

Review of renal pathophysiology

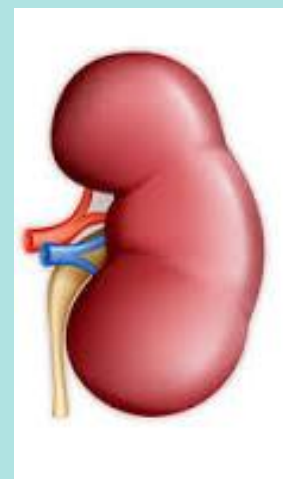
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Melanie Hoenig, MD

Medicine Residency @BIDMC

Nephrology Fellowship @BIDMC

Associate Professor of Medicine@ HMS

- 1st Editor KSAP, ASN
- Course Director, Integrated Human Pathophysiology (endo, renal pathophysiology, required for all 1st HMS Pathways students)
- Feature editor, Core Curriculum AJKD
- Channel your Enthusiasm Podcast
- Clinical focus: transition to adult care, kidney disorders in context of HIV, electrolyte disorders



- Speaker at PriMed, primary care conference
- I served on a multidisciplinary panel on care of patients with cystinosis sponsored by Amgen

Objectives

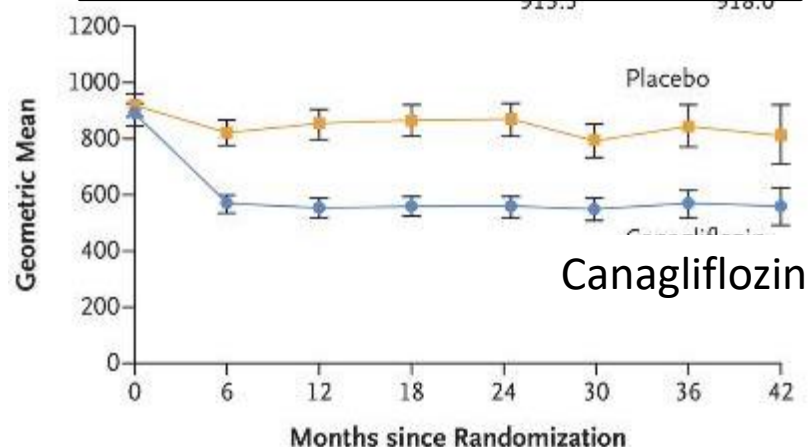
- Explore case vignettes to:
 - Review the components of the nephron, key transporters and essential roles in physiology and pathophysiology

In 2019, CREDENCE thrilled the nephrology community!

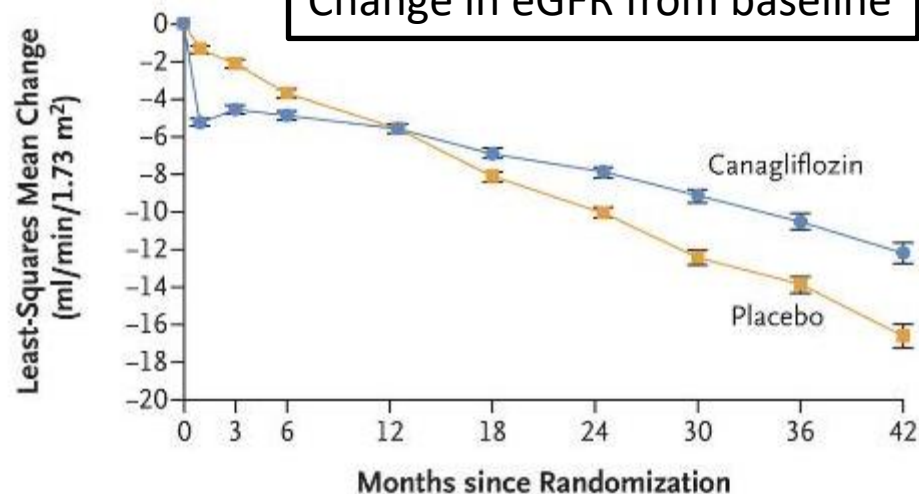
CREDENCE

(Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation)

Urinary albumin to creatinine ratio



Change in eGFR from baseline



Q1. Which of the following is the most likely cause of the findings seen in this study?

- a) Afferent arteriolar vasoconstriction
- b) Afferent arteriolar vasodilation
- c) Efferent arteriolar vasoconstriction
- d) Thinning of the glomerular basement membrane

Terminology

Determinants of glomerular filtration:

Single nephron Glomerular Filtration Rate

$$\text{SNGFR} = K \times A \times (\Delta P - \Delta \pi)$$

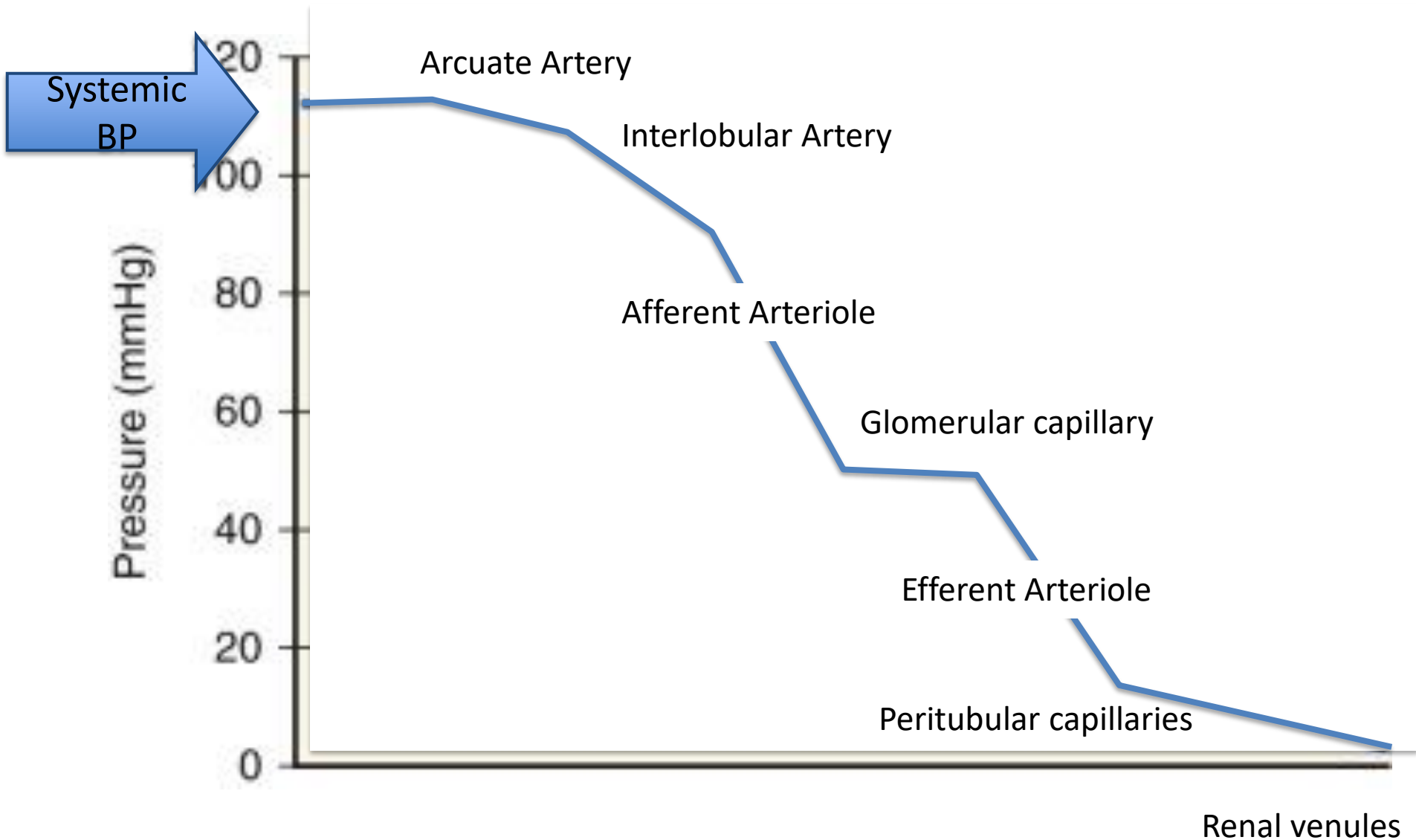
K = hydraulic conductivity

A = surface area

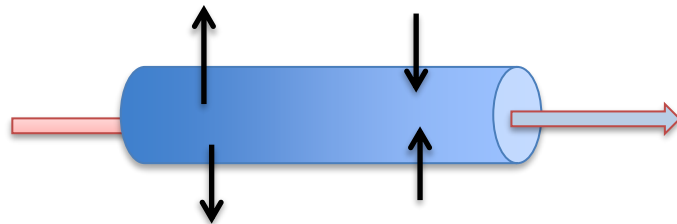
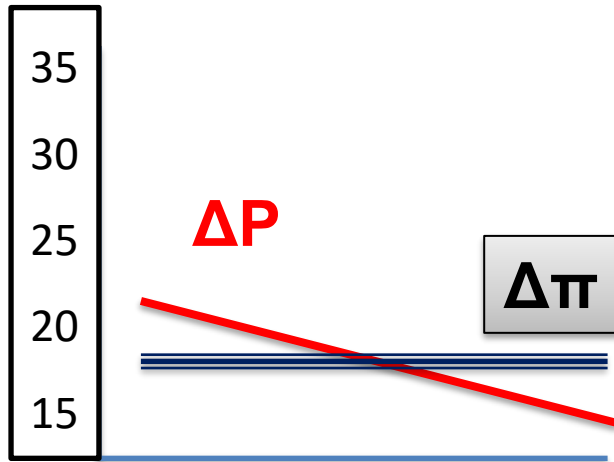
π = colloid osmotic pressure/
oncotic pressure

P = hydraulic pressure
(aka hydrostatic pressure)

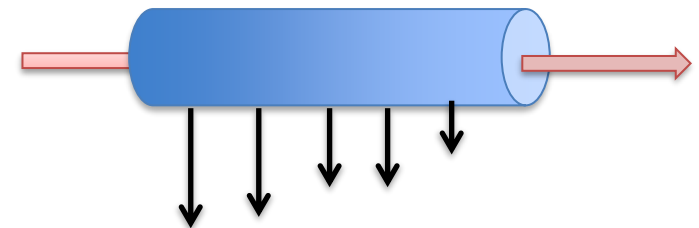
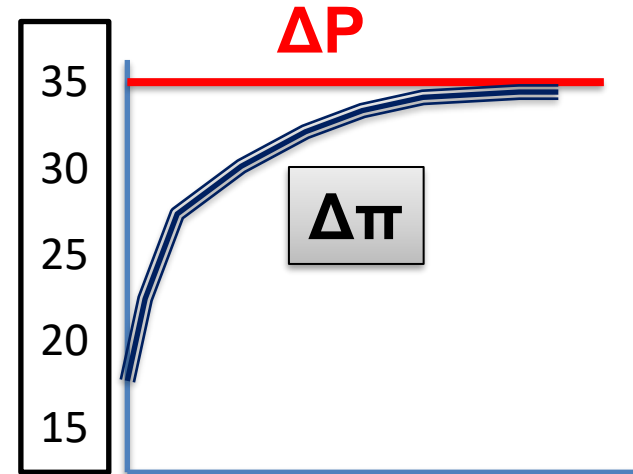
Hydraulic pressure decreases along the renal vasculature



