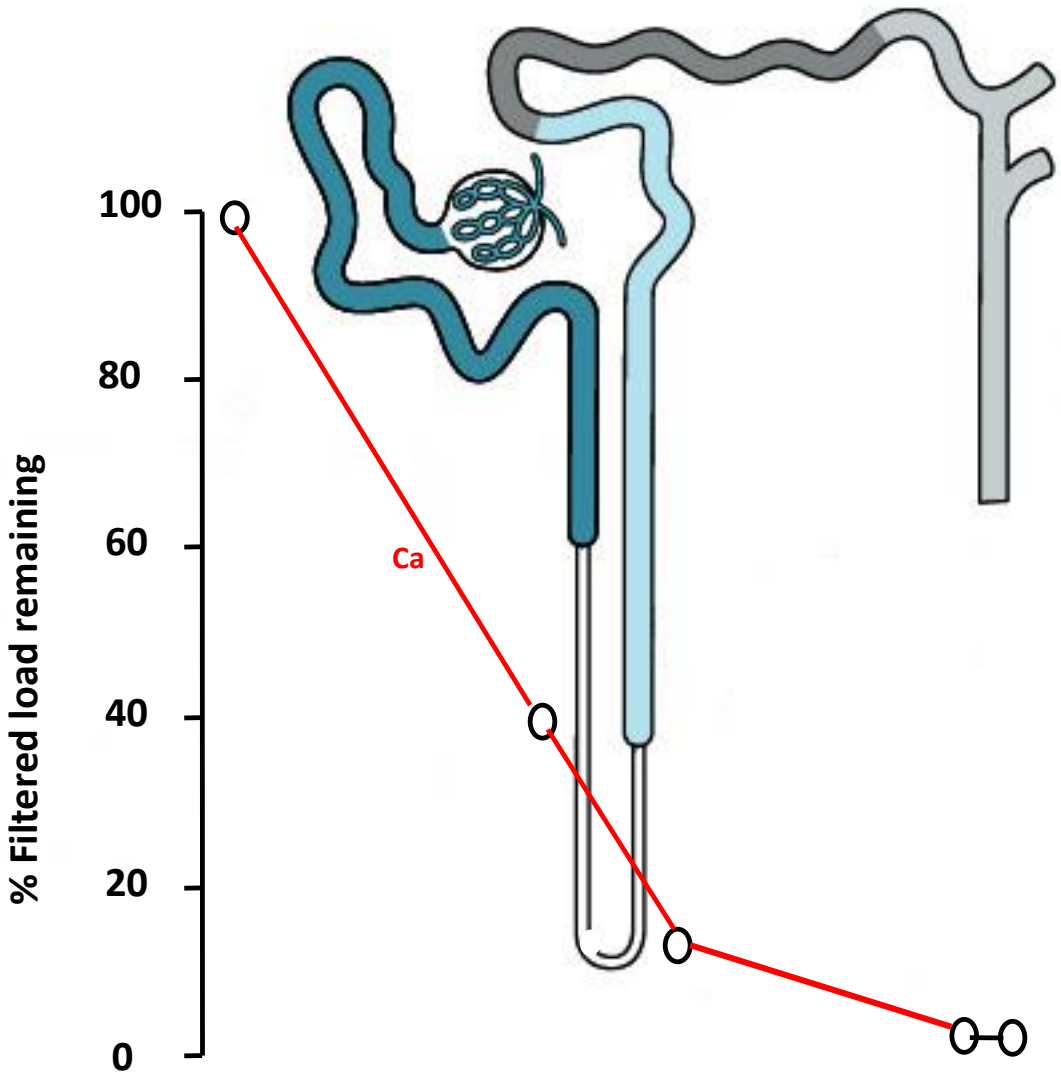
Lupp A et al, Eur J Endocrinol. 2010 May;162(5):979-865

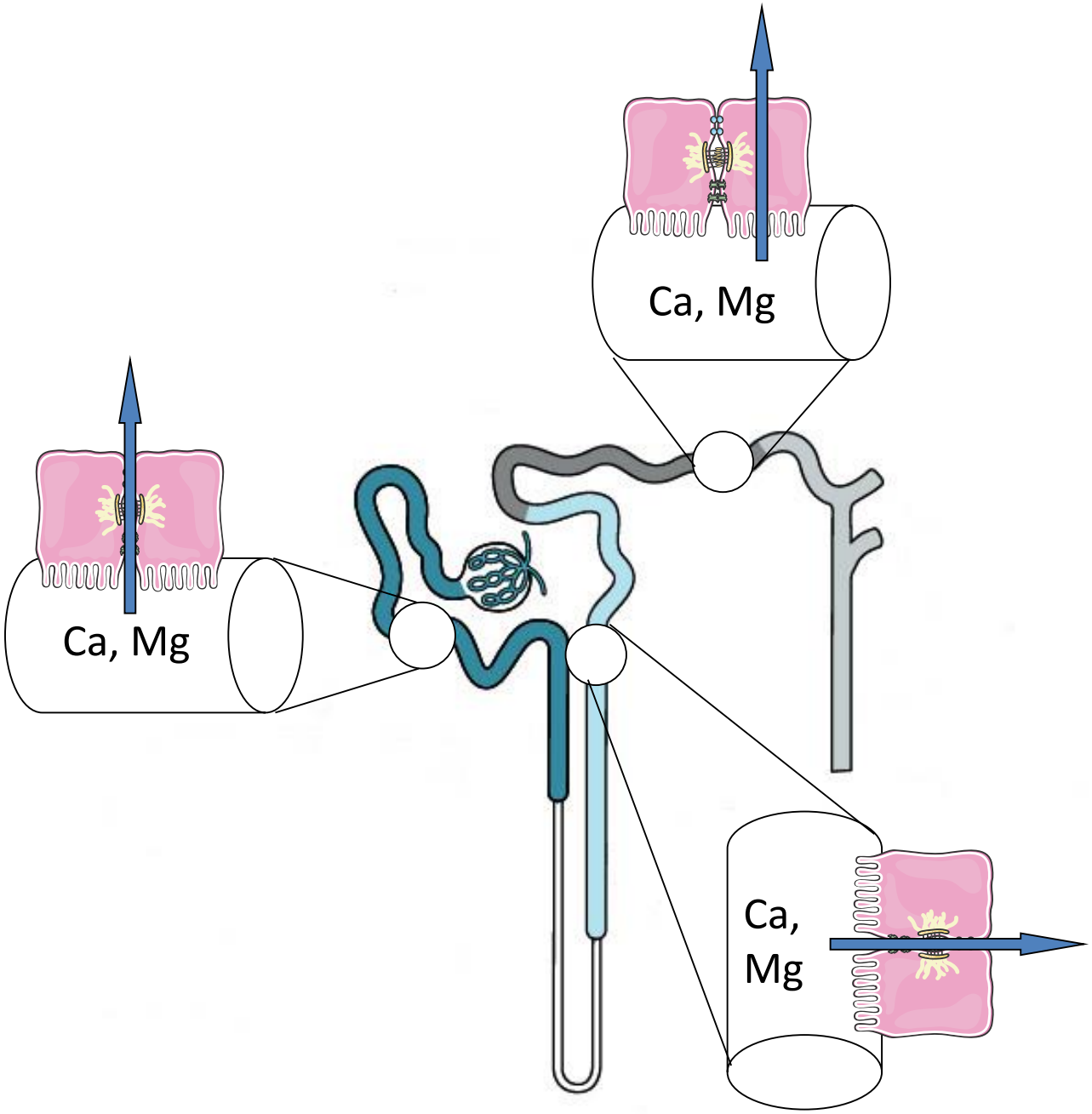
PTH receptor PTH1R along human kidney tubule and sites of calcium reabsorption[1]



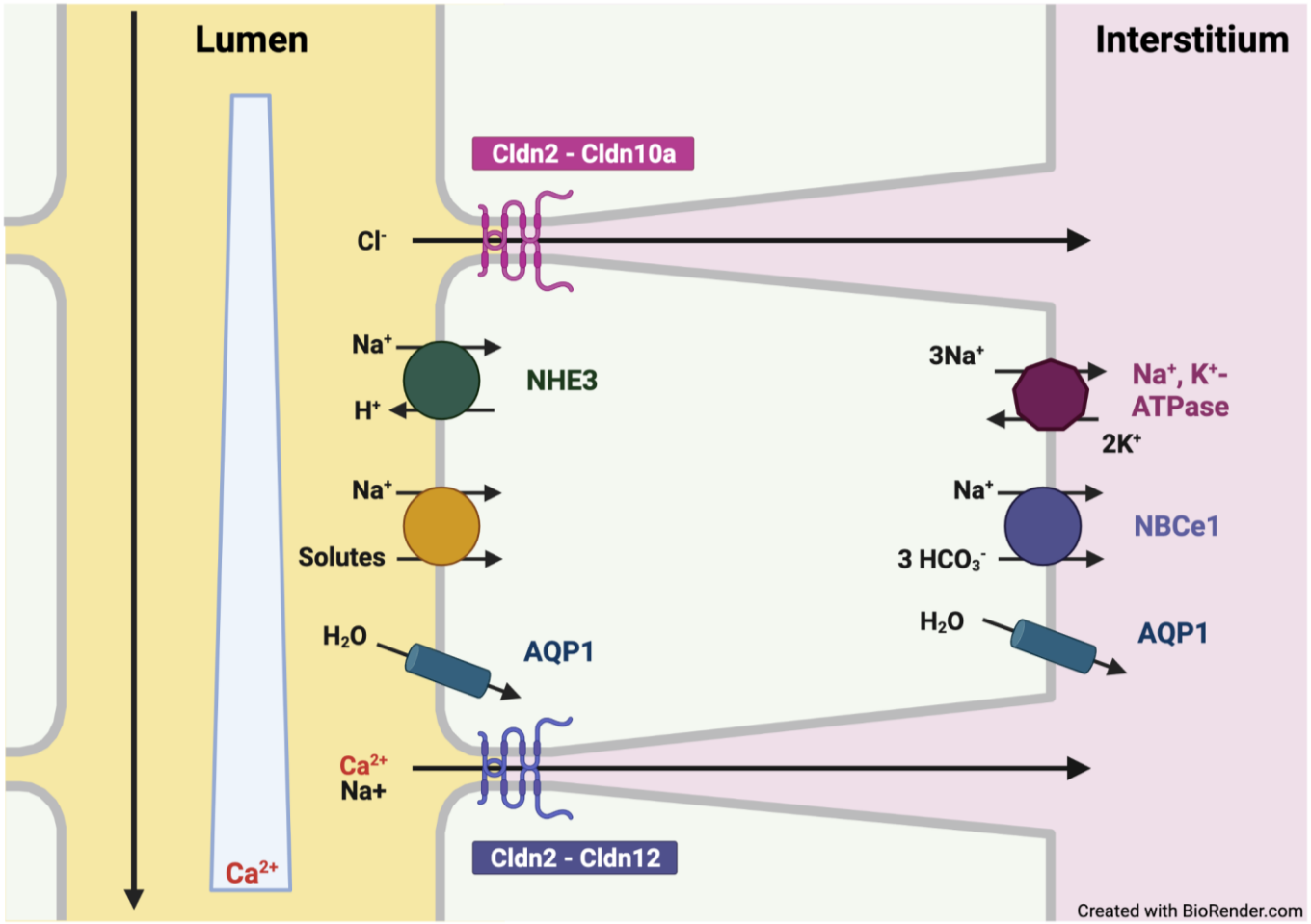
1. Adapted from Houillier P. *Annu Rev Physiol*. 2014;76:411–430.
2. Adapted from Moor MB, et al. *Am J Physiol Renal Physiol*. 2016;310(11):F1337-F1350.
3. Adapted from Jeon US. *Electrolyte Blood Press*. 2008;6(2):68-76.
4. Adapted from Blaine J, et al. *Clin J Am Soc Nephrol*. 2015;10(7):1257-1272.