Pressure in the glomerular capillary differs from a peripheral capillary

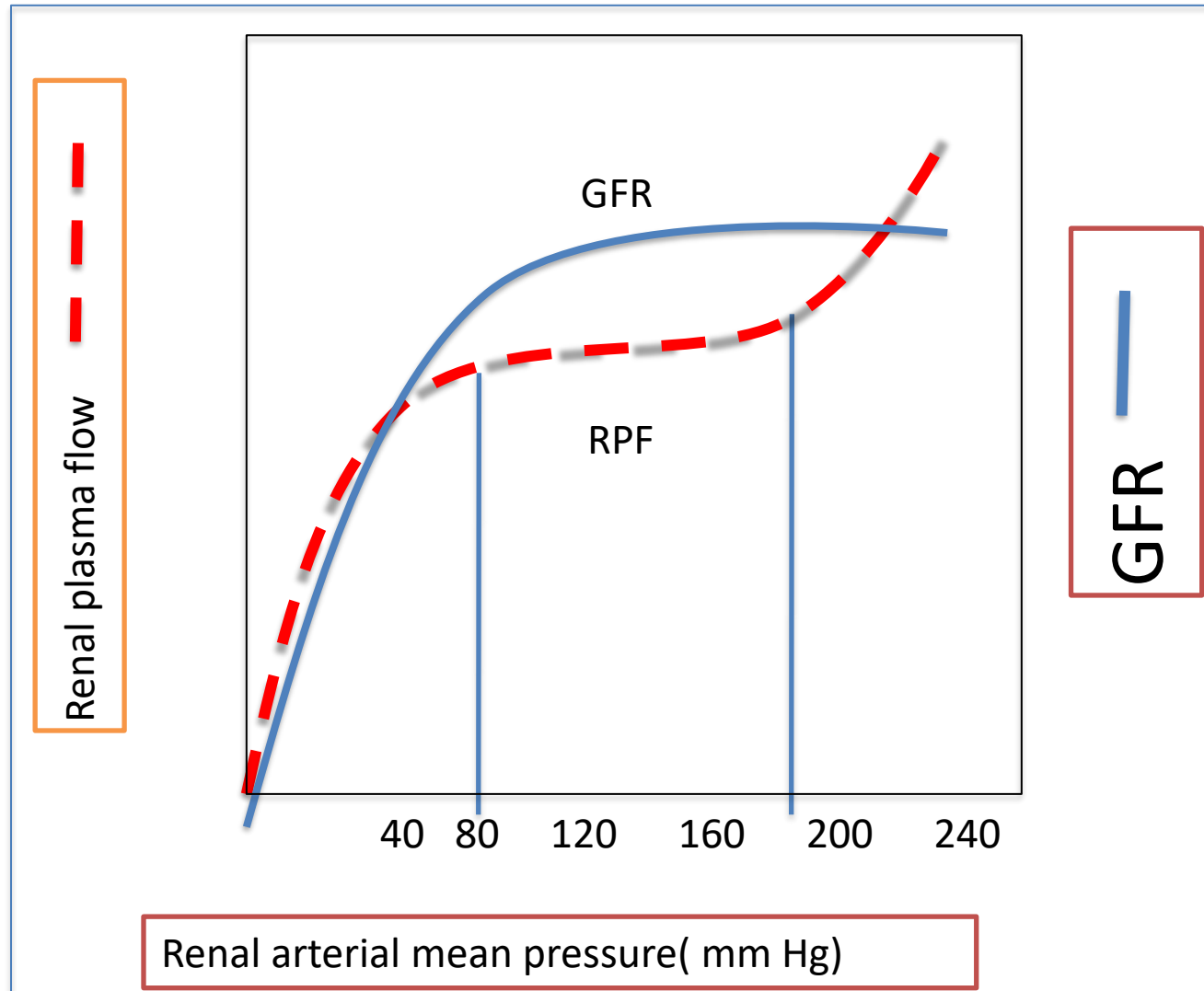


Peripheral capillary



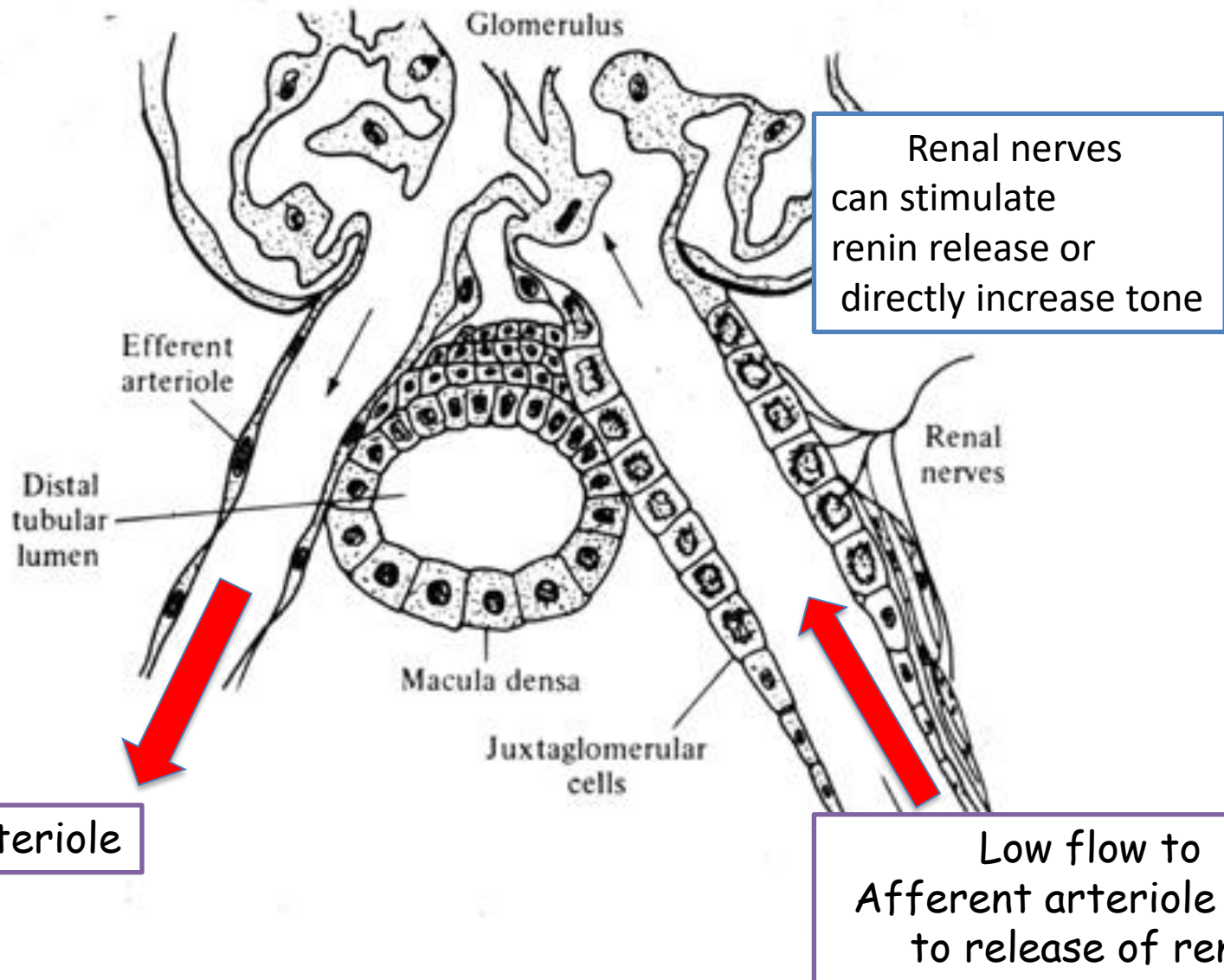
Glomerular capillary

The kidney maintains filtration over a wide range of perfusion pressures

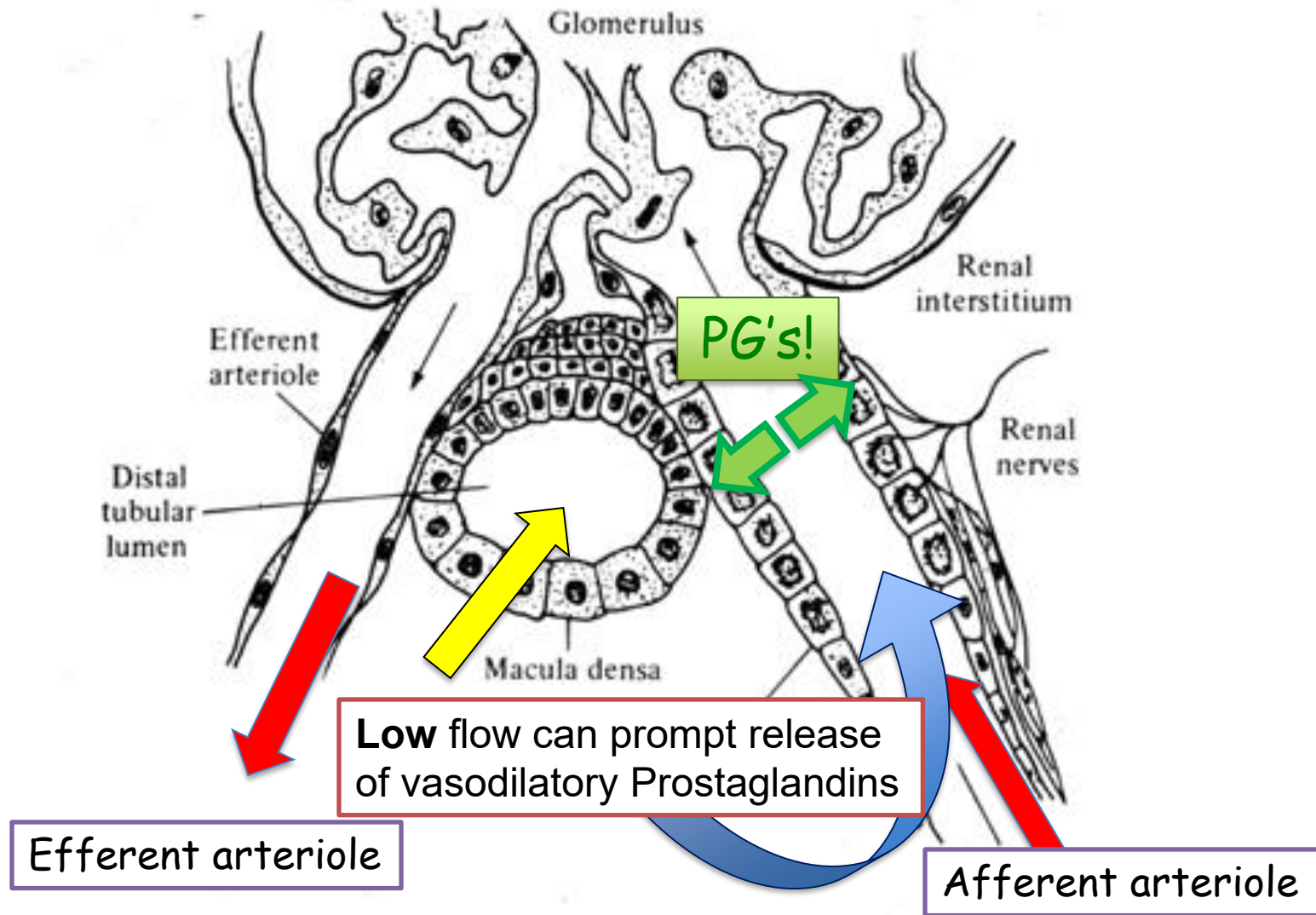


Glomerular filtration is regulated by:

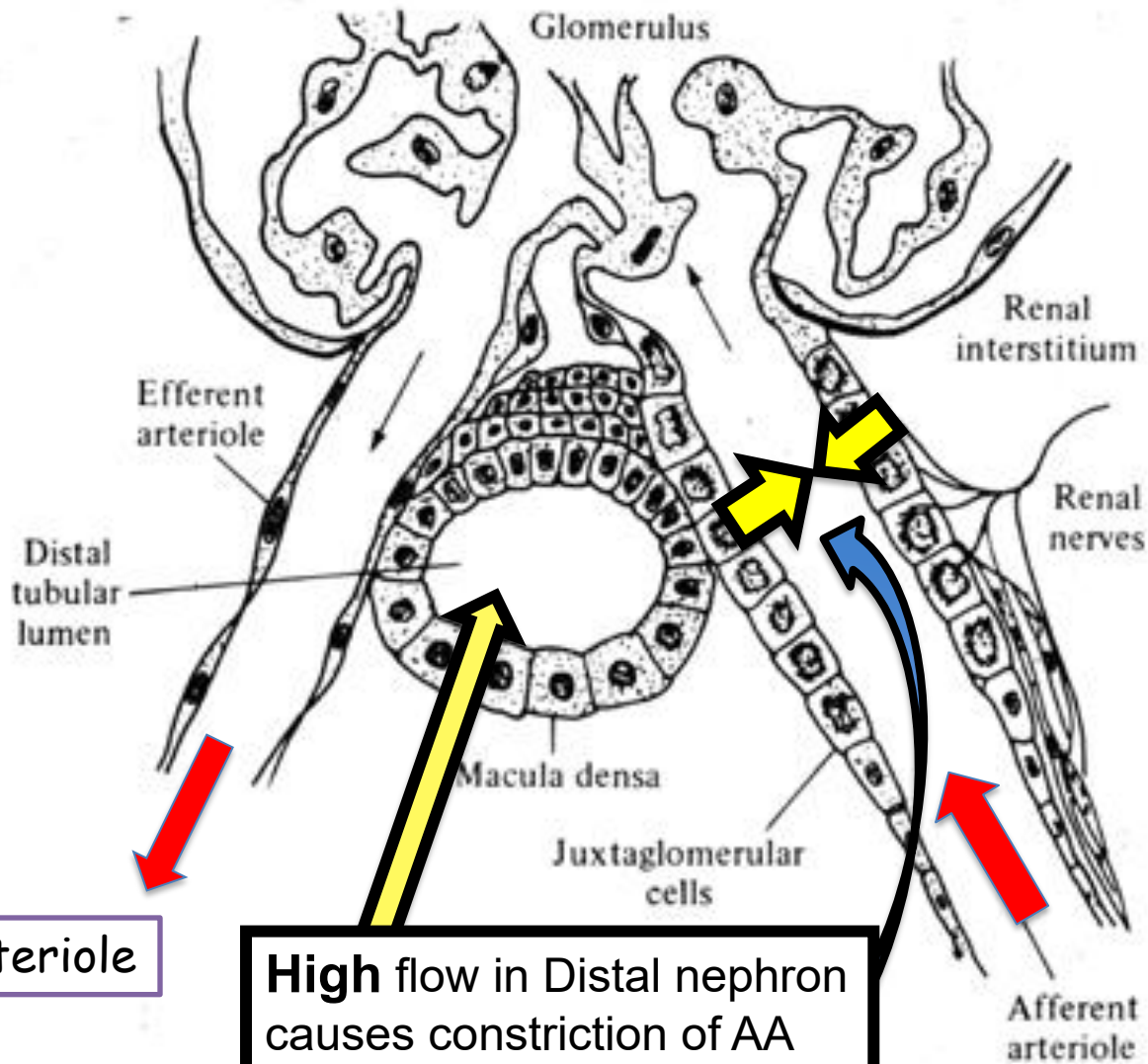
- (1) flow to the arteriole



Glomerular filtration and 2. tubuloglomerular feedback



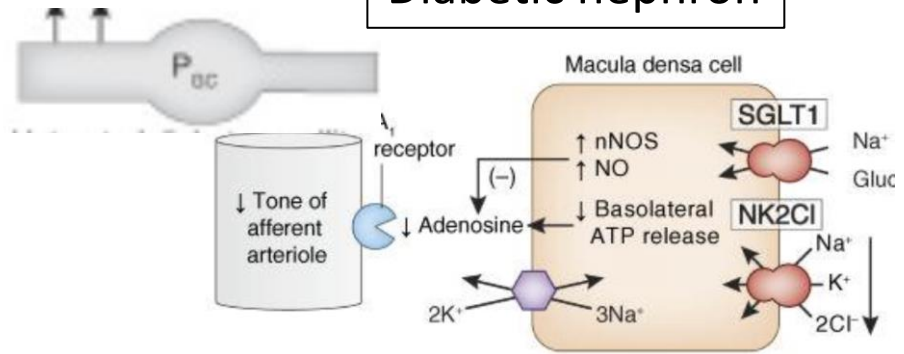
Glomerular filtration and tubuloglomerular feedback



Efferent arteriole

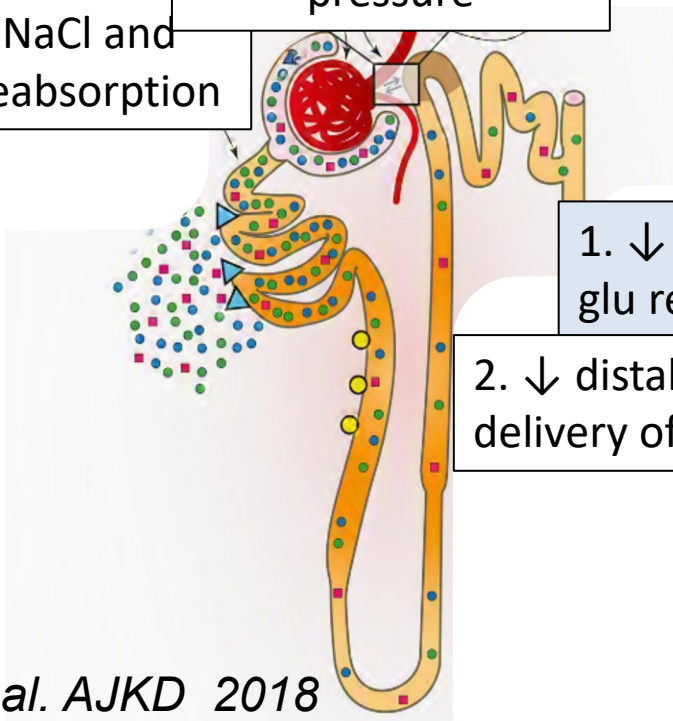
High flow in Distal nephron
causes constriction of AA
through **adenosine**