Segmental handling of calcium



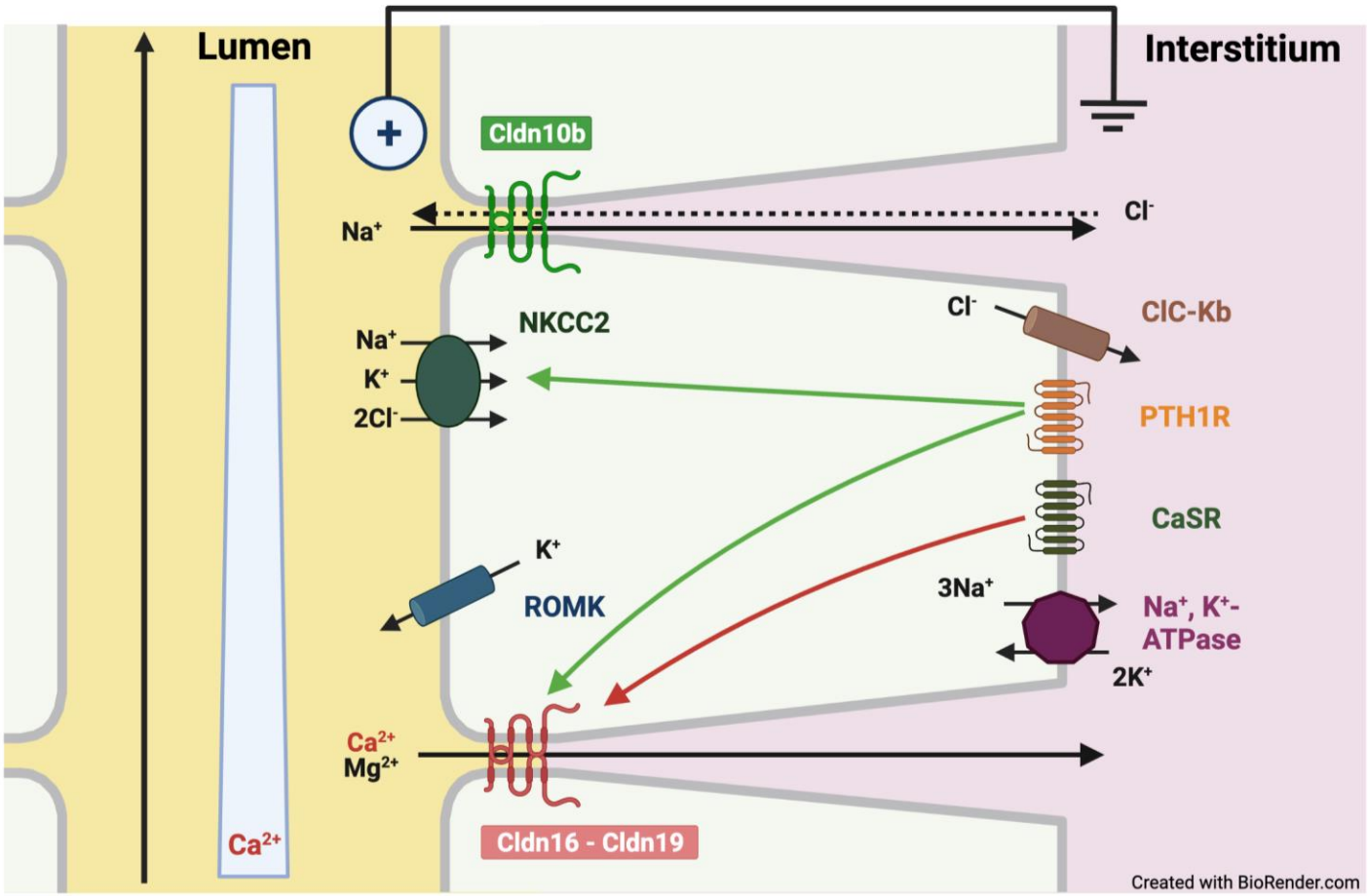

Ca, Mg
Ca, Mg
Ca,
Mg

Model of transport in the **proximal tubule**



P Houillier et al, Pflugers Arch 2022

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



P Houillier et al, Pflugers Arch 2022

Net calcium absorption is proportional to transepithelial voltage in the TAL

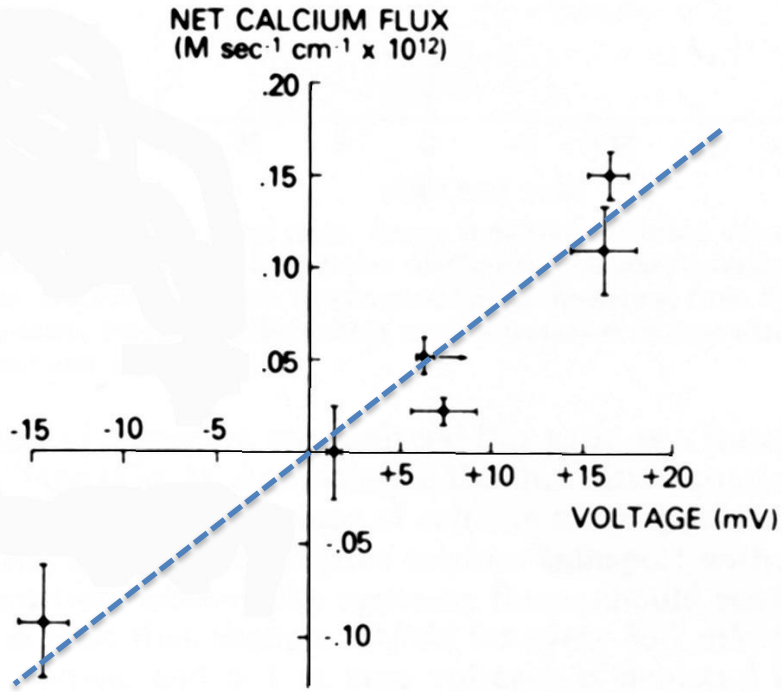
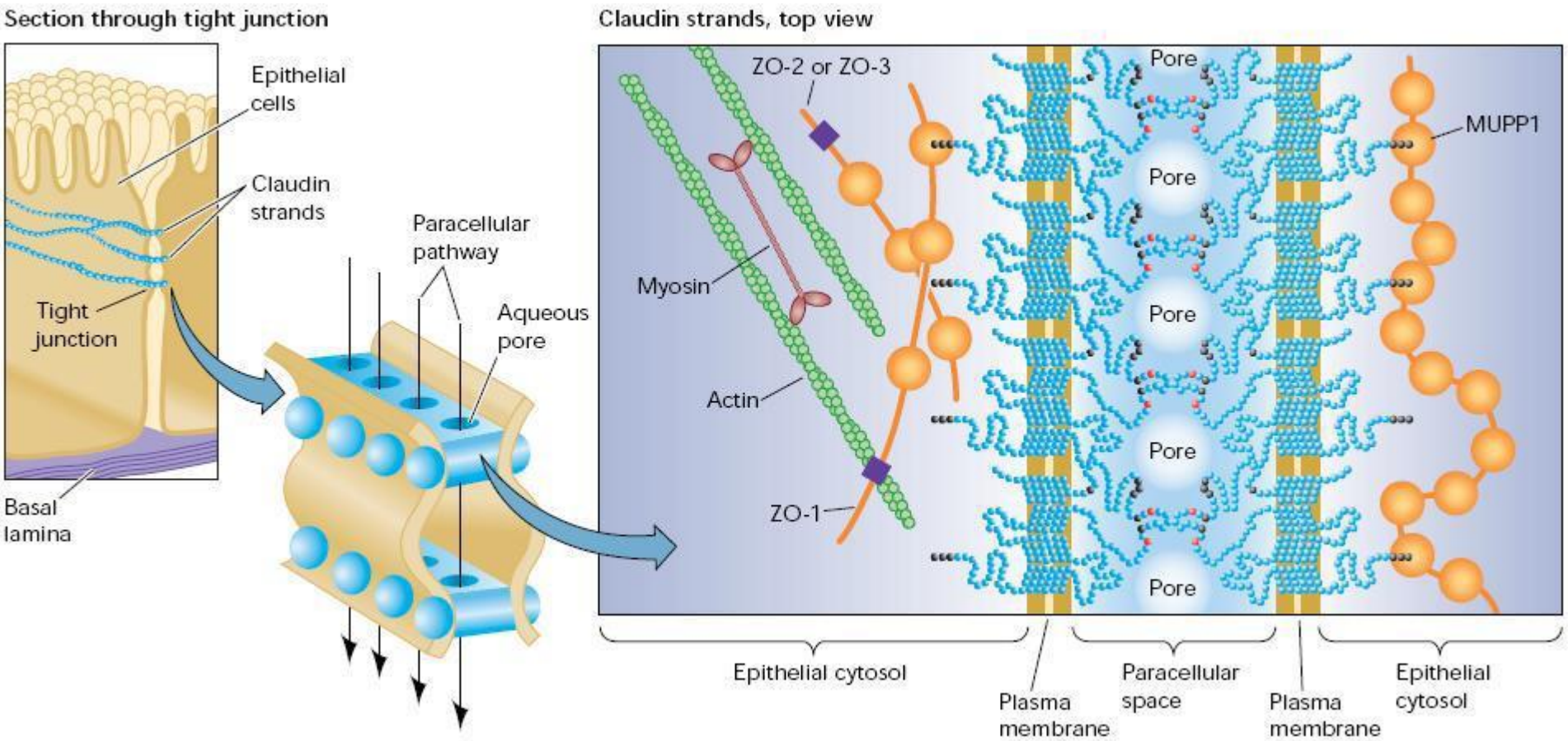


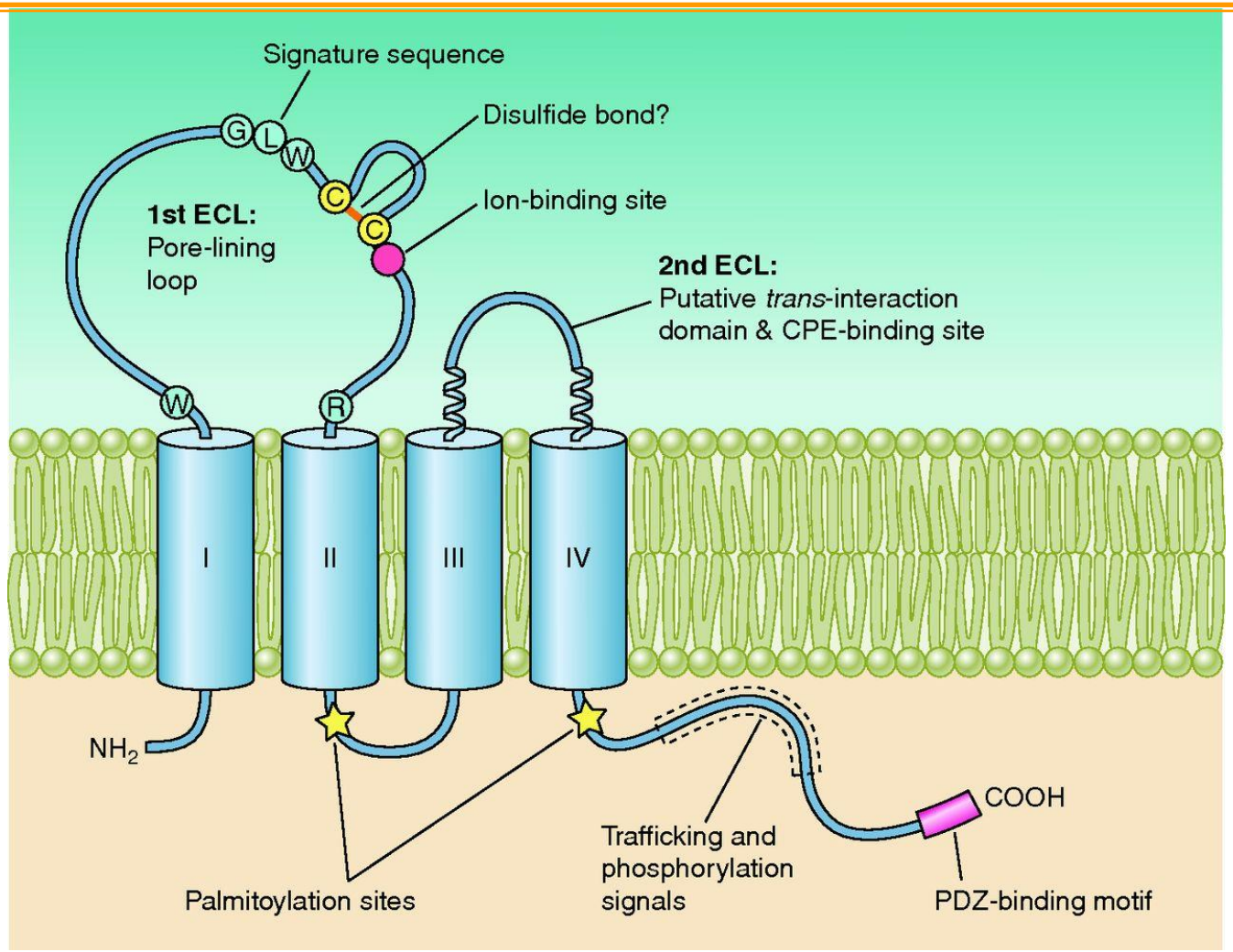
FIG. 4. Net calcium flux. Positive values indicate net transport from lumen to bath. Mean values of voltage and net flux are bracketed ± 1 SE. Arrow indicates corrected voltage for this group of tubules (see text for explanation). Correlation coefficient for linear regression is 0.97 ($P < 0.05$).

J.E Bourdeau and M. Burg, Am J Physiol, 1979

The important of the ‘tight junction’



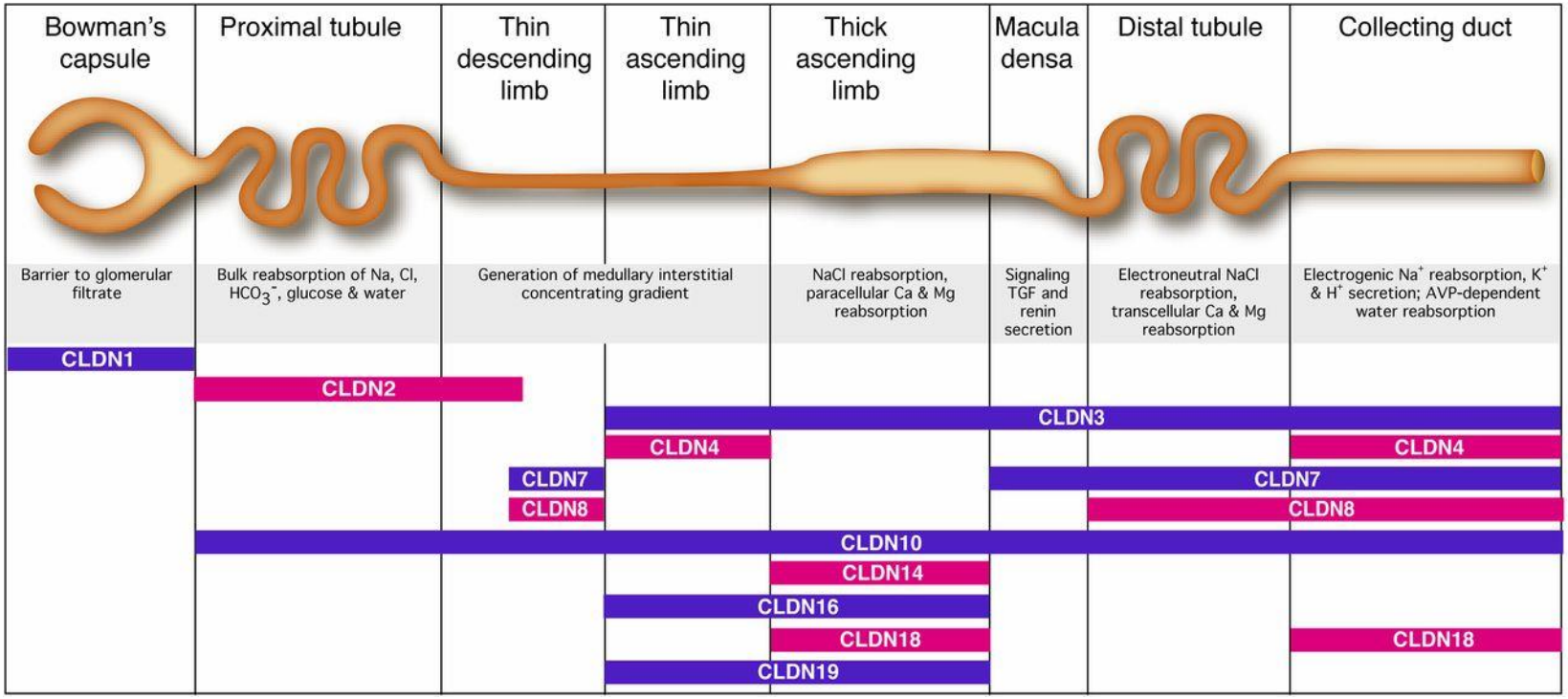
Model of claudin protein showing predicted topology and secondary structure as well as putative functional domains.



Dorothee Günzel, and Alan S. L. Yu Physiol Rev 2013;93:525-569

Physiological Reviews

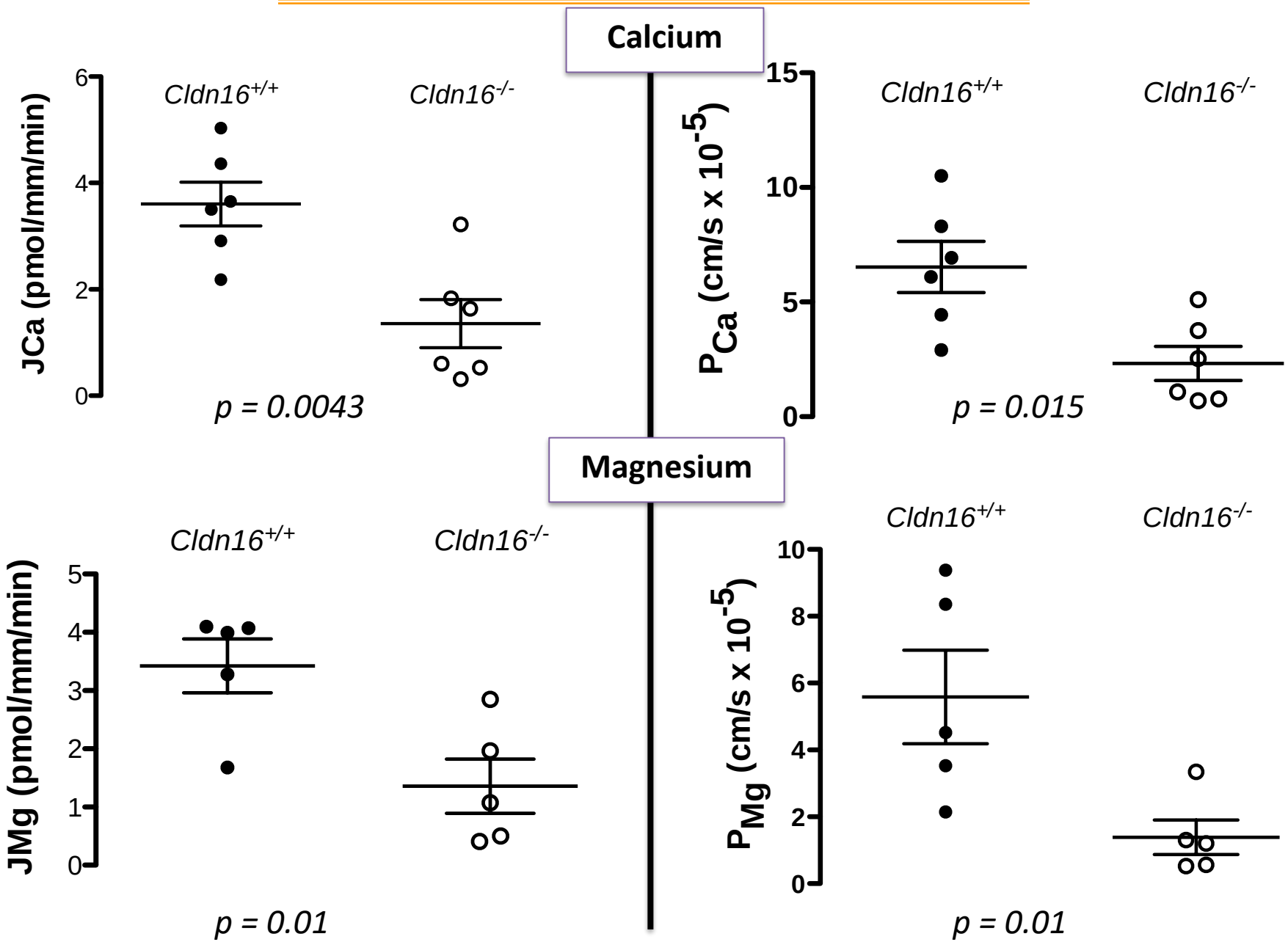
Localization of claudins along the adult mammalian renal tubule