Diabetic nephron



3. feedback from macula densa to increase glomerular pressure

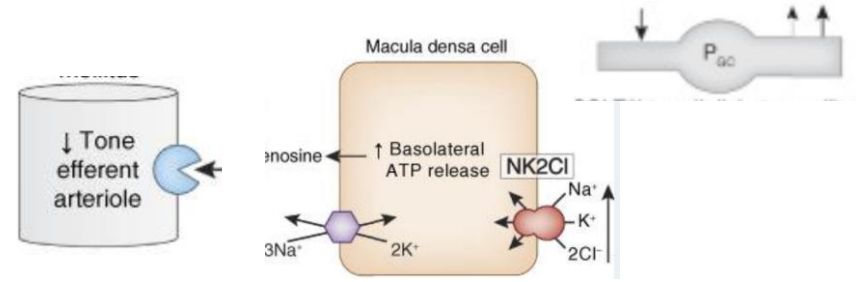
1. $\uparrow$ NaCl and glu reabsorption



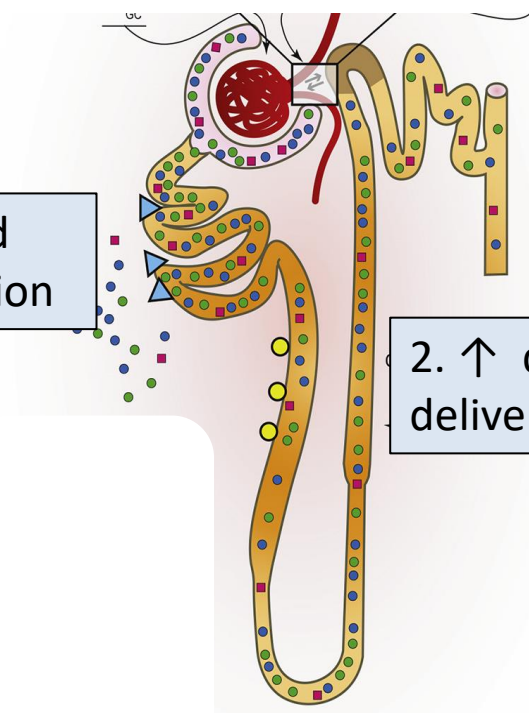
1. $\downarrow$ NaCl and glu reabsorption

2. $\downarrow$ distal delivery of NaCl

Diabetic nephron + SGLT2i



3. signal to decrease glomerular pressure @ macula densa



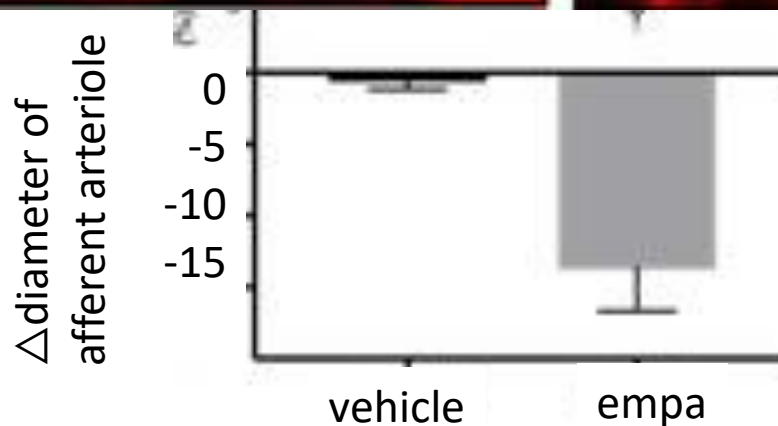
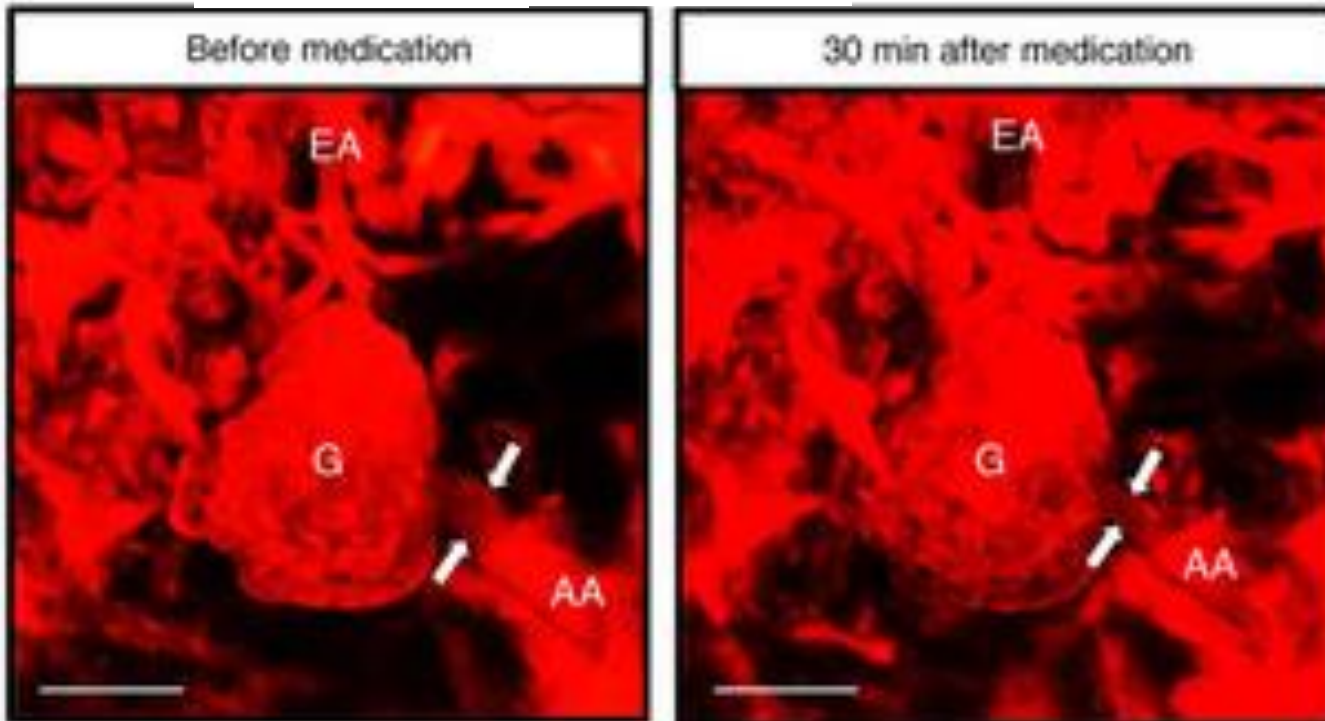
2. $\uparrow$ distal delivery of NaCl

1st measurement of AA diameter

2nd measurement of AA diameter



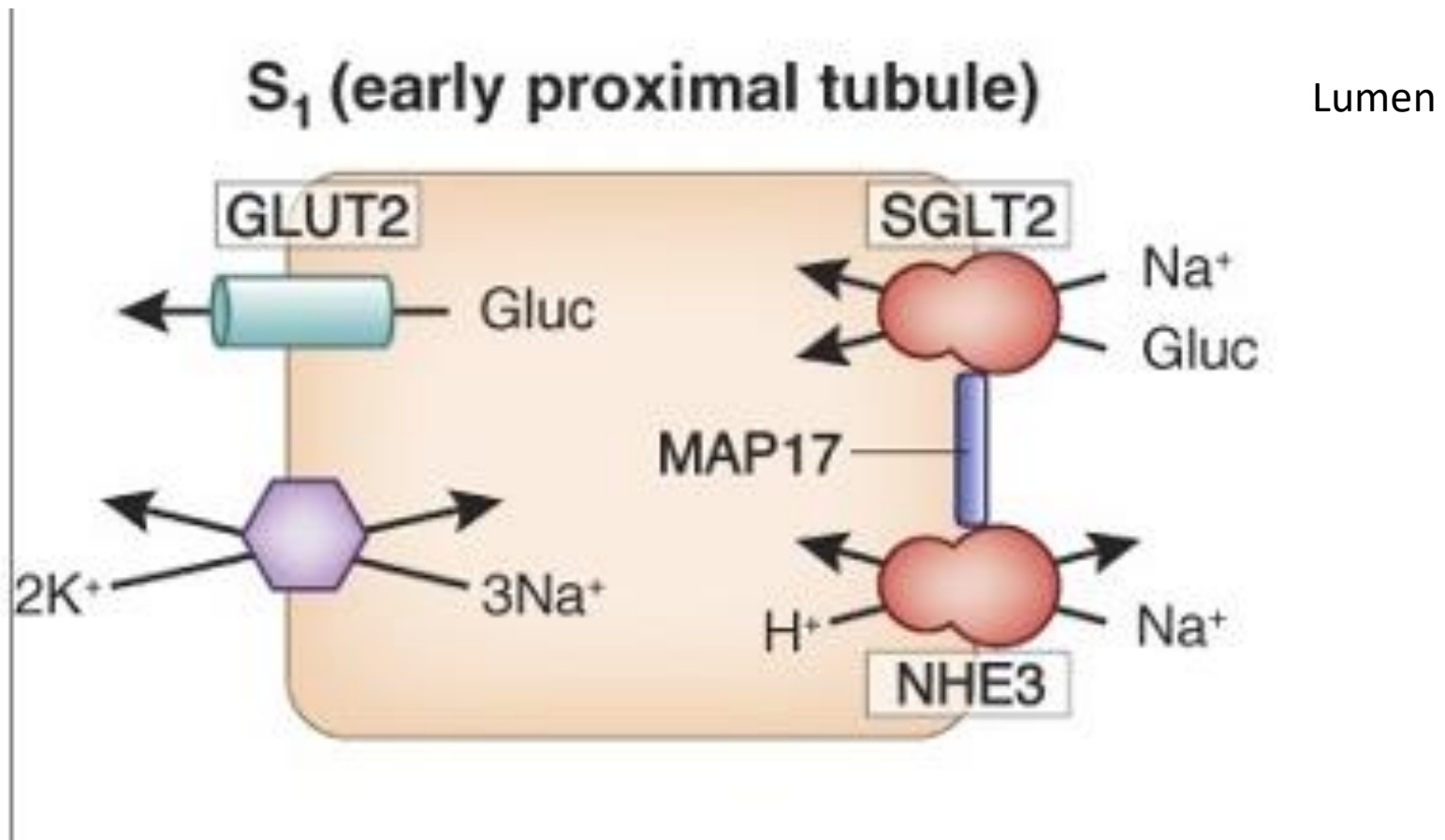
catheterization Empla 5 mg/kg



And similar graph for SNGFR!

Likely a range of other benefits from SGLT2i-

SGLT2 shares a common scaffolding protein with NHE3



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- a) Afferent arteriolar vasoconstriction**
- b) Afferent arteriolar vasodilation
- c) Efferent arteriolar vasoconstriction
- d) Thinning of the glomerular basement membrane

Q2. A 35-year-old man is evaluated for darkened urine. He is using PrEP (pre-exposure prophylaxis) for HIV for several years.

On exam, he appeared well with a BP of 116/82 mm Hg

Na 138 mEq/L

Cl 114 mEq/L

K 3 mEq/L

HCO₃ 16 mEq/L

BUN 20 mg/dl

Creat 1.6 mg/dl

Phos 2.3 mg/dl

Uric acid 2.8 mEq/L

Urine: pH 5 no blood, trace protein, + glucose

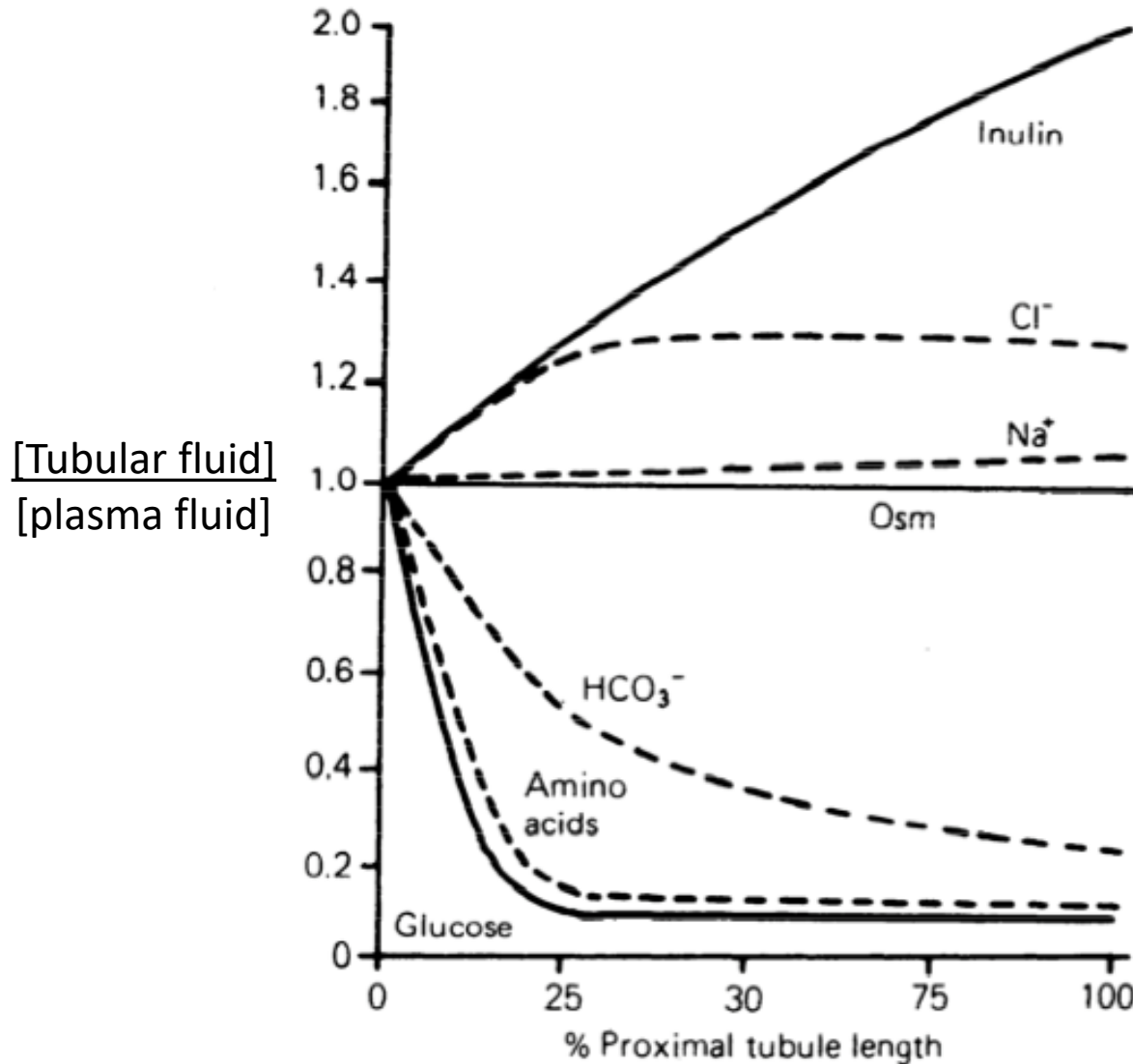
Urine protein to creatinine ratio is 1.0 mg/mg

Urine albumin to creatinine ratio is 250 mcg/mg

The most likely cause of the laboratory abnormalities is

- a) Classic distal renal tubular acidosis
- b) Proximal renal tubular acidosis
- c) Type IV renal tubular acidosis