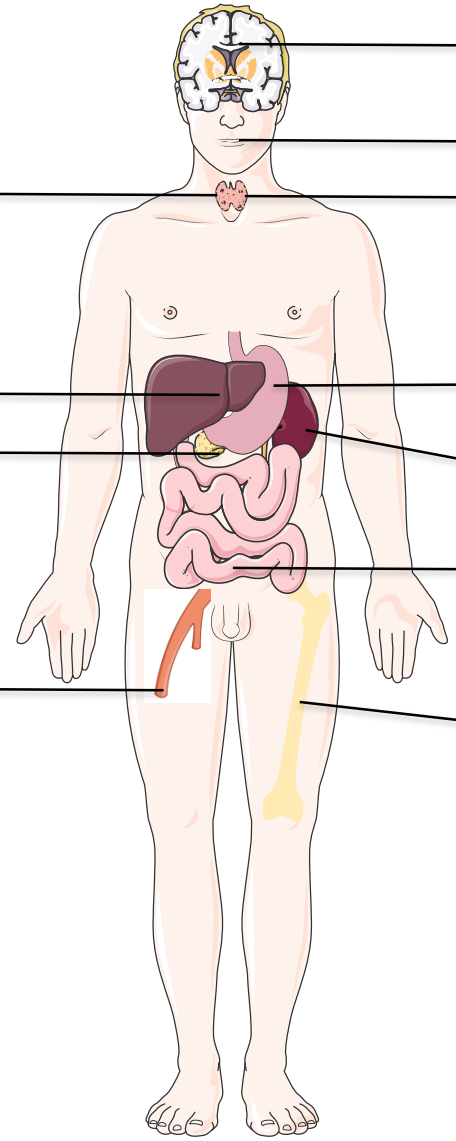
Alan S.L. Yu JASN 2015

JASN

Paracellular permeability in Cldn16$^{-/-}$ mice

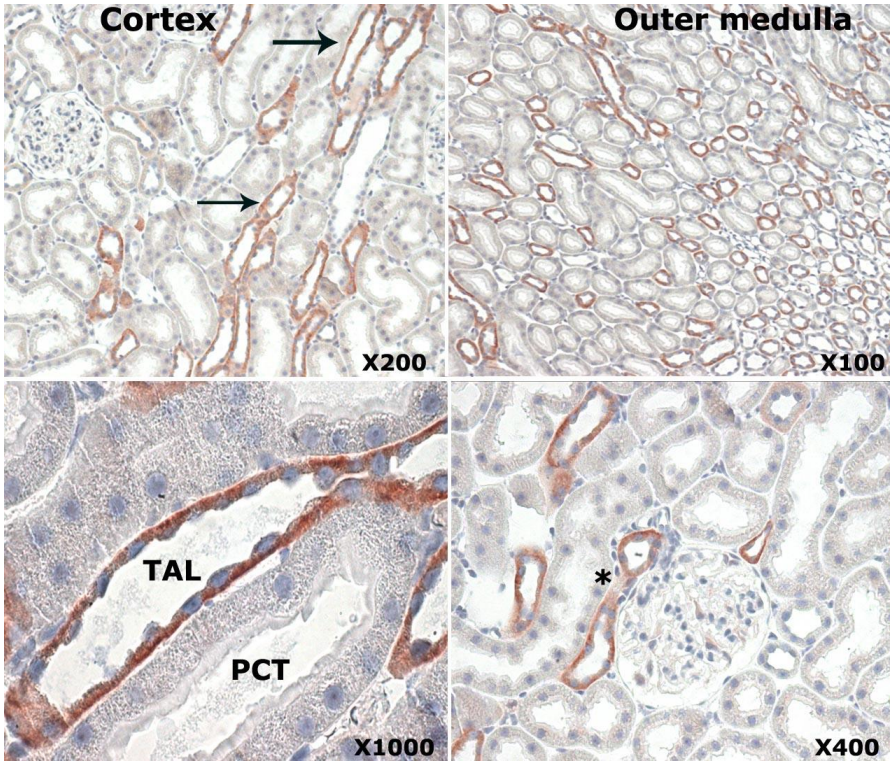


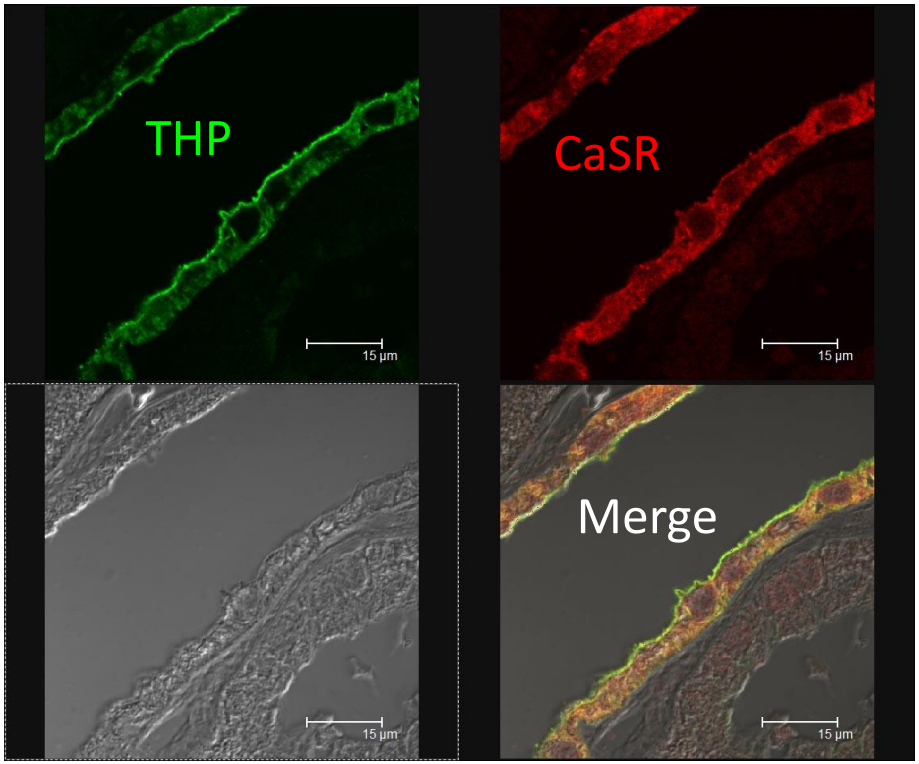
CaSR is expressed outside the parathyroid glands



Where is CaSR expressed along the renal tubule?

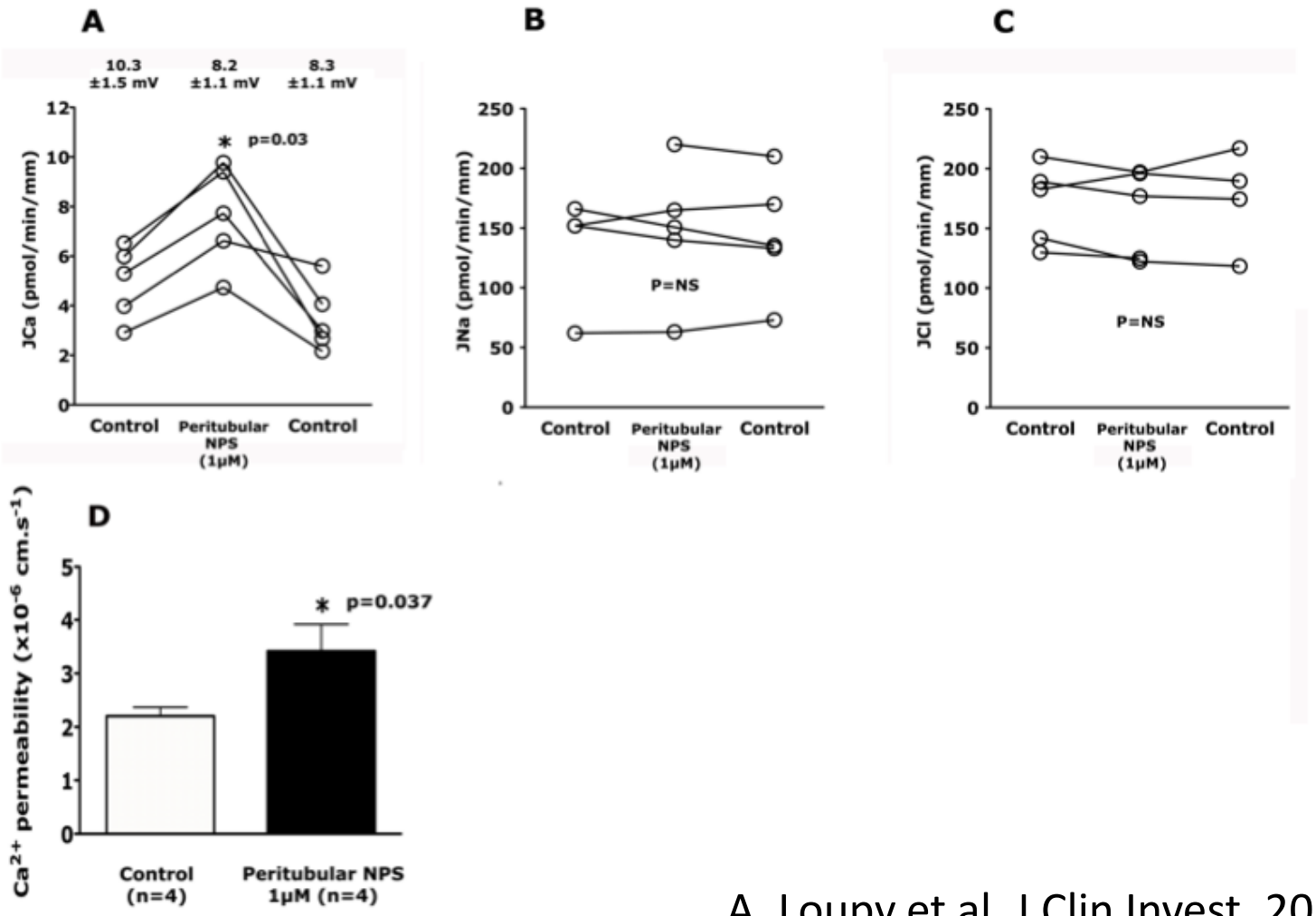
Immunohistochemistry & IF (Rat)





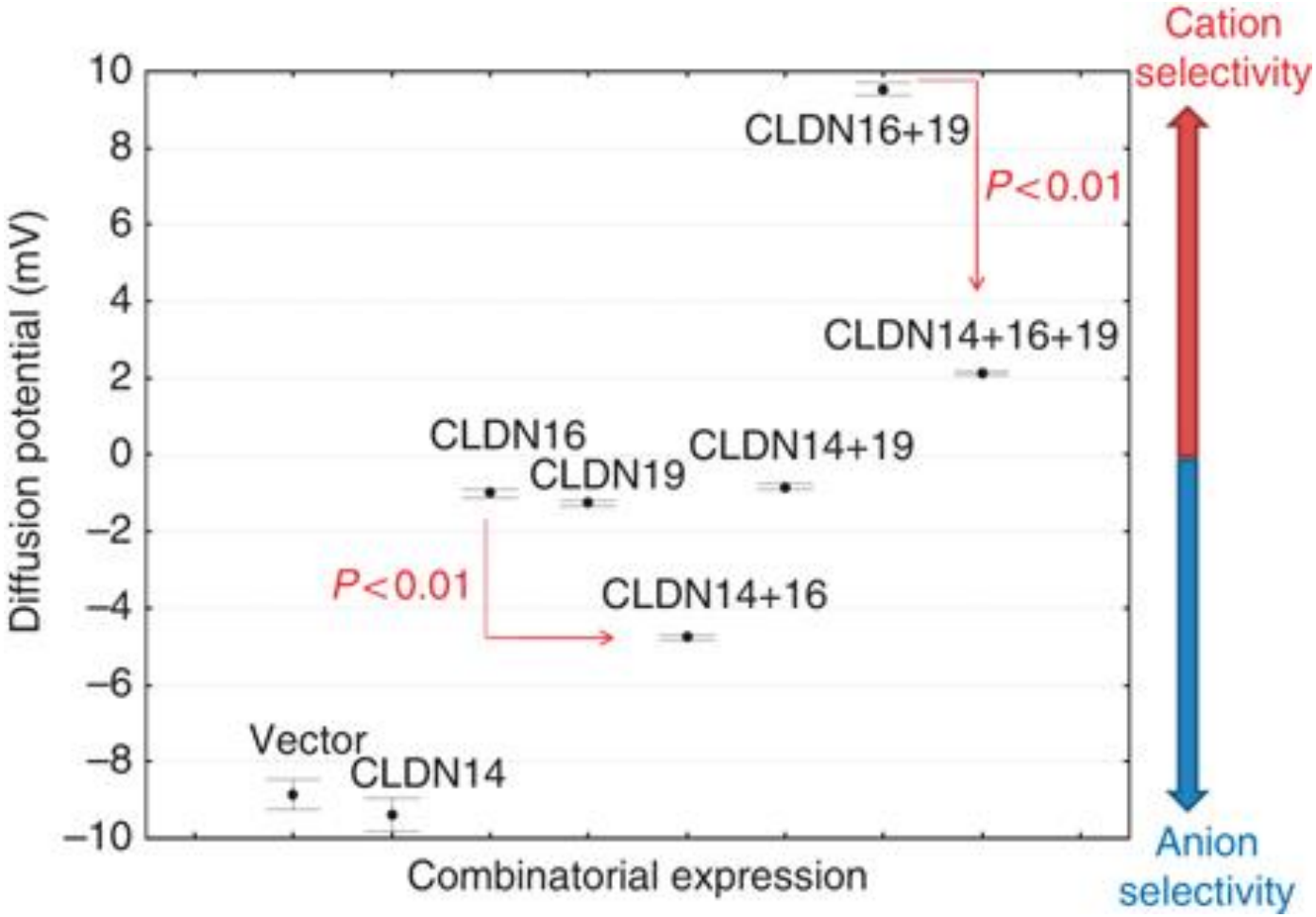
A. Loupy et al, J Clin Invest, 2012

What CaSR does in the thick ascending limb ?
Short term effects of a calcilytic drug: *In vitro* microperfusion studies

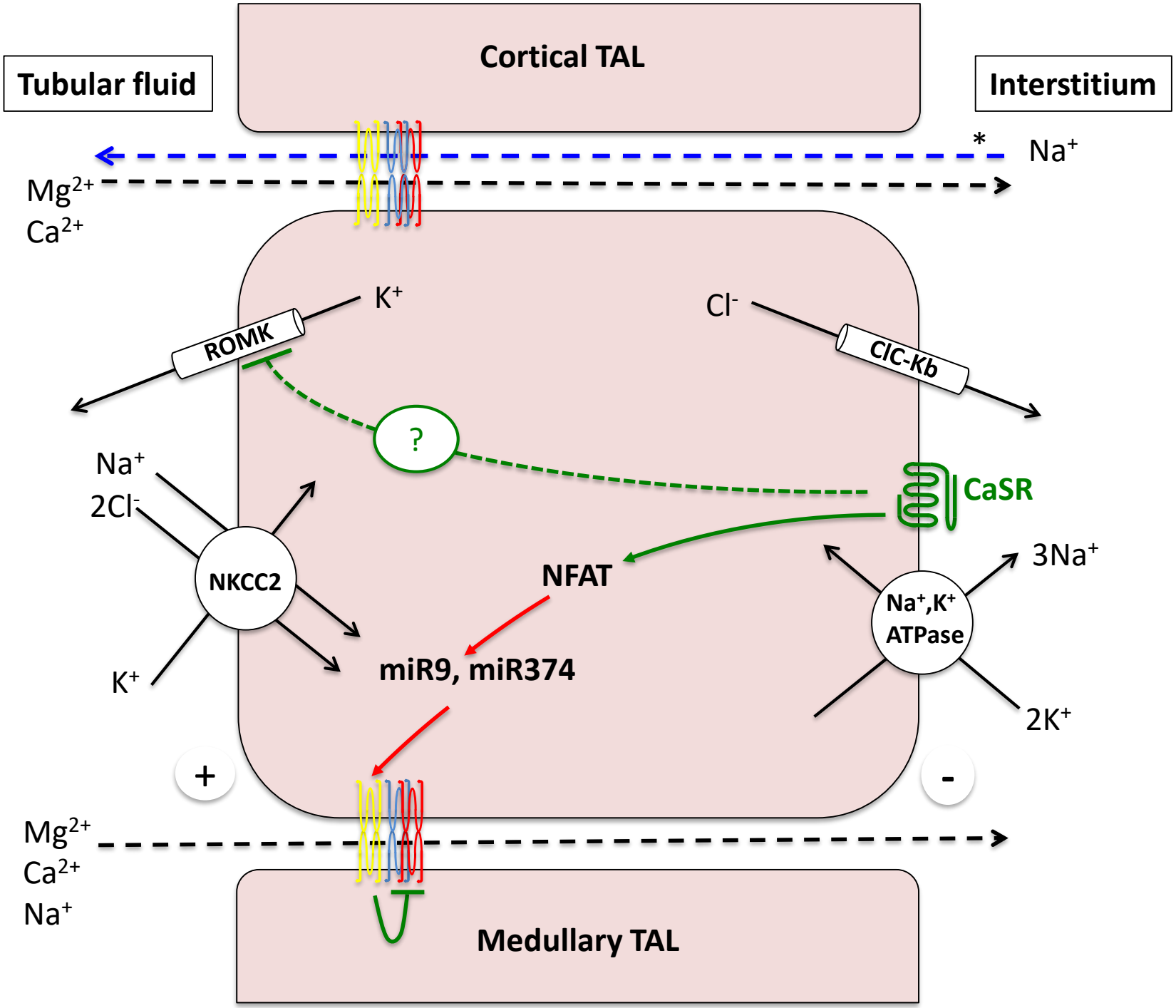


A. Loupy et al, J Clin Invest, 2012

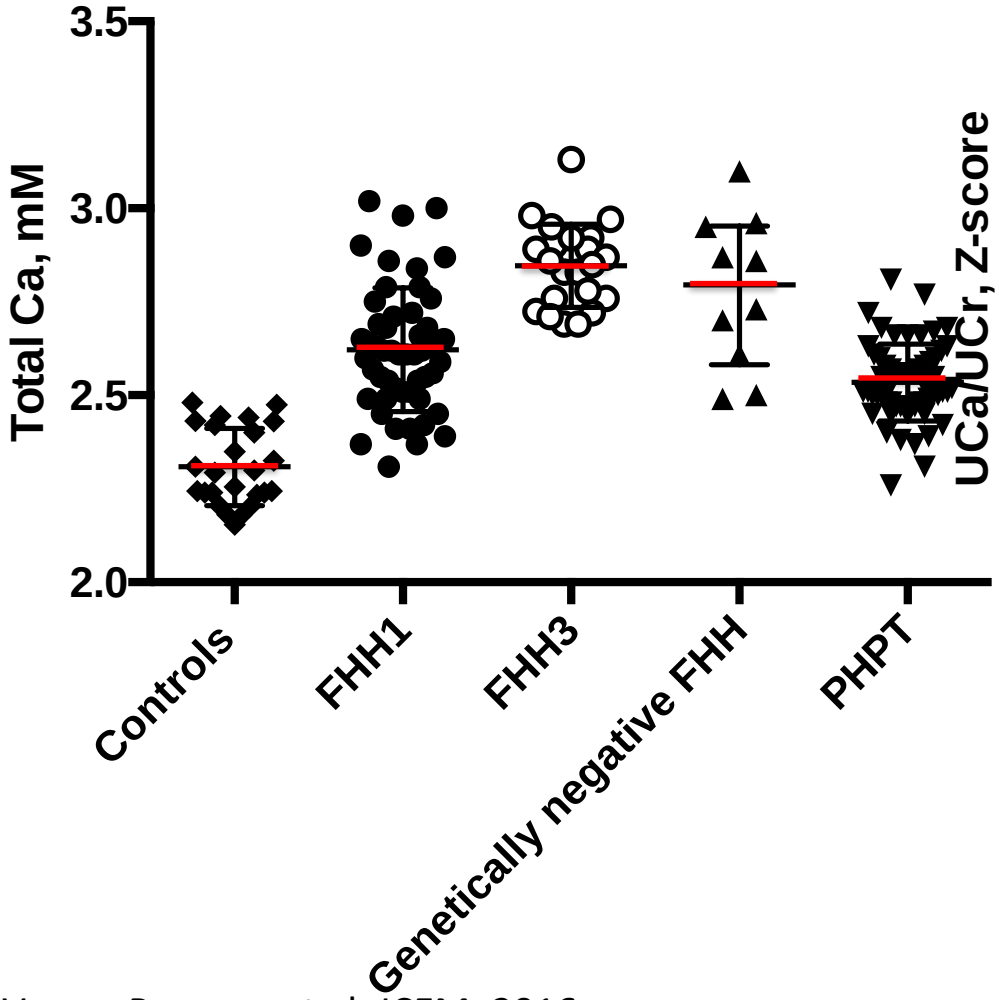
How do various claudins interact at the tight junction?

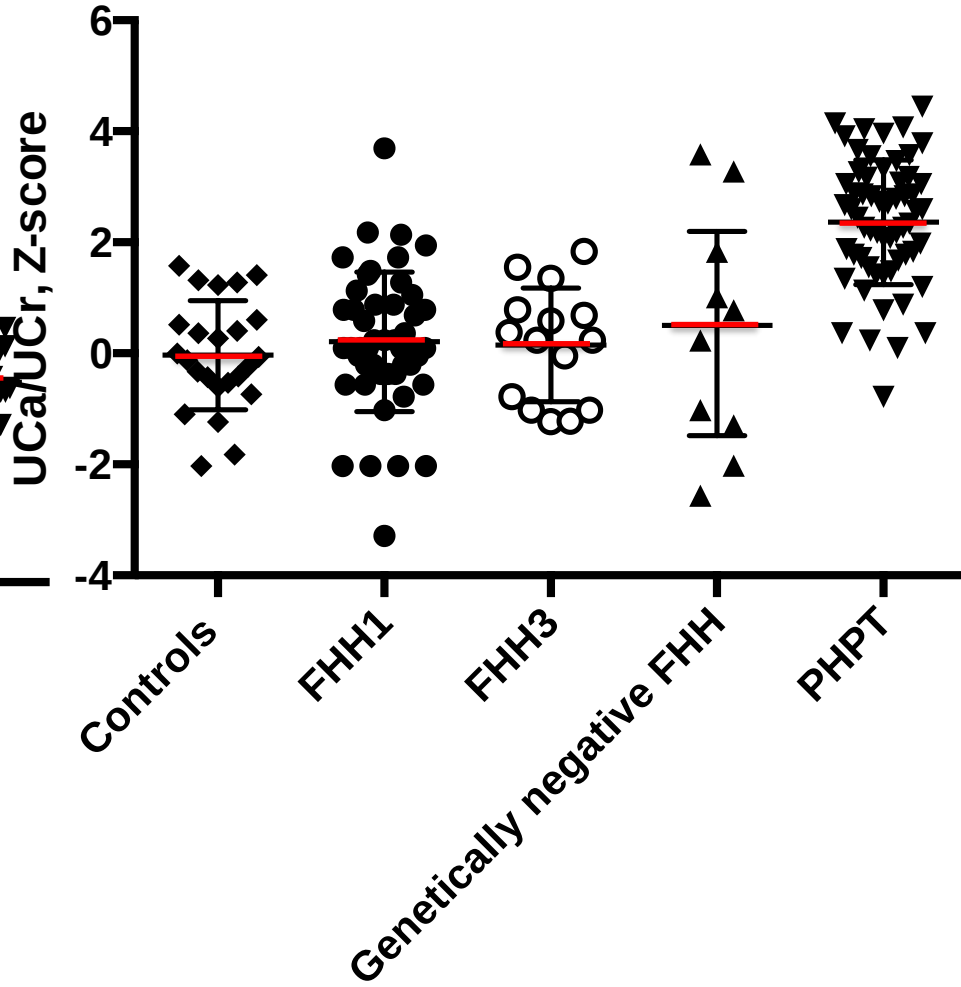


Gong Y. et al, EMBO J., 2012


Tubular fluid
Cortical TAL
Interstitium
*
Na+
Mg2+
Ca2+
K+
ROMK
Cl-
ClC-Kb
?
Na+
2Cl-
CaSR
NKCC2
NFAT
3Na+
Na+,K+
ATPase
K+
miR9, miR374
2K+
+
-
Mg2+
Ca2+
Na+
Medullary TAL

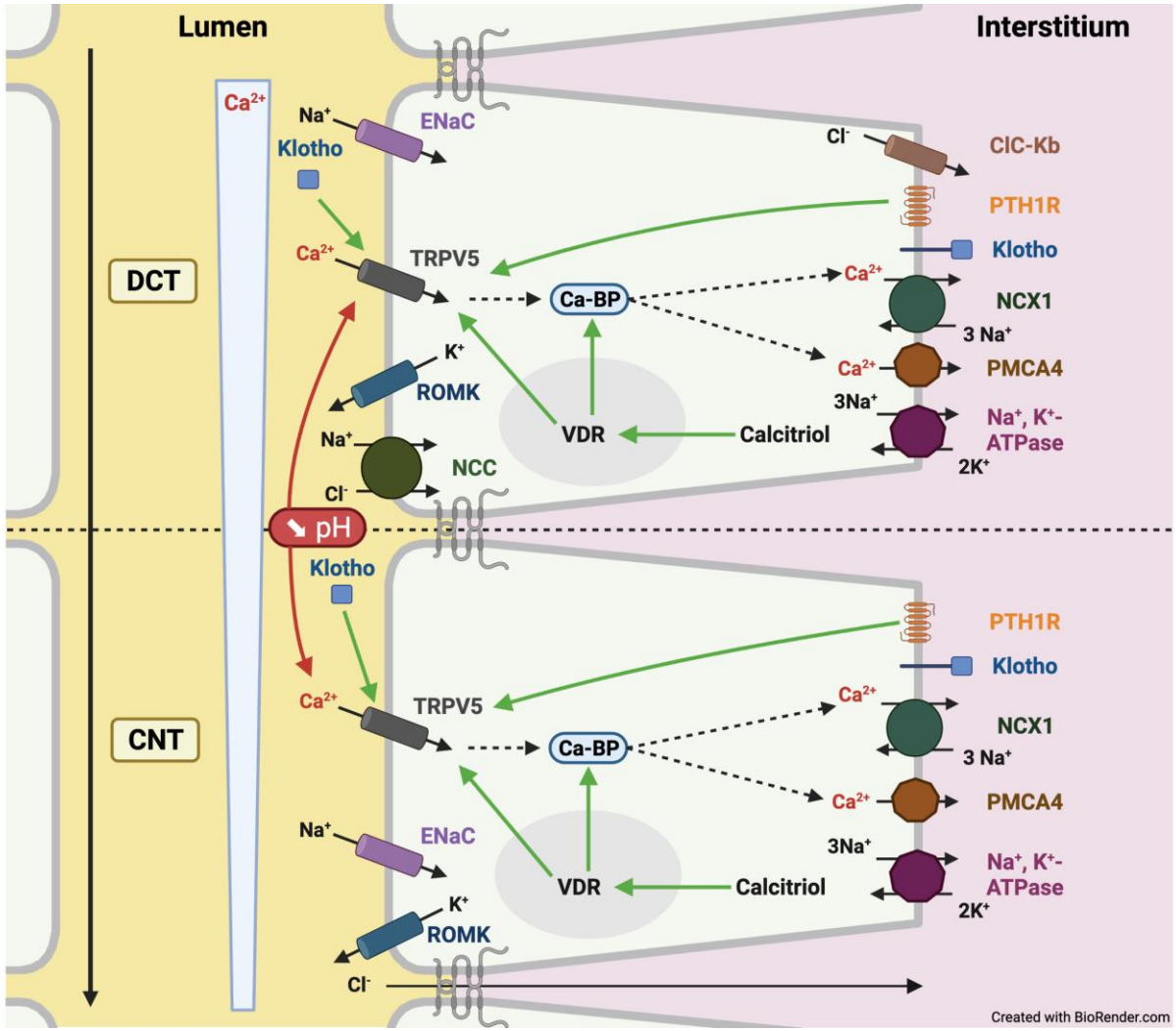
Effect of long-term inactivation of *CASR* on calcium homeostasis