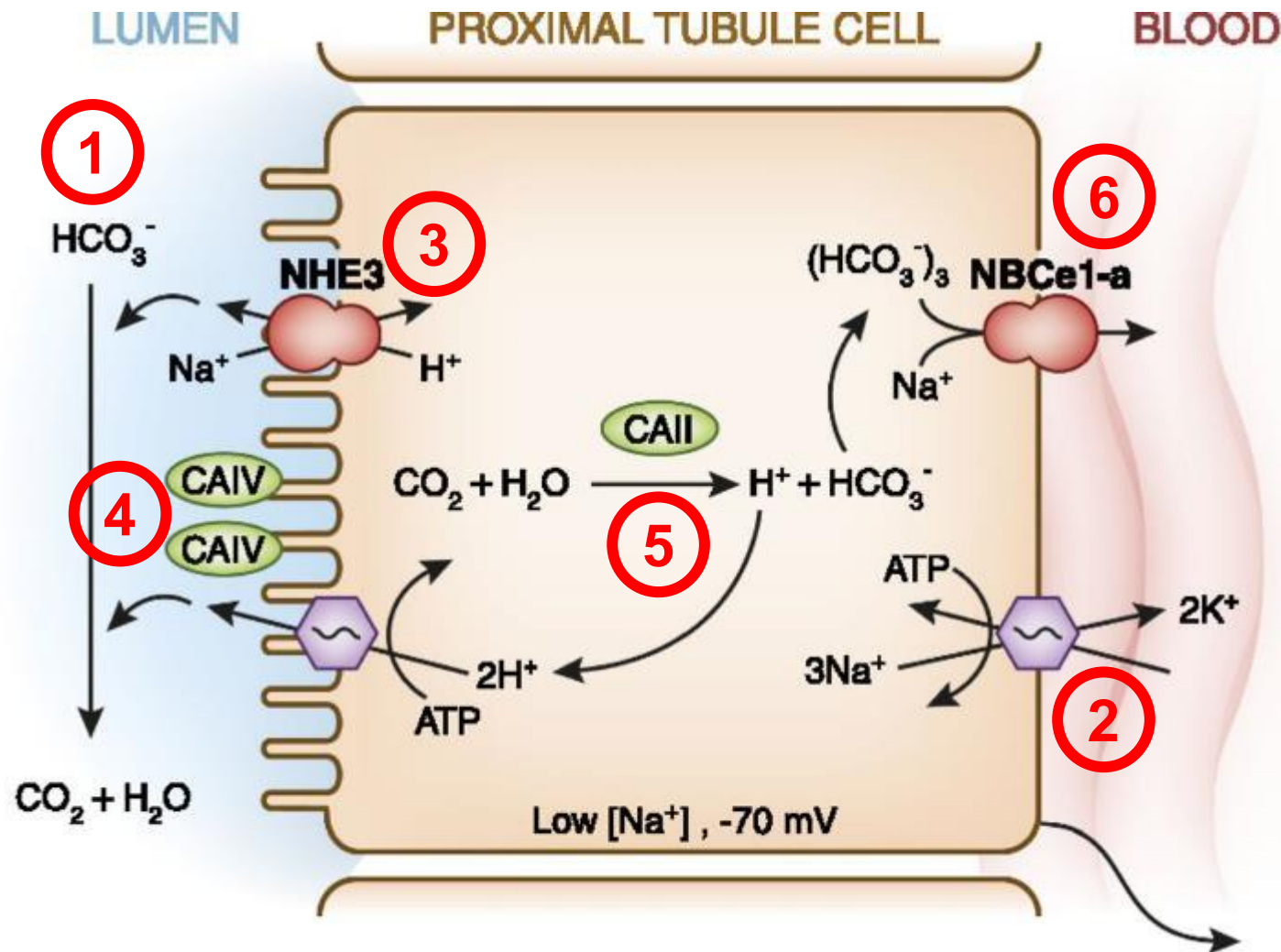
The proximal tubule is the site of reabsorption of most of the filtrate



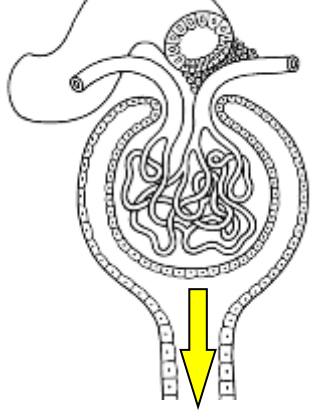
Near isotonic reabsorption

Lots of activity over very short distance



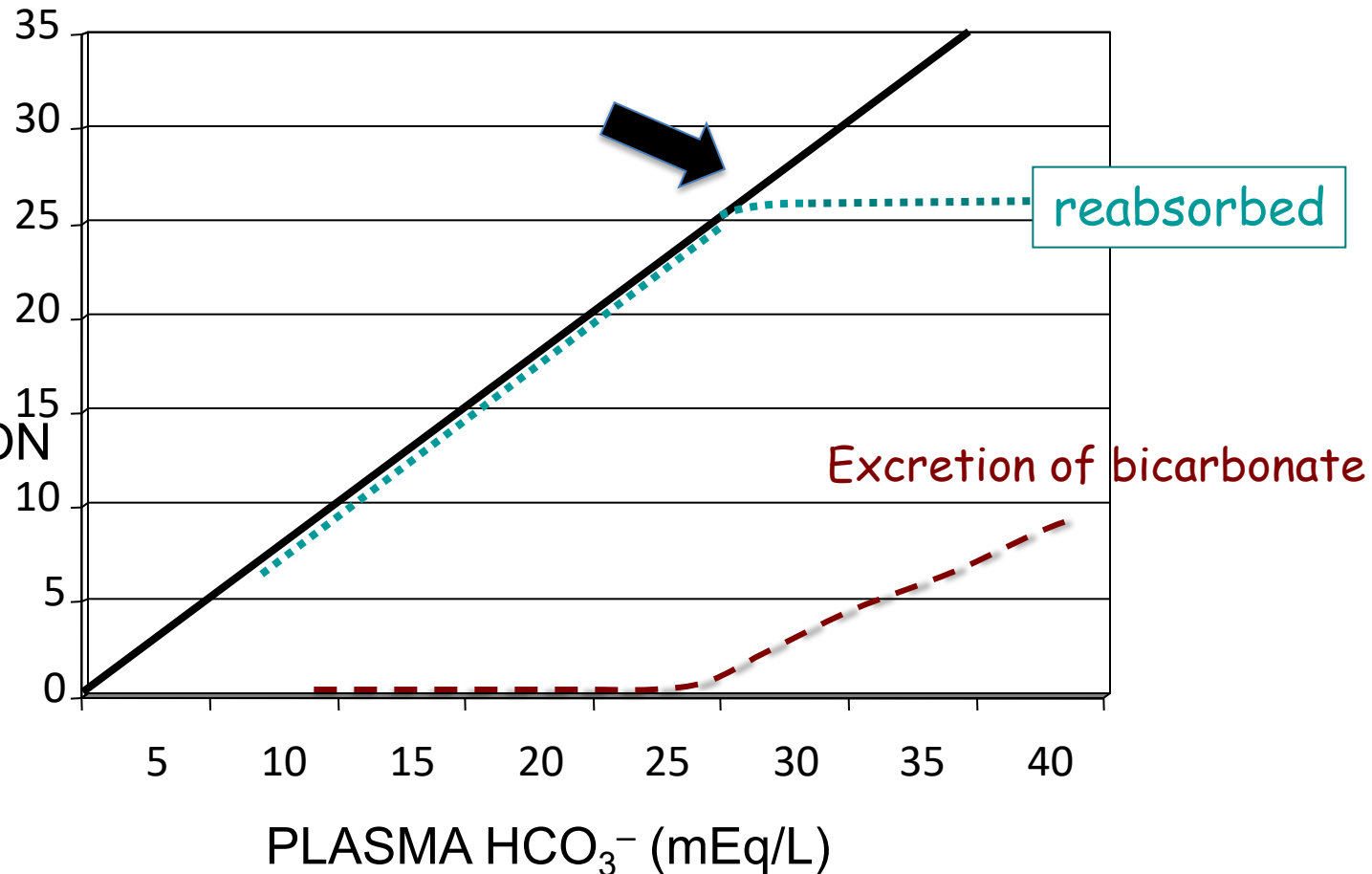


$GFR \times HCO_3^-$

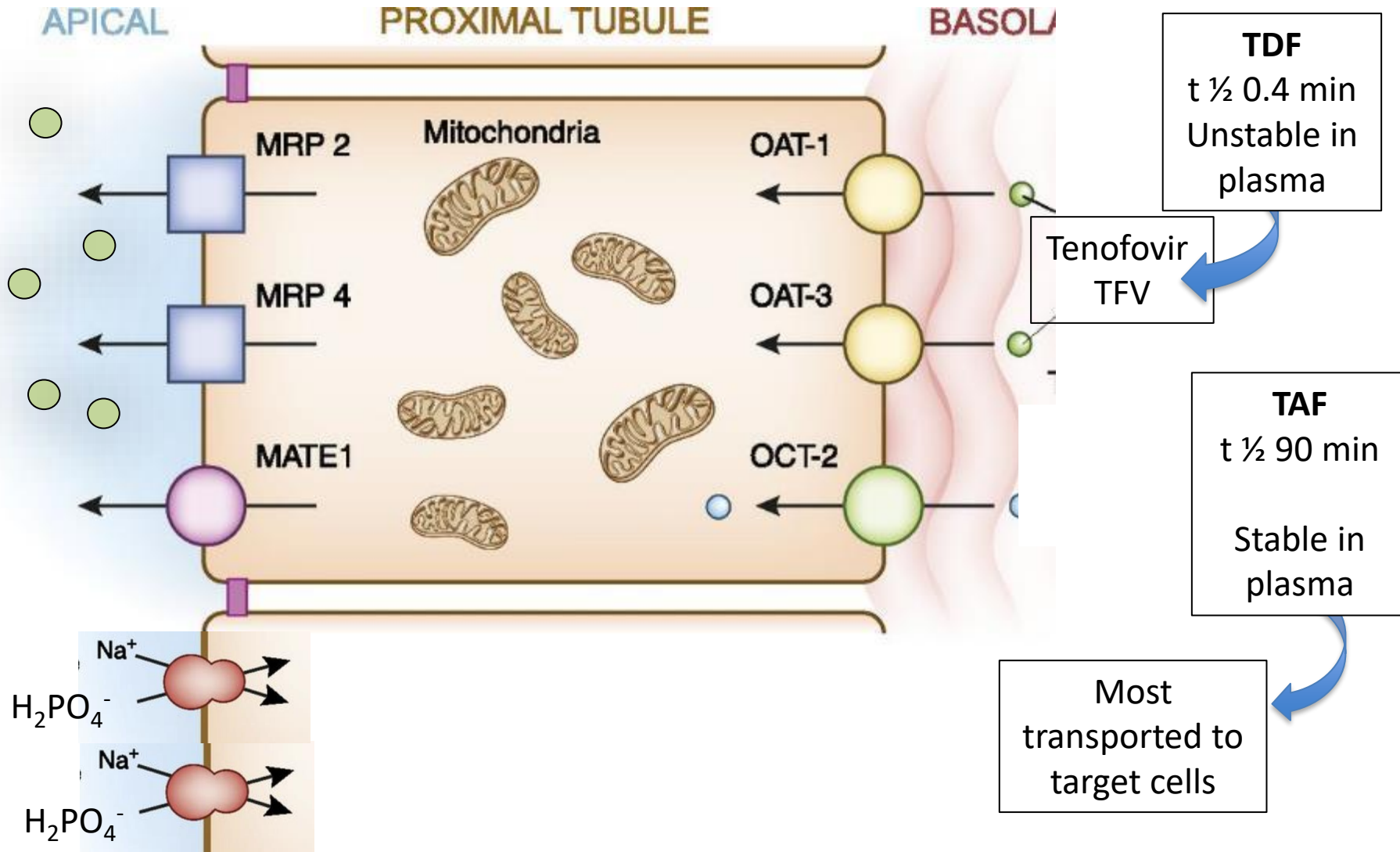


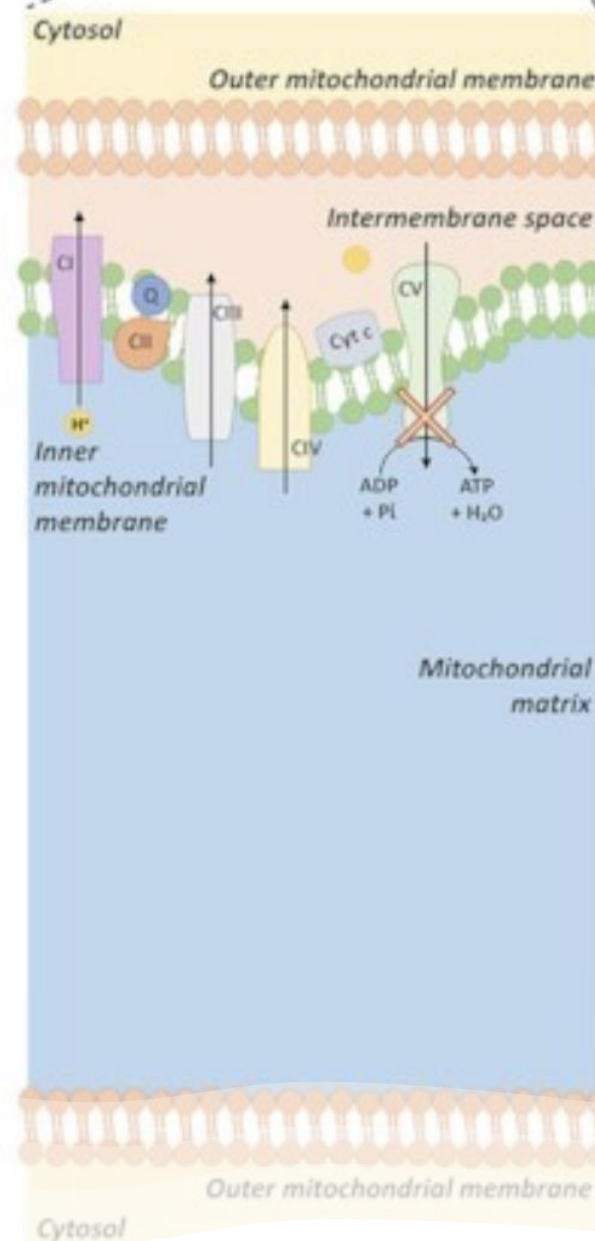
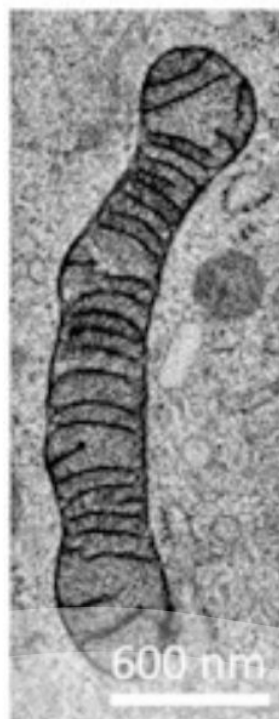
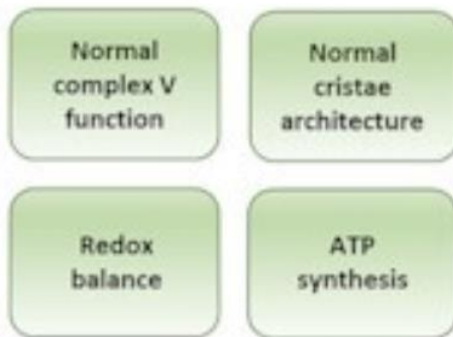
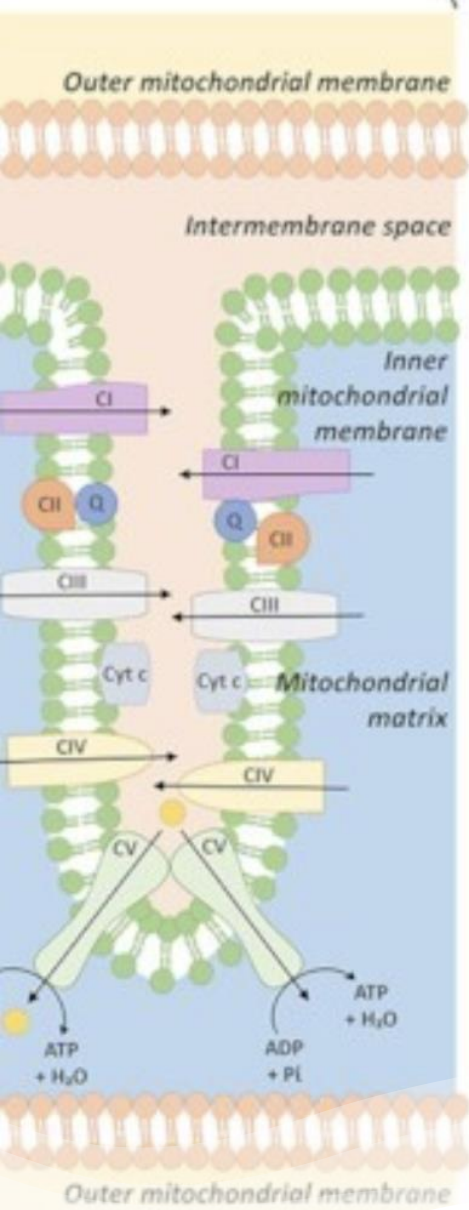
Proximal reclamation of HCO_3^- relates to the plasma bicarbonate level (under normal circumstances)