Vargas-Poussou et al, JCEM, 2016

Model of transport in the **distal convoluted/connecting tubule.**



P Houillier et al, Pflugers Arch 2022

Factors affecting the tubular reabsorption of calcium

Increase

- Parathyroid hormone
- PTH-rP
- 1,25$(OH)_2$ vitamin D
- CaSR antagonists (hypocalcemia,…)
- Metabolic alkalosis
- Decreased ECF
- Thiazide diuretics

Decrease

- CaSR agonists (hypercalcemia)
- Depletion in magnesium
- Metabolic acidosis
- Increased ECF
- Loop diuretics

Causes of clinically significant disturbances in calcium reabsorption : extrinsic

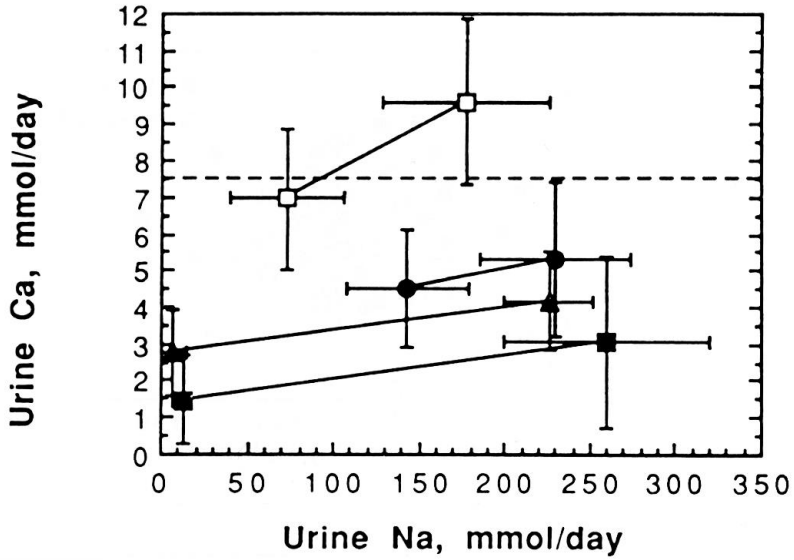
Increased

- Hyperparathyroidism
- Primary excess in 1,25$(OH)_2$ vitamin D
- CaSR inactivation (familial « hypocalciuric » hypercalcemia)

Decreased

- Hypoparathyroidism/Resistance to PTH
- CaSR activation (autosomal dominant hypocalcemia)
- Too much salt
- Too much meat

High Na intake increases urinary Ca excretion



J Lemann, Jr, 1992

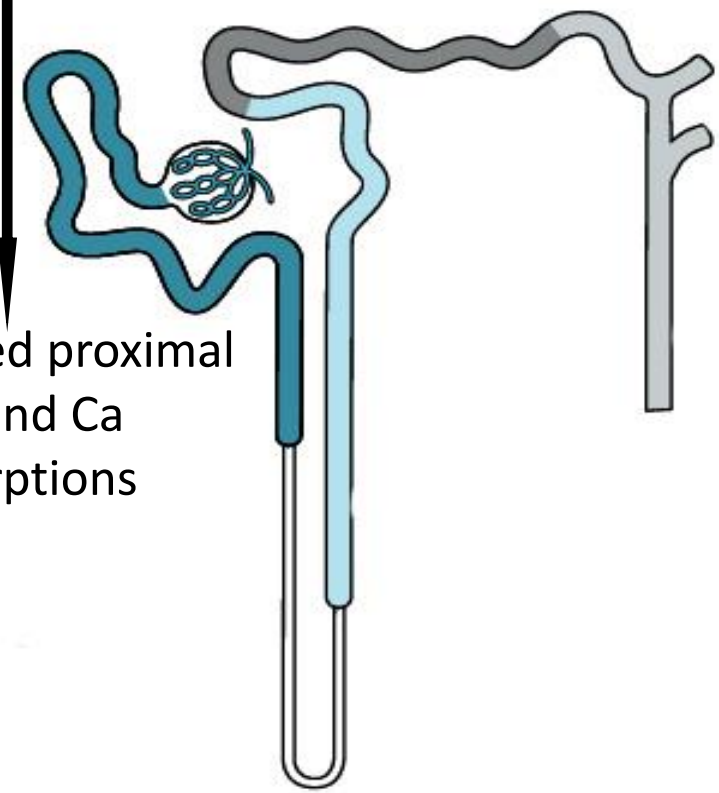
High Na intake

↓

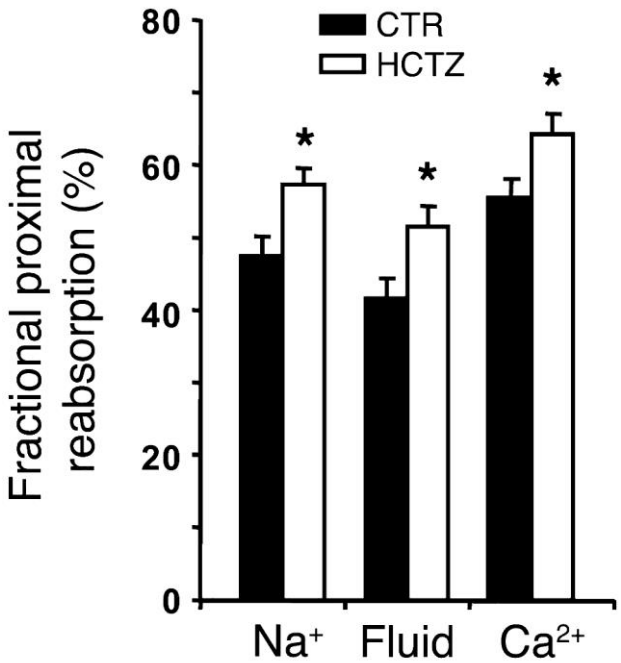
Increased ECF volume

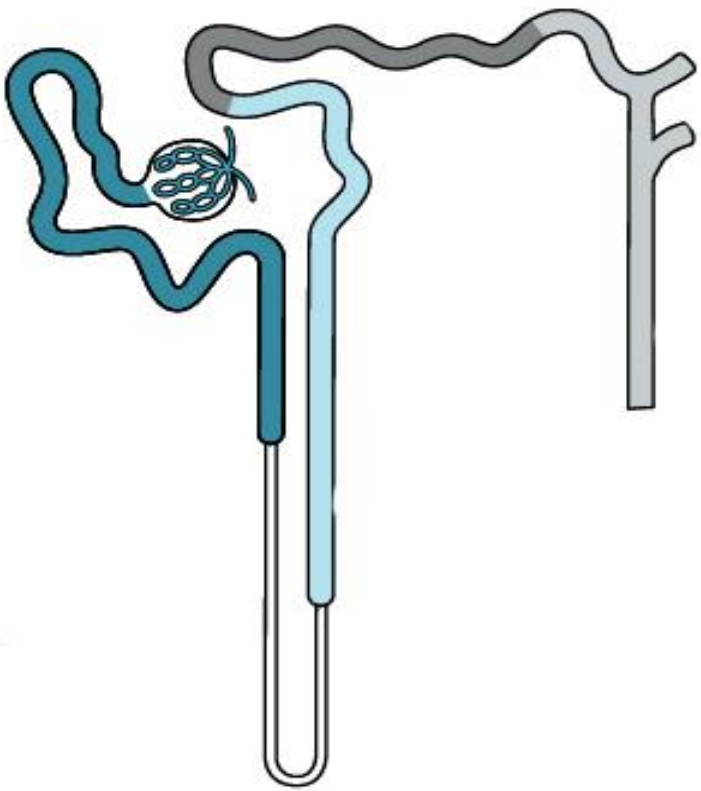
↓

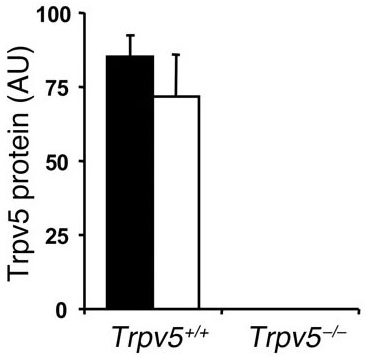
Decreased proximal Na and Ca absorptions

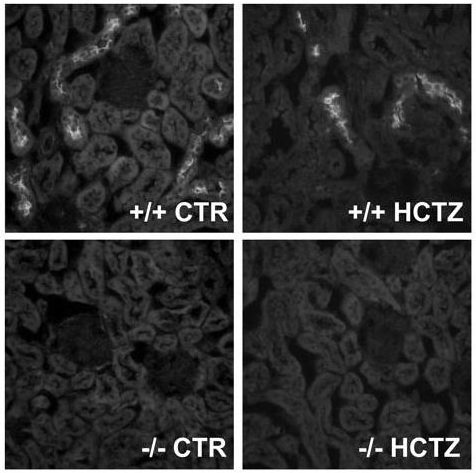


Thiazides reduce urinary calcium excretion through a decrease in ECF volume



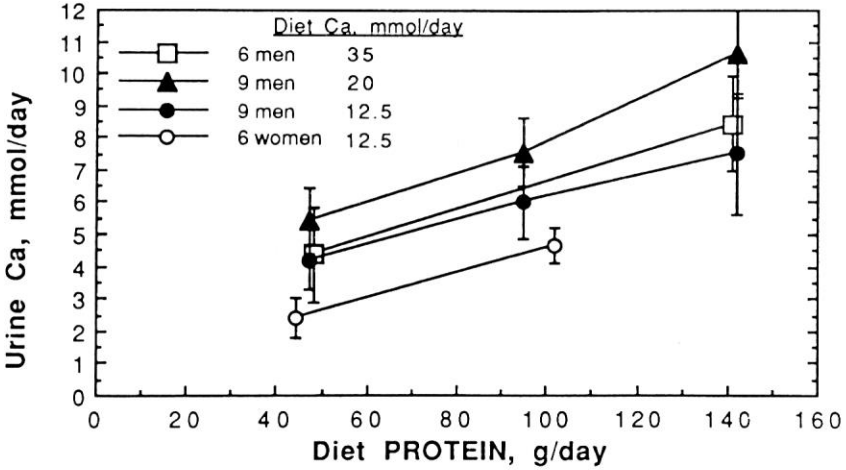






T Nijenhuis et al, JCI, 2005

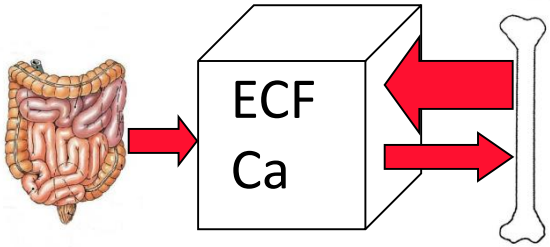
High dietary protein intake increases urinary Ca excretion

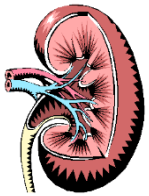


J Lemann, Jr, 1992

Increased animal protein intake :
Increased acid load

Increased bone resorption





Decreased tubular Ca reabsorption

Hypercalciuria

Causes of clinically significant disturbances in calcium reabsorption : intrinsic

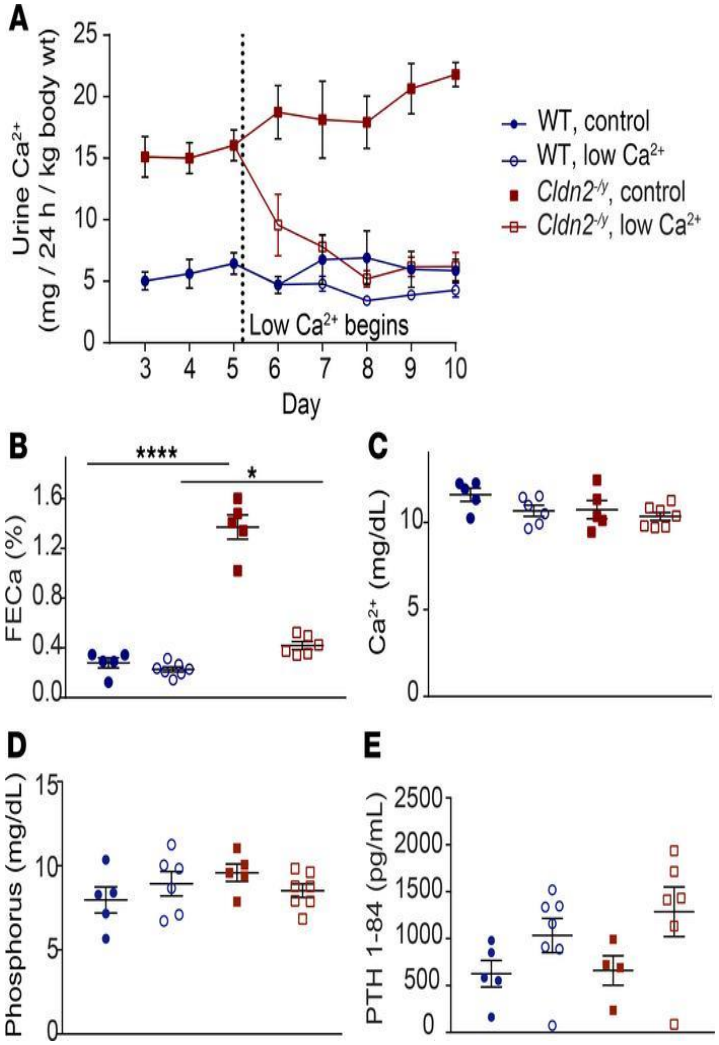
Increased

- TAL
  - HELIX syndrome (*CLDN10B*)
- DCT
  - Gitelman syndrome (*SLC12A3*)

Decreased

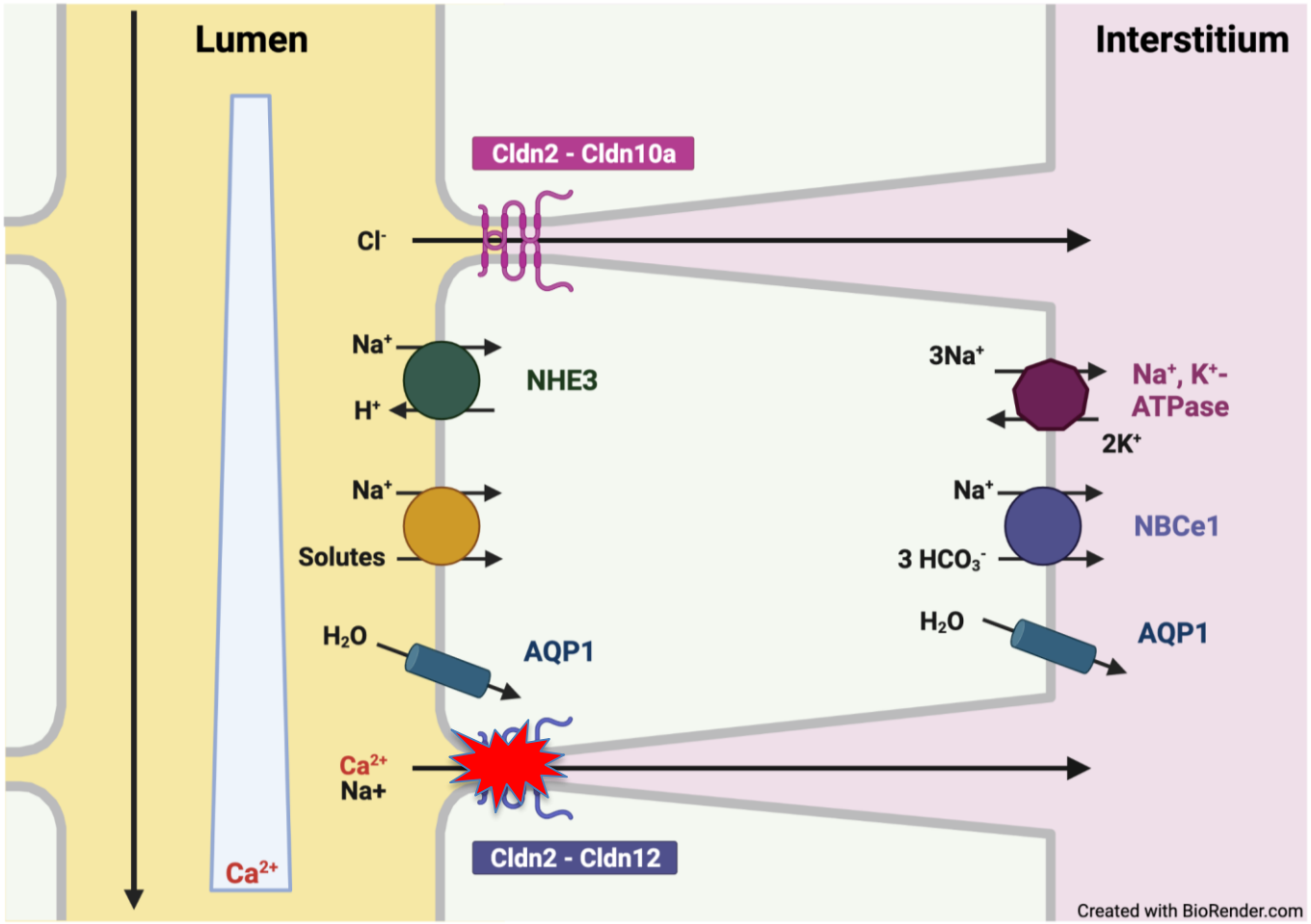
- Proximal tubule
  - OAZON (*CLDN2*)
- TAL
  - Bartter syndrome (*SLC12A1, KCNJ1, CLCNKB, BSND*)
  - Familial hypomagnesemia with hypercalciuria and nephrocalcinosis (*CLDN16, CLDN19*)

Claudin-2 deficiency associates with hypercalciuria in mice and human kidney stone disease