HCO_3^-
REABSORPTION
(mEq/L)



The proximal kidney tubule is the target for tenofovir-associated nephrotoxicity





Tenofovir inhibits ATPase (complex V) in mitochondria

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Urine: pH 5 no blood, trace protein, + glucose

Urine protein to creatinine ratio is 1.0 mg/mg

Urine albumin to creatinine ratio is 250 mcg/mg

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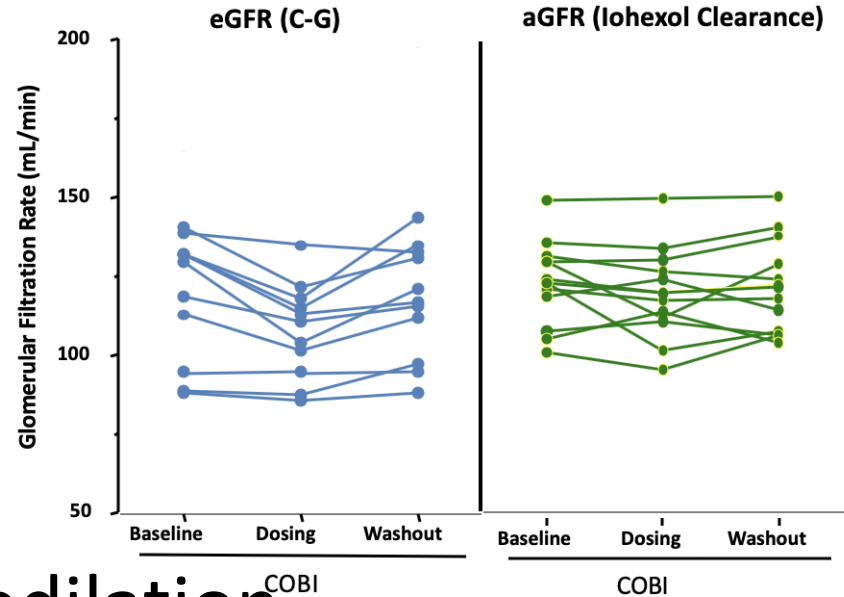
a) Classic distal renal tubular acidosis

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c) Type IV renal tubular acidosis

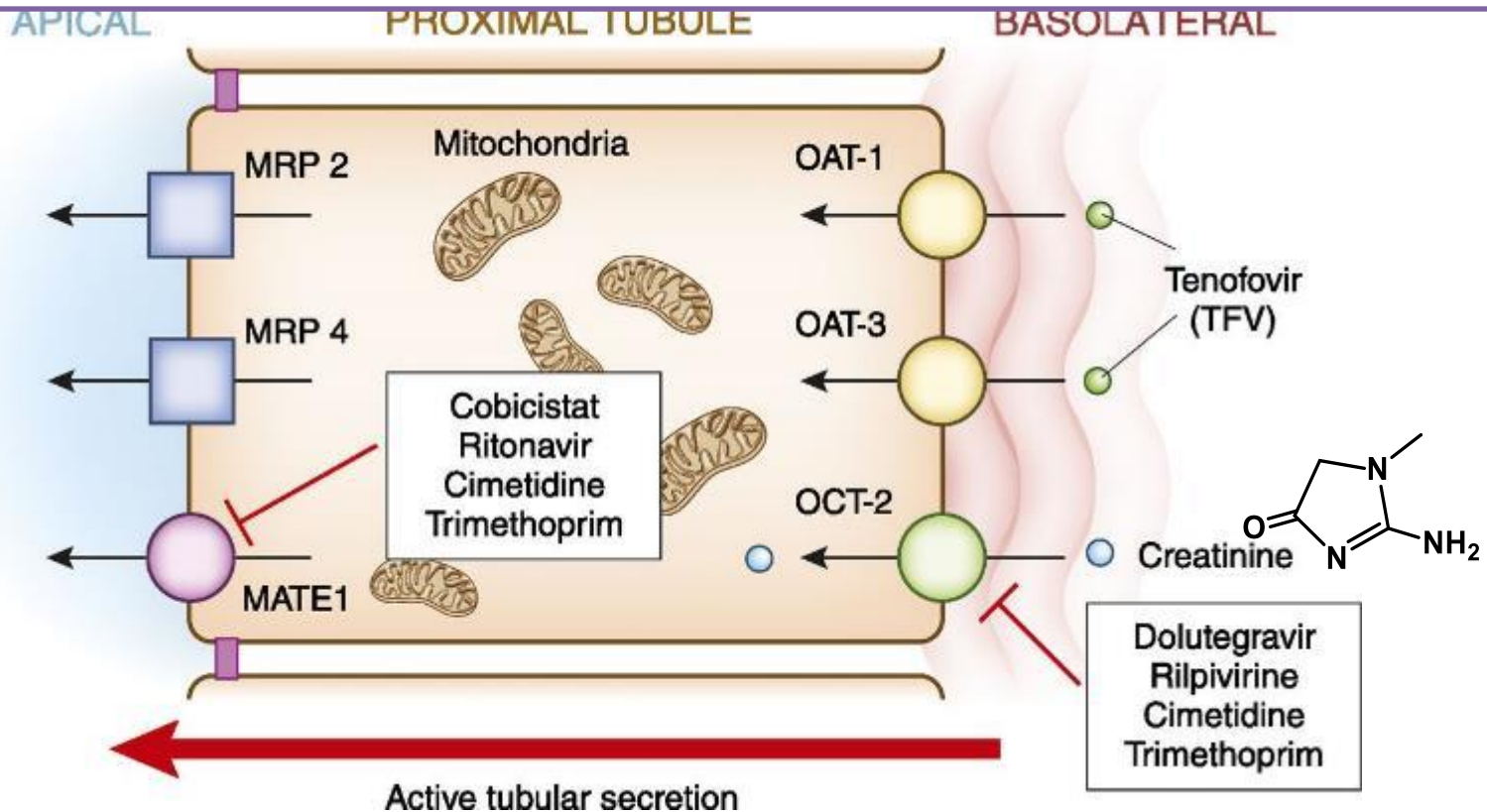
Q3. Cobicistat is in combination pills with tenofovir. In mild to moderate renal impairment, this leads to a decline in eGFR

. What is the mechanism of altered eGFR?



- a) Effective arteriolar vasodilation
- b) Organic cation transporter inhibition
- c) Proximal tubulopathy
- d) Tubular intraluminal obstruction

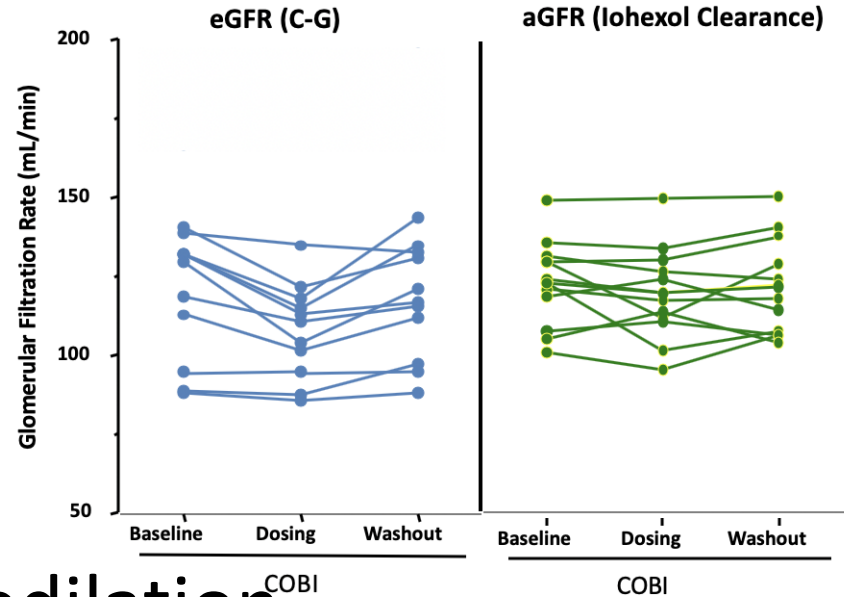
Inhibition or competition at the organic cation transporters may ↑ serum creatinine without altering filtration (and therefore no change in GFR)



Dolutegravir (Marketed alone as Tivicay)
(Or co-formulated with ABC+3TC as Triumeq)
Bictegravir (co-formulated with TAF +FTC as Biktarvy)
No dose reduction to eGFR > 30 ml/min

Q3. Cobisistat is in combination pills with tenofovir. In mild to moderate renal impairment, this leads to a decline in eGFR

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Q 4. A group of nephrology fellows celebrate completion of 1st year by eating at a local restaurant but succumb to symptoms of norovirus with nausea and vomiting. **Several days later**, one presents with malaise, weakness and vomiting.

Laboratory Data:

Na 142 mEq/L

Cl 110 mEq/L

HCO₃ 30 mEq/L

K 3.0 mEq/L

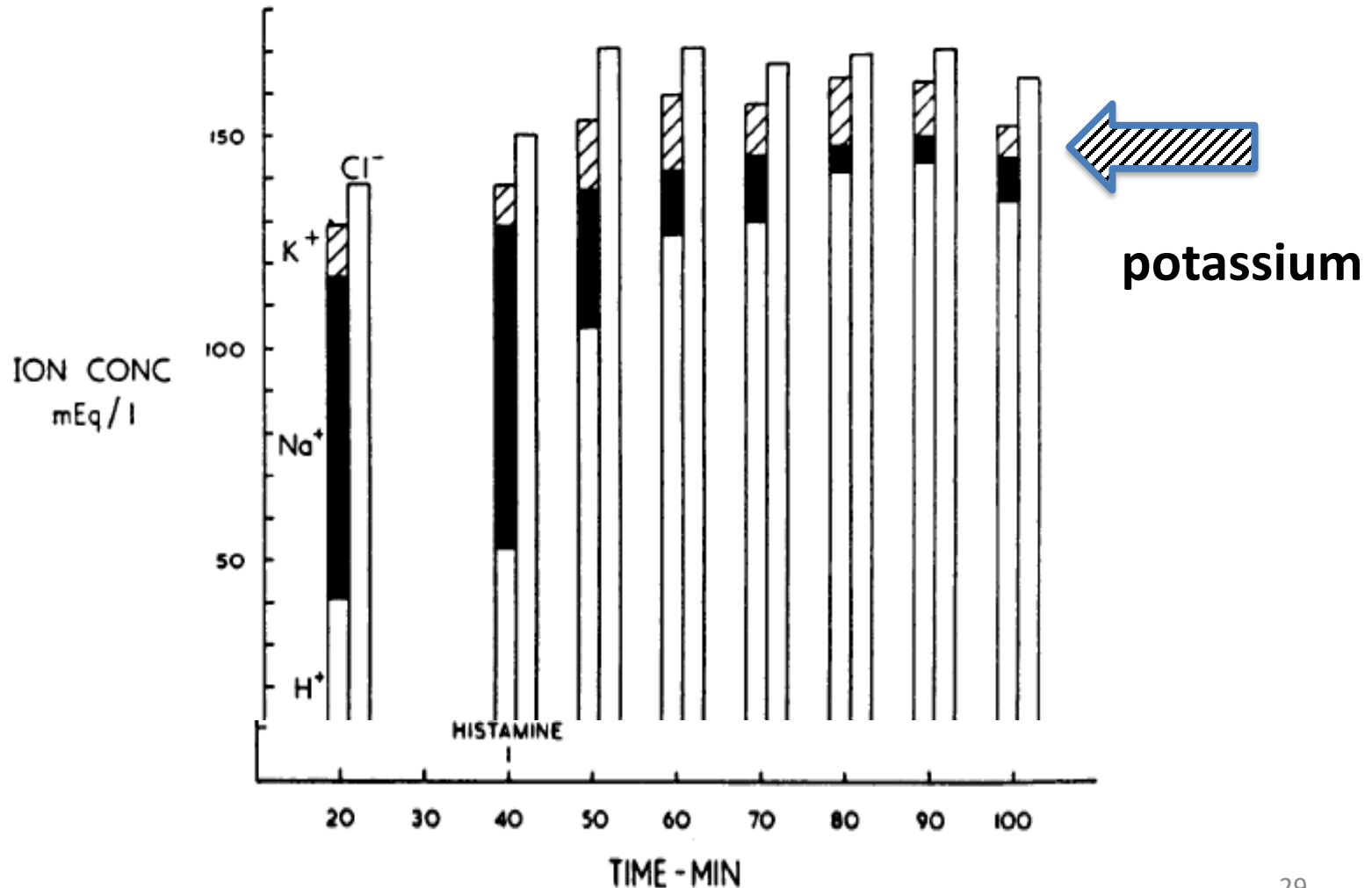
BUN 34 mg/dL

Creatinine 1.8 mg/dL

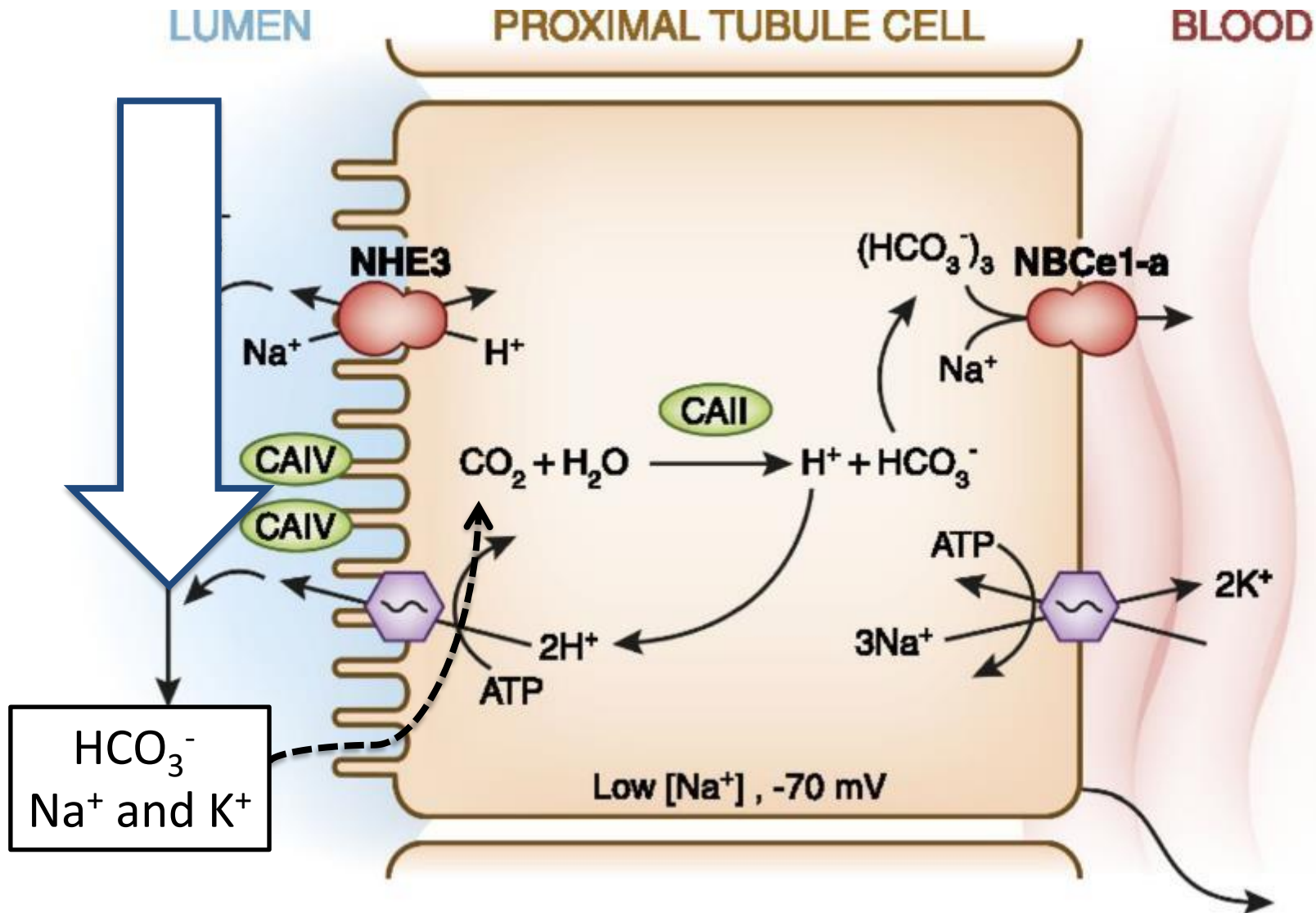
The most likely cause of the hypokalemia is

- a) Potassium loss in emesis
- b) Secondary hyperaldosteronism
- c) Shift of potassium out of the cells
- d) Urinary loss with bicarbonaturia

Electrolyte concentration in the gastric fluid of normal subjects



When HCO_3^- is not reabsorbed proximally, it is excreted with a cation



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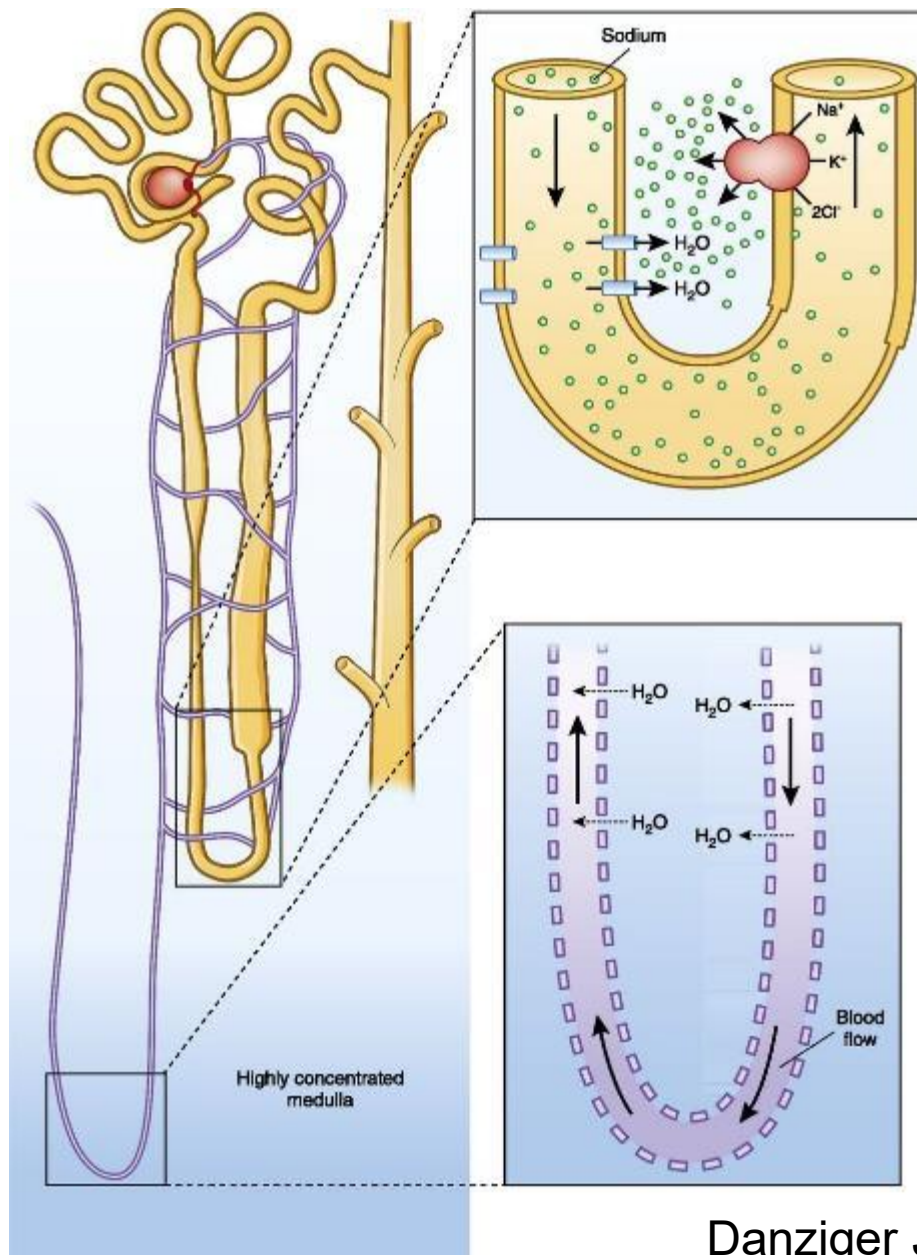
Q5. a 68-year-old man is evaluated for management of hypertension and longstanding hyponatremia. He takes HCTZ, lisinopril and carbamazepine for a distant history of seizure disorder. His blood pressure is 150/88 mmHg and he has no edema.

He is not willing to stop the carbamazepine. A trial without HCTZ does not improve his serum sodium **and the urine Osm is 600 mOsm/kg**. Which of the following is the next best intervention for this patient?

- a) Add amlodipine
- b) Begin torsemide
- c) Prescribe chlorthalidone
- d) Restart the HCTZ
- e) Start tolvaptan

Production of a maximally concentrated urine requires:

1. Maintenance of the concentrated medulla
2. Activity of vasopressin

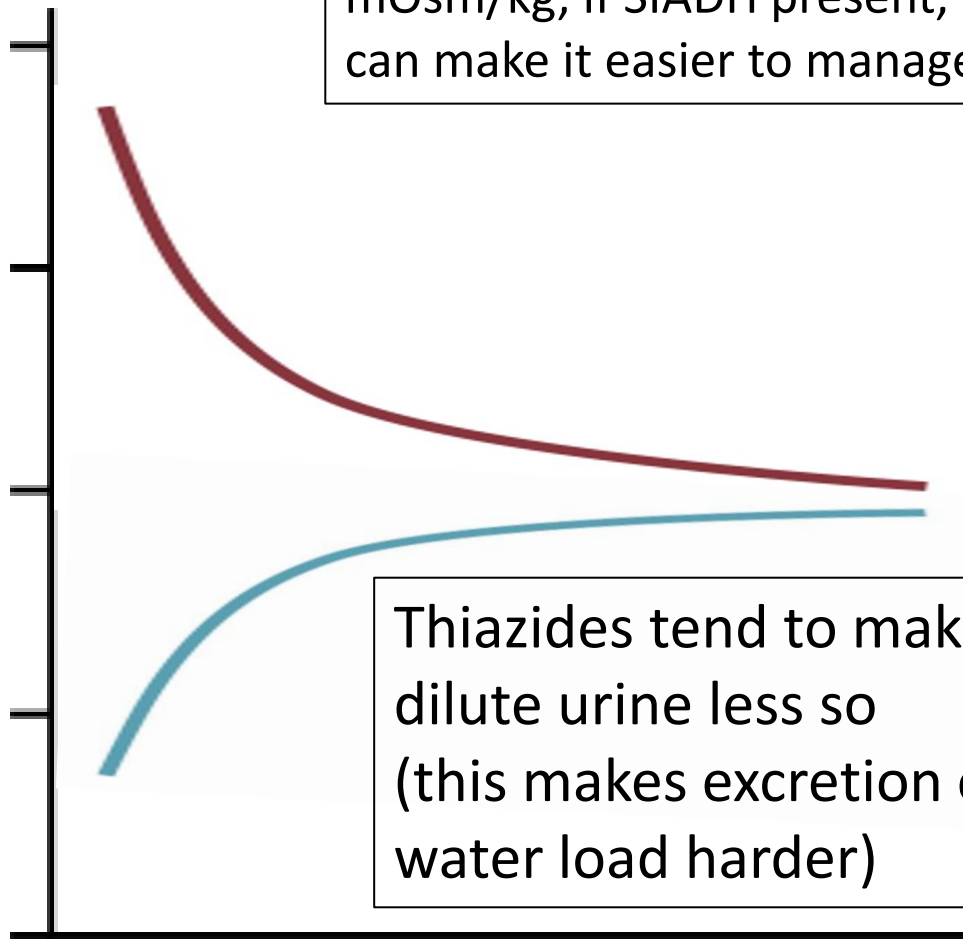


$U_{Osm} (mOsm/kg)$

600
450
300
150
0

Loop diuretics tend to make concentrated urine less concentrated (closer to 300 mOsm/kg; if SIADH present, this can make it easier to manage)

Thiazides tend to make dilute urine less so (this makes excretion of a water load harder)



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Q6. An 8-year-old boy is seen for evaluation and delayed growth. His blood pressure is 90/60 mmHg and his heart rate is 96 b/min

Na 138 mEq/L

Cl 114 mEq/L

K 2.8 mEq/L

HCO₃ 12 mEq/L

BUN 14 mg/dl

Creat 0.7 mg/dl

Ca²⁺ 9.9 mg/dL(9.6-10.3)

Alk phos 520 U/L (35-120)