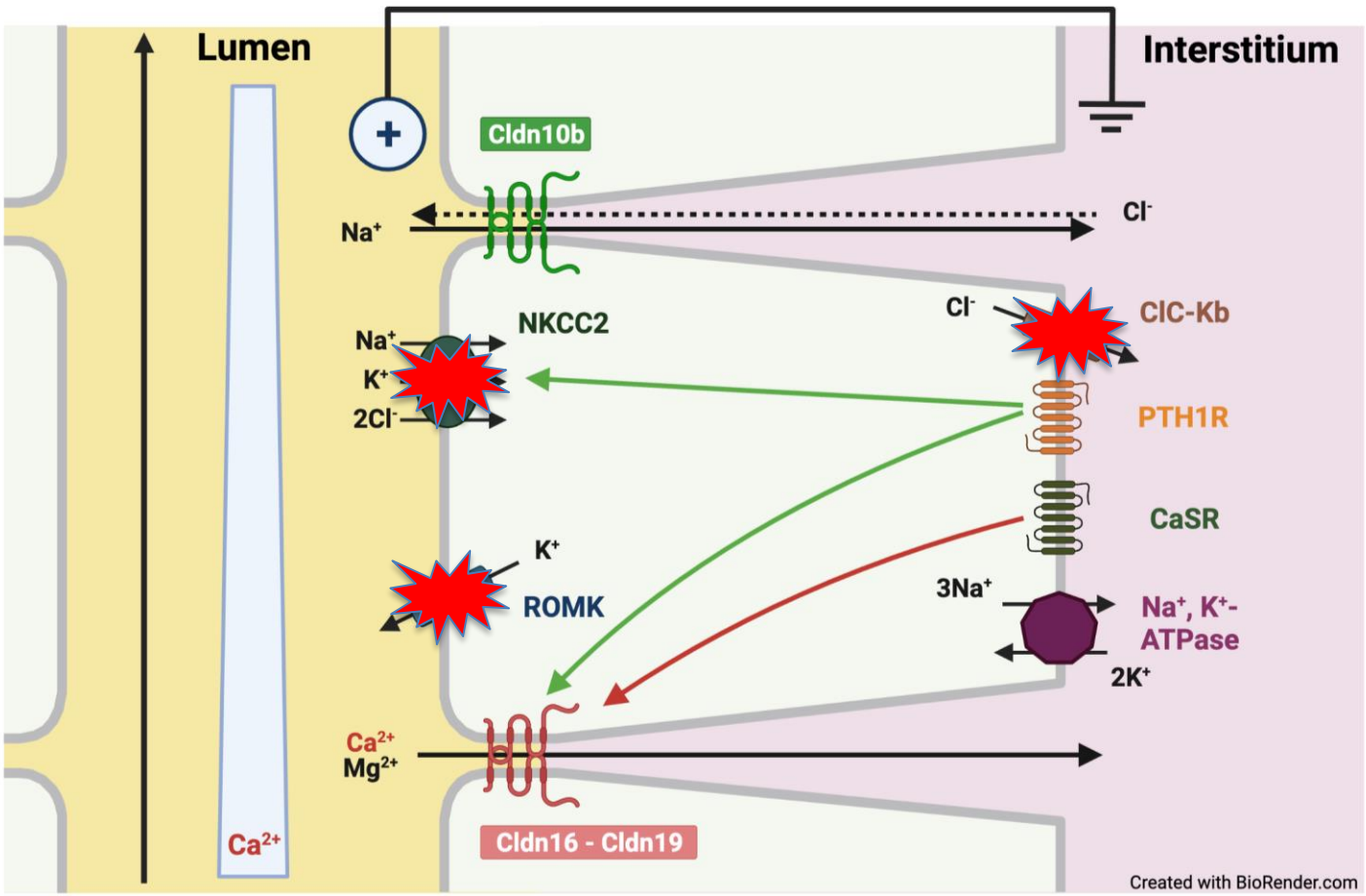
J Clin Invest DOI: 10.1172/JCI127750

OAZON syndrome : Azoospermia, obstructive, with nephrolithiasis



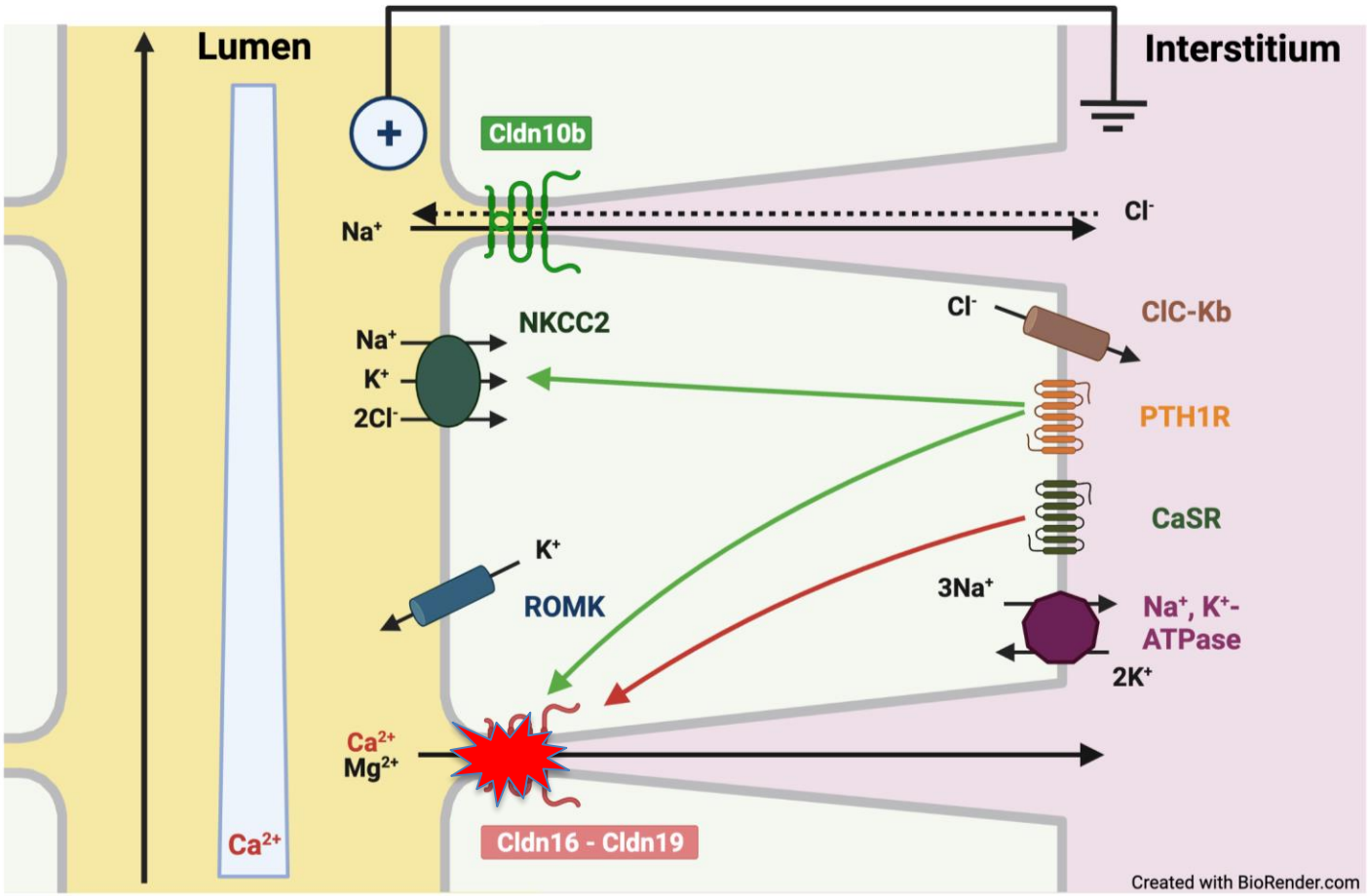
P Houillier et al, Pflugers Arch 2022

Bartter syndrome



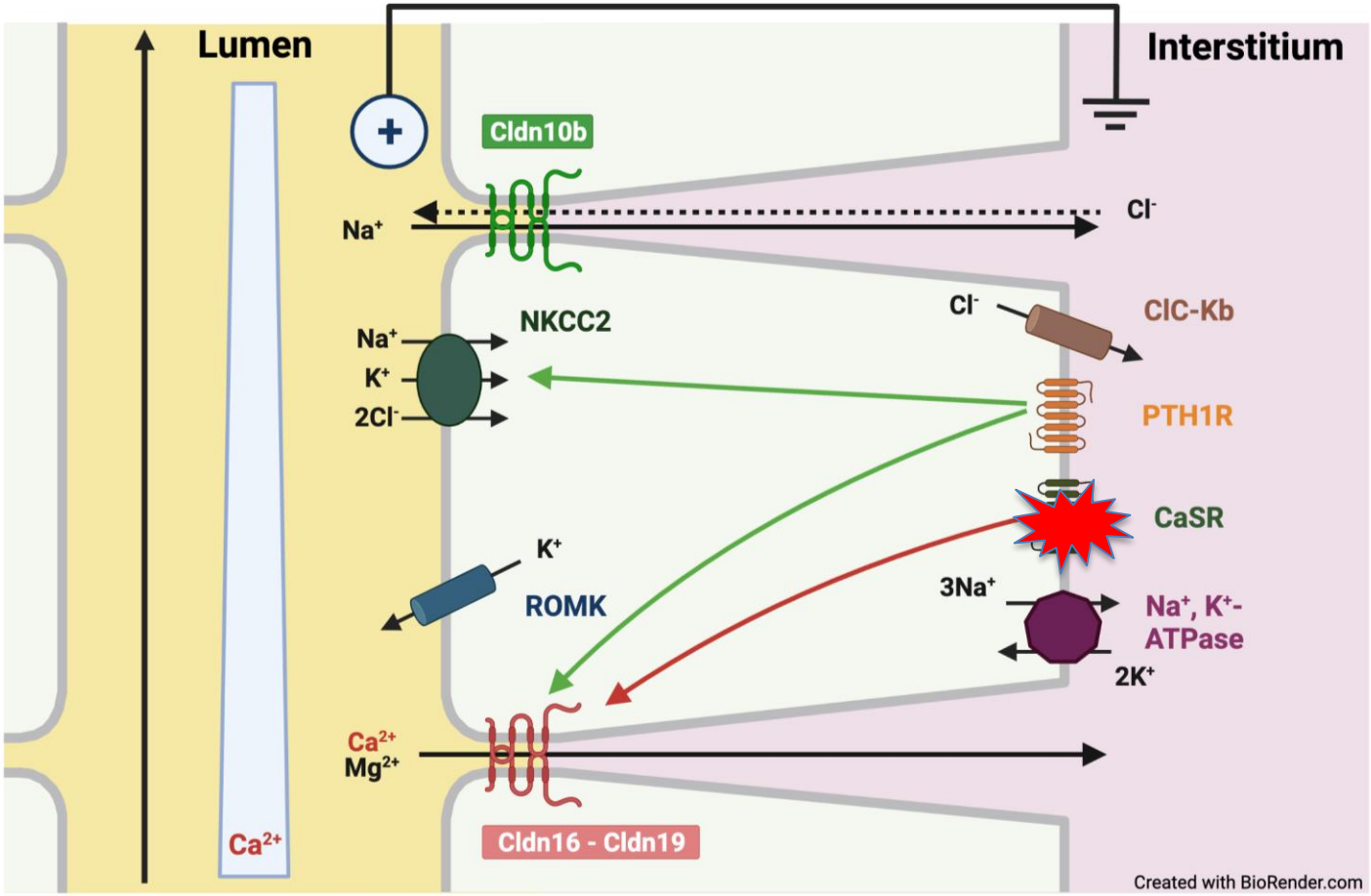
P Houillier et al, Pflugers Arch 2022

Familial hypomagnesemia with hypercalciuria and nephrolithiasis



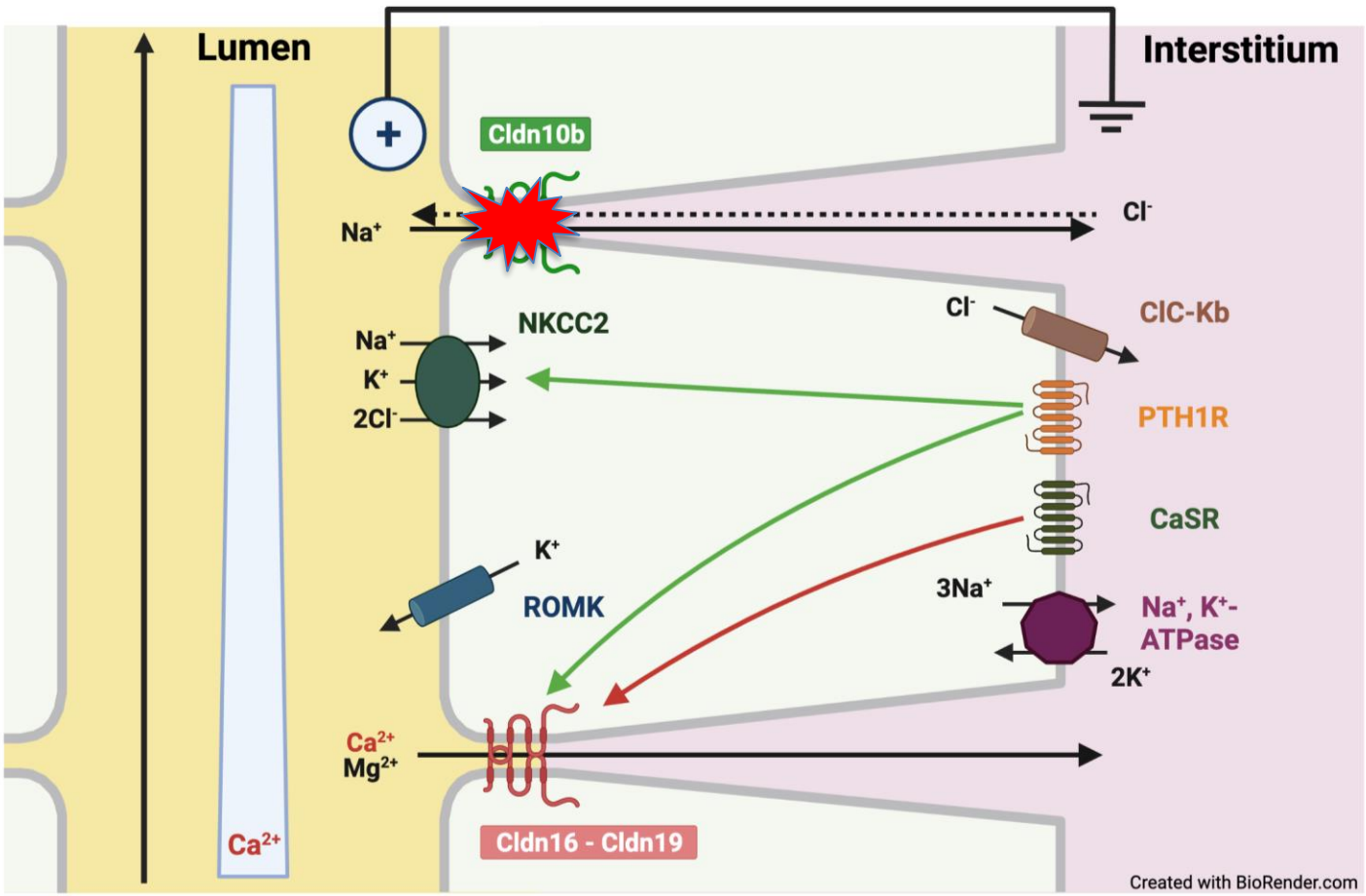
P Houillier et al, Pflugers Arch 2022

Autosomal dominant hypocalcemia/Familial « hypocalciuric » hypercalcemia



P Houillier et al, Pflugers Arch 2022

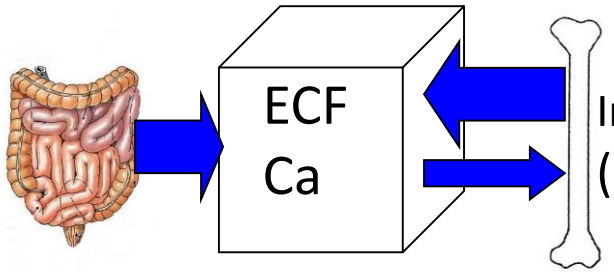
HELIX syndrome



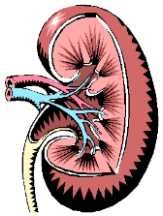
P Houillier et al, Pflugers Arch 2022

Pathophysiology of human idiopathic hypercalciuria

Increased intestinal
Ca absorption



Increased Ca release
(especially on a low Ca diet)



Decreased renal tubular
Ca reabsorption

Hypercalciuria

Primary or secondary disorders ?

Summary - Conclusion

- Adequate renal calcium handling is mandatory to maintain extracellular calcium homeostasis
- On steady state, urinary calcium excretion does not tell you how much calcium is reabsorbed along the renal tubule, but how much calcium enters the ECF
- Disorders of renal calcium handling are common: they can be extrinsic or intrinsic

NEXT WEBINARS

16/05/23

Syndromic Ciliopathies (Bardet Biedel)
Jens König (ERKNet) & Hélèn Dollfus (ERN-Eye)

06/06/23

Physiology of Podocytophathies
Tobias Huber (Hamburg, Germany)

27/06/23

Immune glomerulopathies: a pathogenesis and treatmentoriented approach for clinical management
Paola Romagnani (Florence, Italy)

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