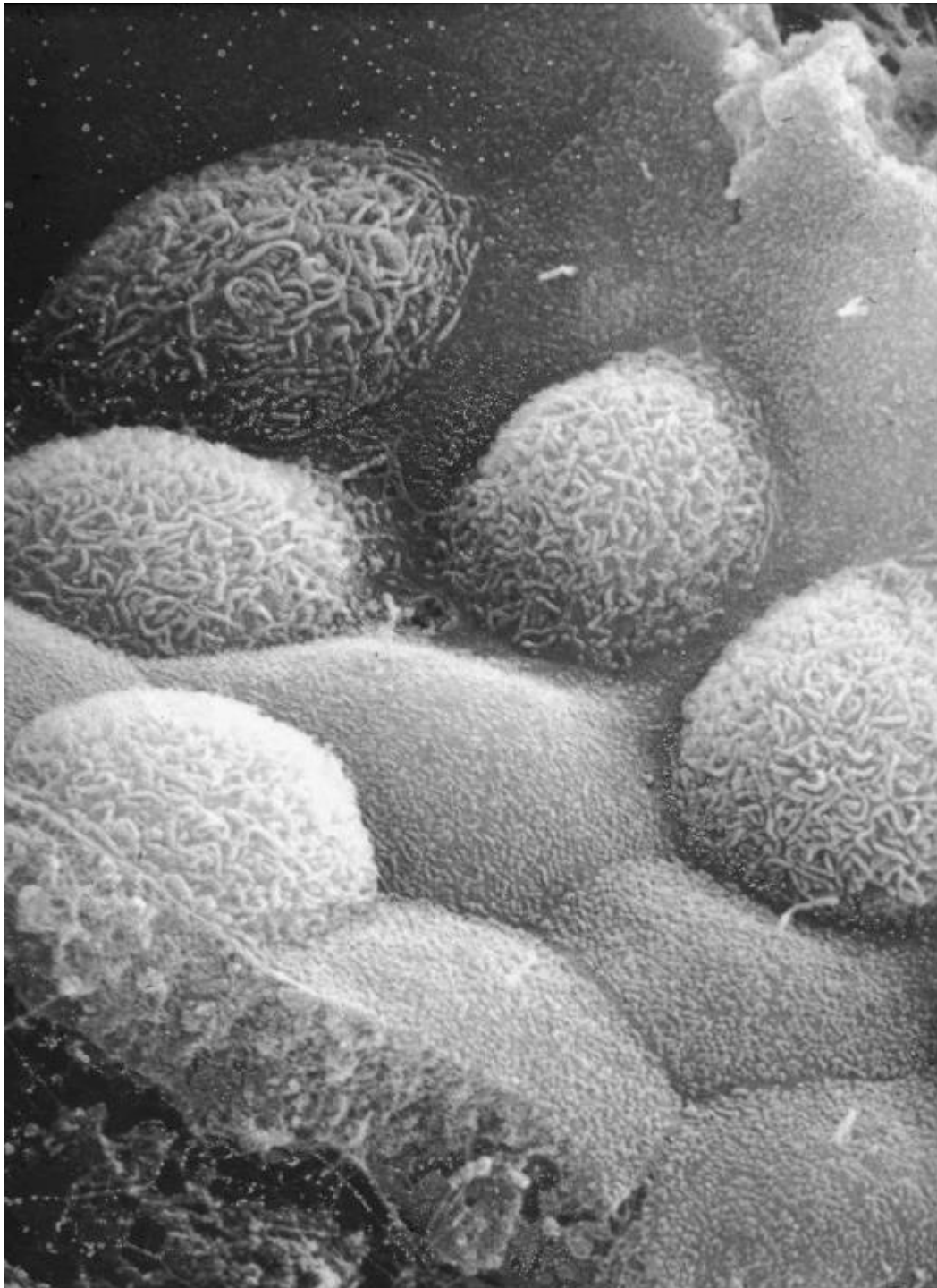
Urine pH 6.5 no blood, trace protein

Urine protein to creatinine ratio is 0.1 mg/mg

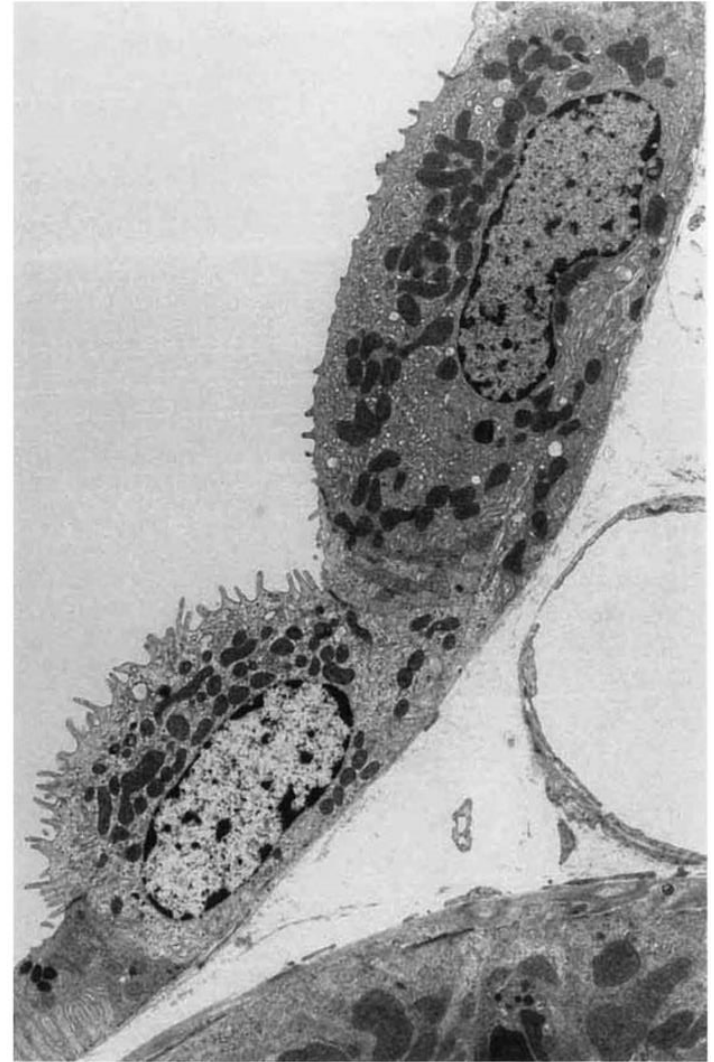
Urine Ca²⁺ to creat ratio 0.3 (normal <0.2)

What is the most likely cause of this patient's laboratory abnormalities?

- a) Chronic diarrhea
- b) Classic distal renal tubular acidosis
- c) Gitelman's syndrome
- d) Hypocalcemic hypercalciuria

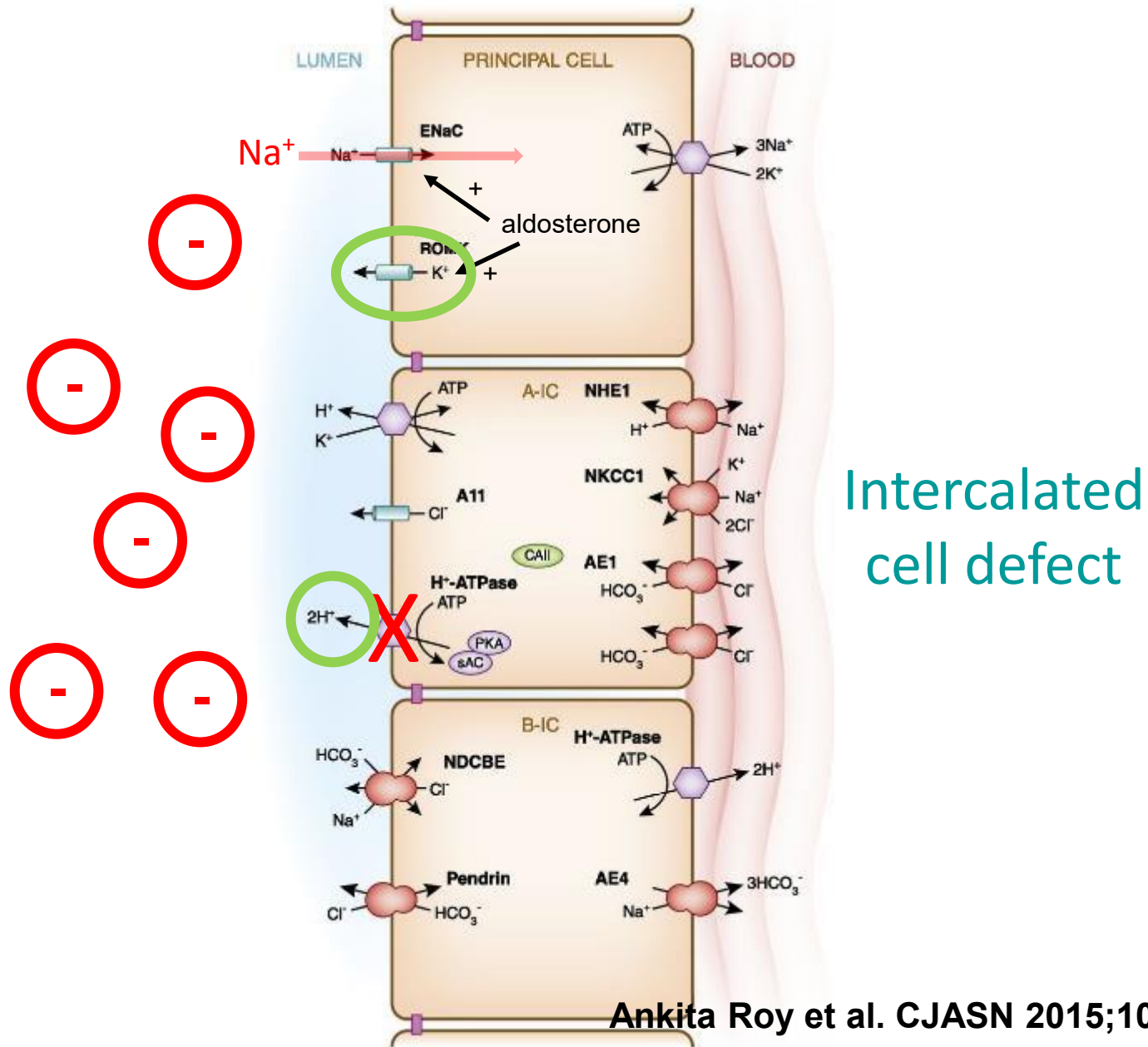


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Roy CJASN 2015

Classic distal (type I) RTA



Q6. An 8-year-old boy is seen for evaluation and delayed growth. His blood pressure is 90/60 mmHg and his heart rate is 96 b/min

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Q 7. Our fellow with vomiting is still feeling poorly and now back in the ED and BP is 90/70 mmHg.

Recall his laboratory data:

Na 142 mEq/L

K 3.0 mEq/L

Cl 110 mEq/L

BUN 34 mg/dL

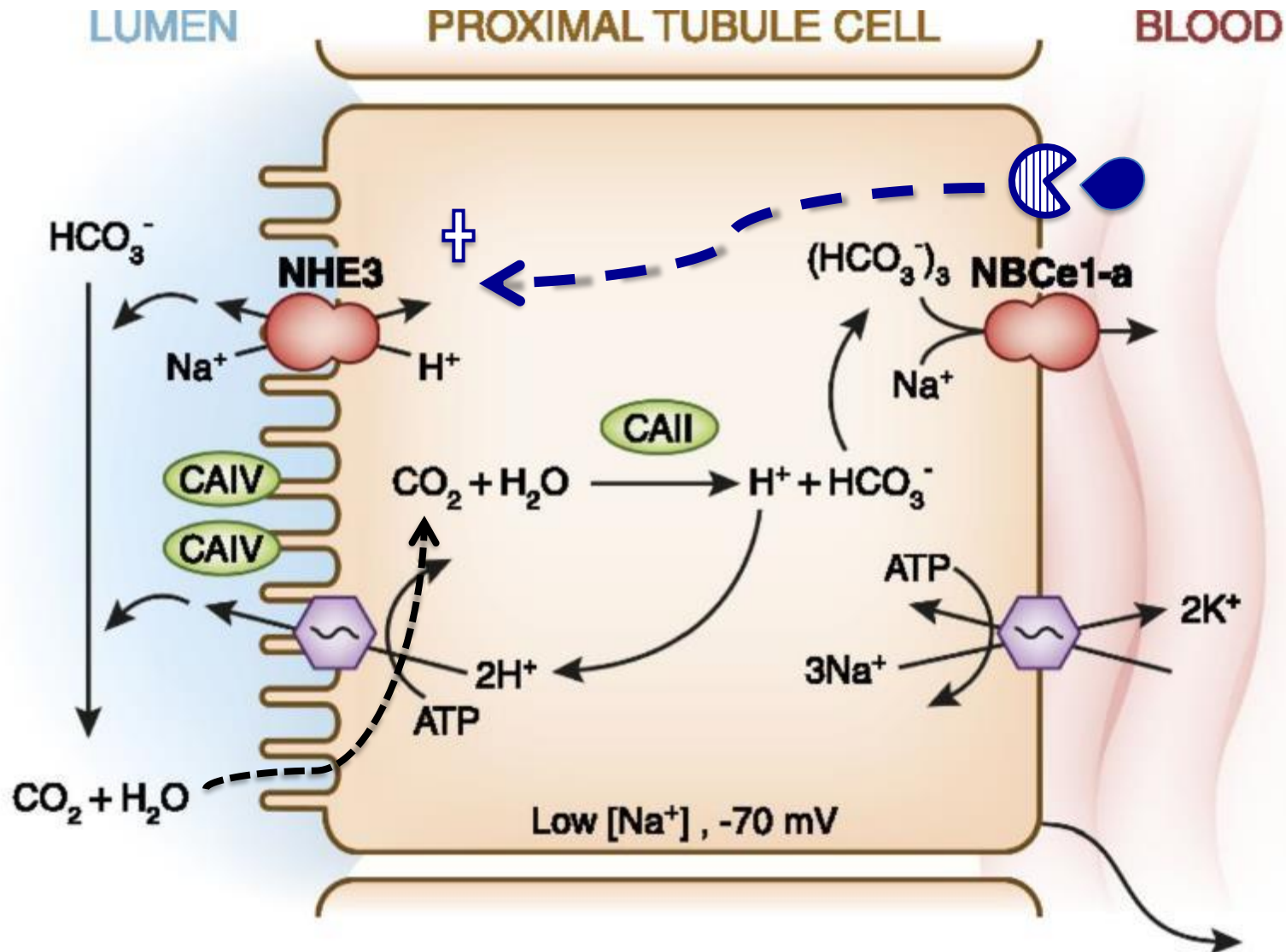
HCO₃⁻ 30 mEq/L

Creatinine 1.8 mg/dL

Which of the following is most likely to represent urinary electrolytes?

Urine	pH	Na	K	Cl
a.	↓	↑	↓	↓
b.	↓	↓	↓	↓
c.	↓	↓	↑	↓
d.	↑	↑	↑	↓
e.	↑	↓	↑	↓

In the setting of volume depletion and RAAS activation, Ang II increases proximal tubule sodium reabsorption



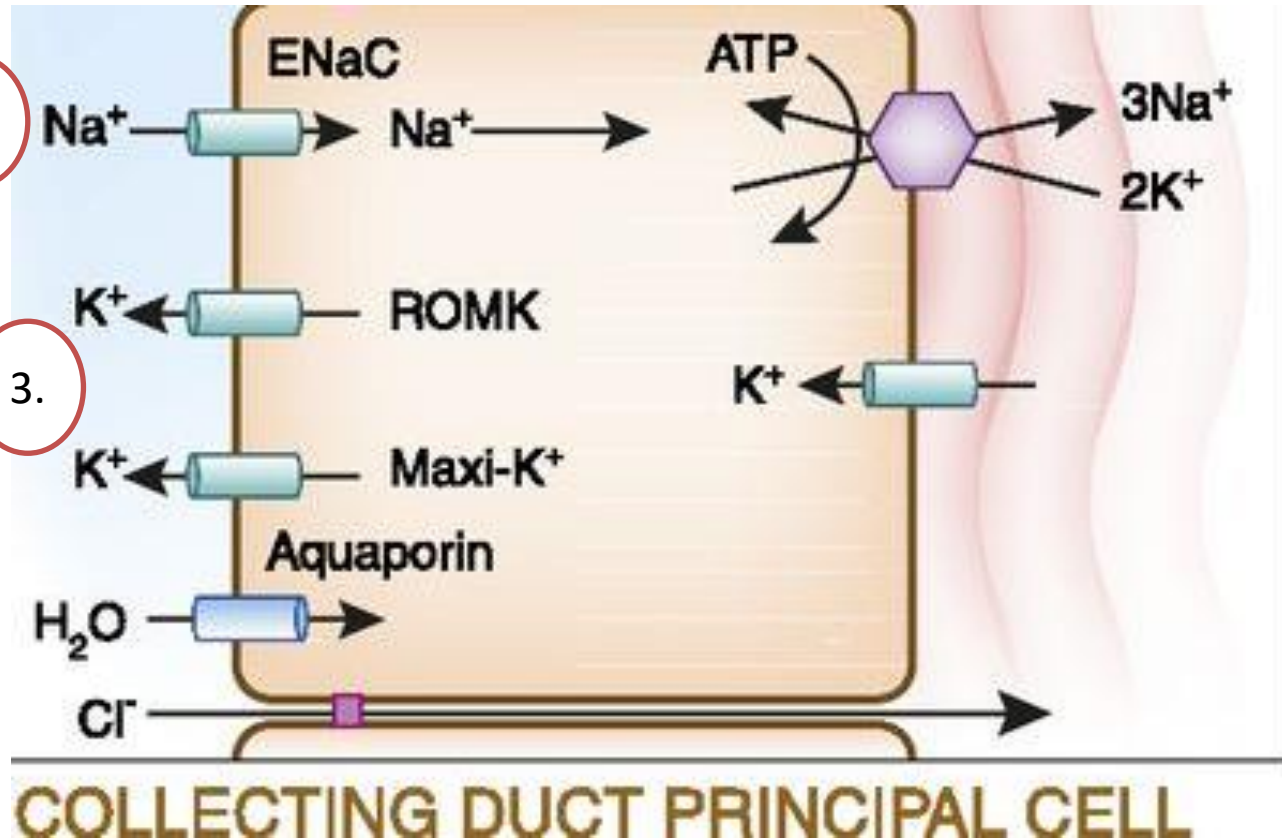
2. Lumen becomes electronegative

Na⁺ is absorbed

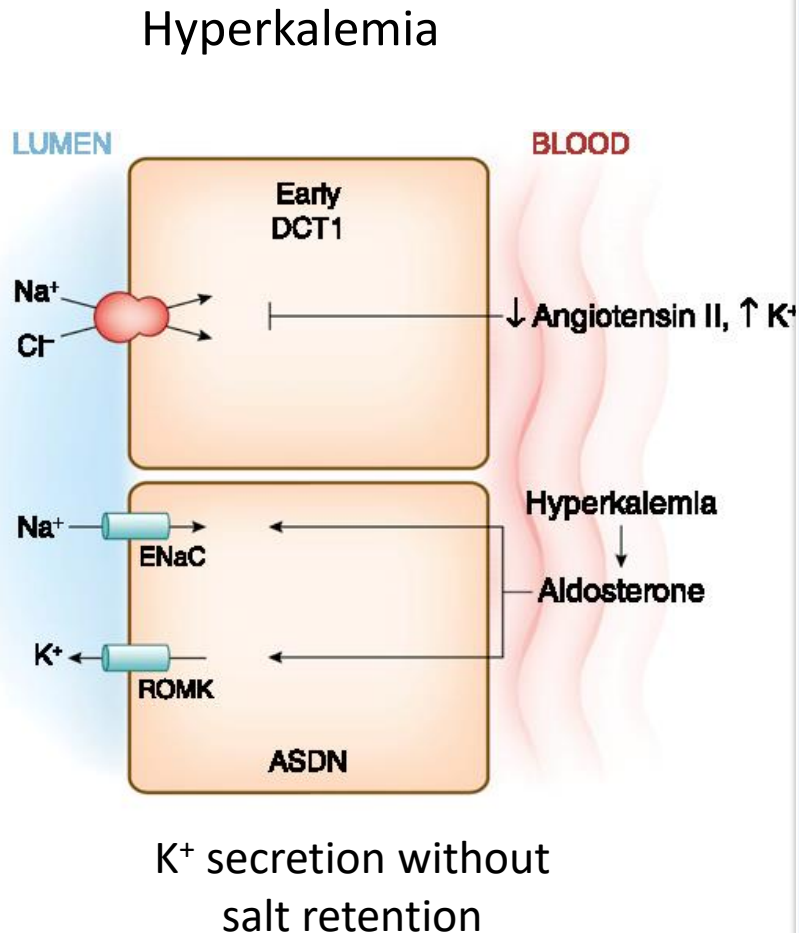
1.

K⁺ is secreted

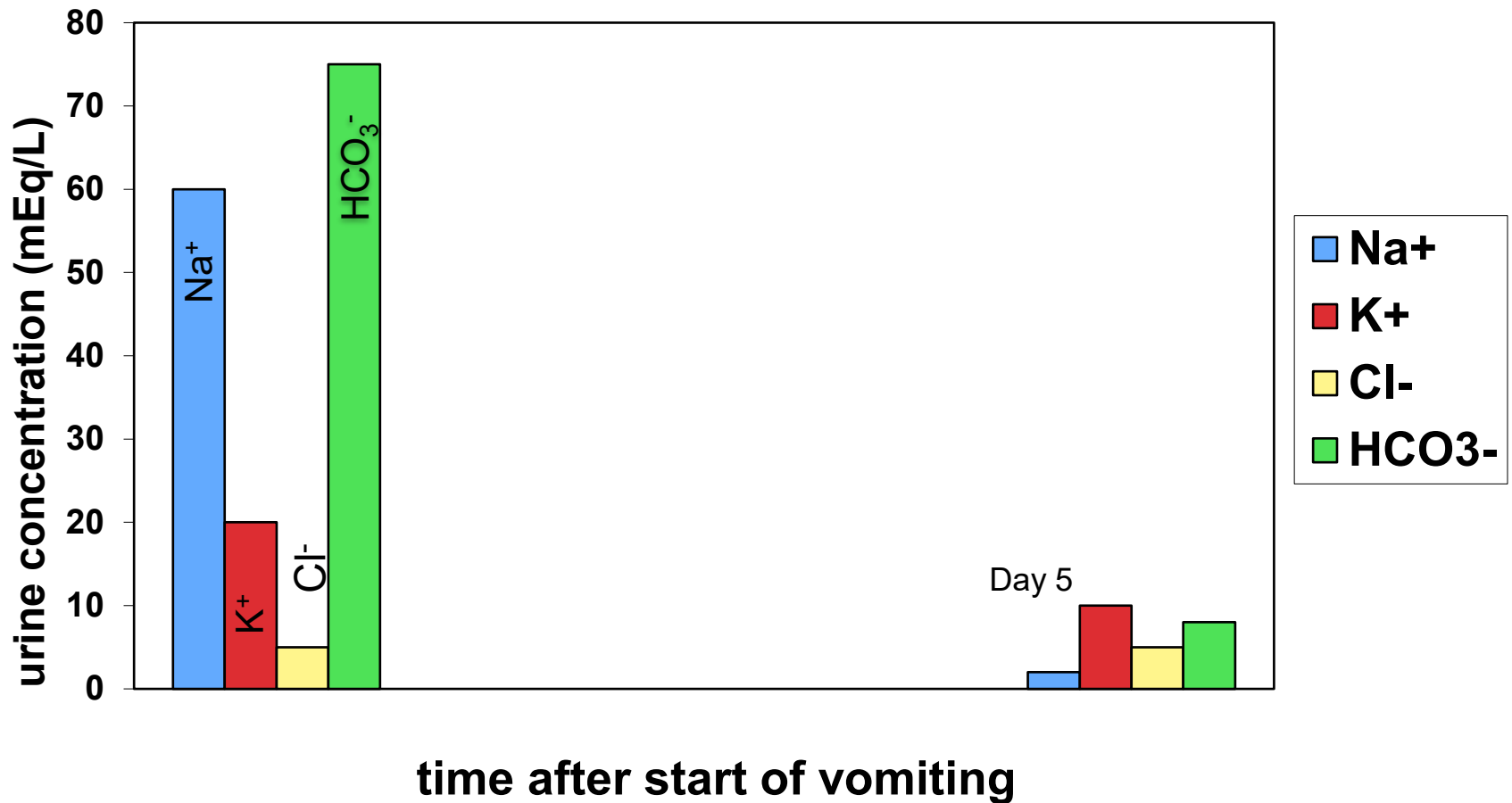
3.



Differential phosphorylation of the mineralocorticoid receptor in hyperkalemia vs. volume depletion explains **the aldosterone paradox!**



Urinary electrolytes change over time following vomiting



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d.	↑	↑	↑	↓
e.	↑	↓	↑	↓

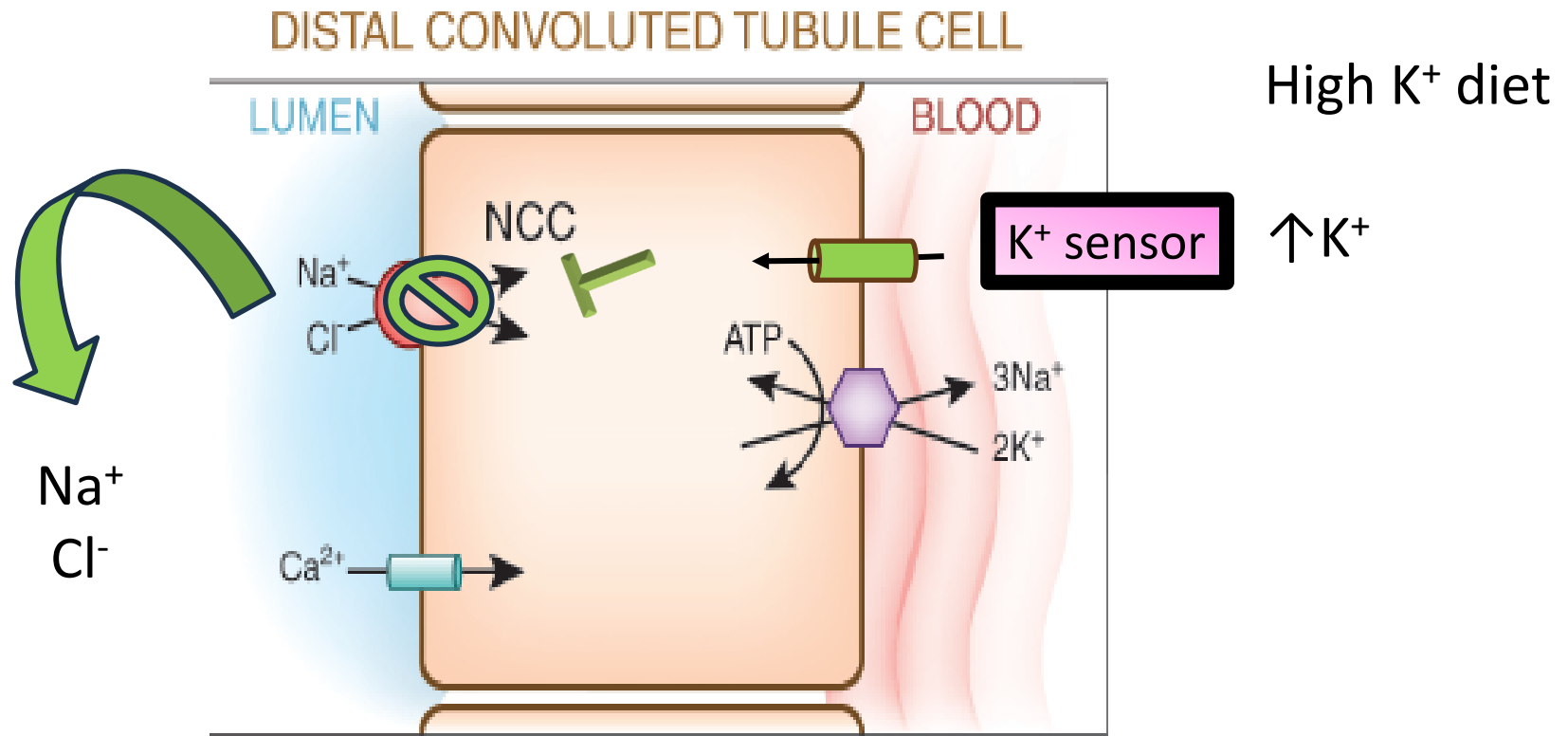


8. A 55-year-old man is evaluated for hypertension. Dietary recall-- high in sodium and protein: eggs and bacon for breakfast, "luncheon meats" for lunch, steak or "TV dinner." Anti-hypertensive therapy is recommended but he wonders whether he can improve his BP without meds and shifts to a plant-based diet. Several weeks later, his BP has improved by 10/5 mmHg.

Which of the following is a possible explanation for this improvement?

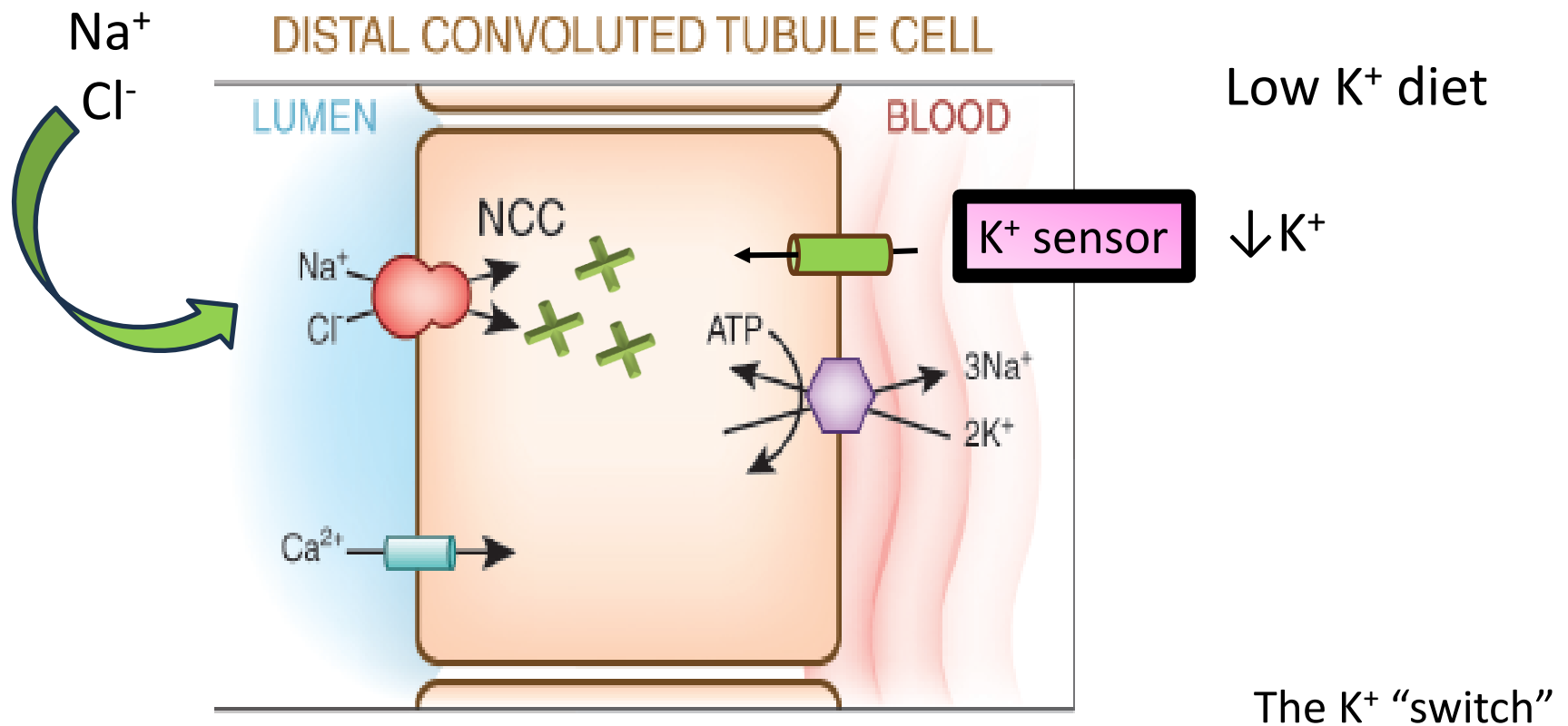
- a. Activation of the pendrin channel on intercalated cells
- b. Basolateral K^+ channel mediated NCC inhibition in DCT
- c. Decreased in glomerular hyperfiltration
- d. Downregulation of epithelial sodium channel (ENaC)

Dietary potassium influences the thiazide sensitive cells



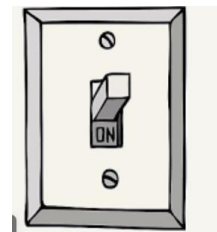
High K⁺ diet leads to

- ↑ K⁺ excretion
- Mild naturesis



High K⁺ diet leads to

- ↑ K⁺ excretion
- Mild naturiesis



What role does Pendrin play?

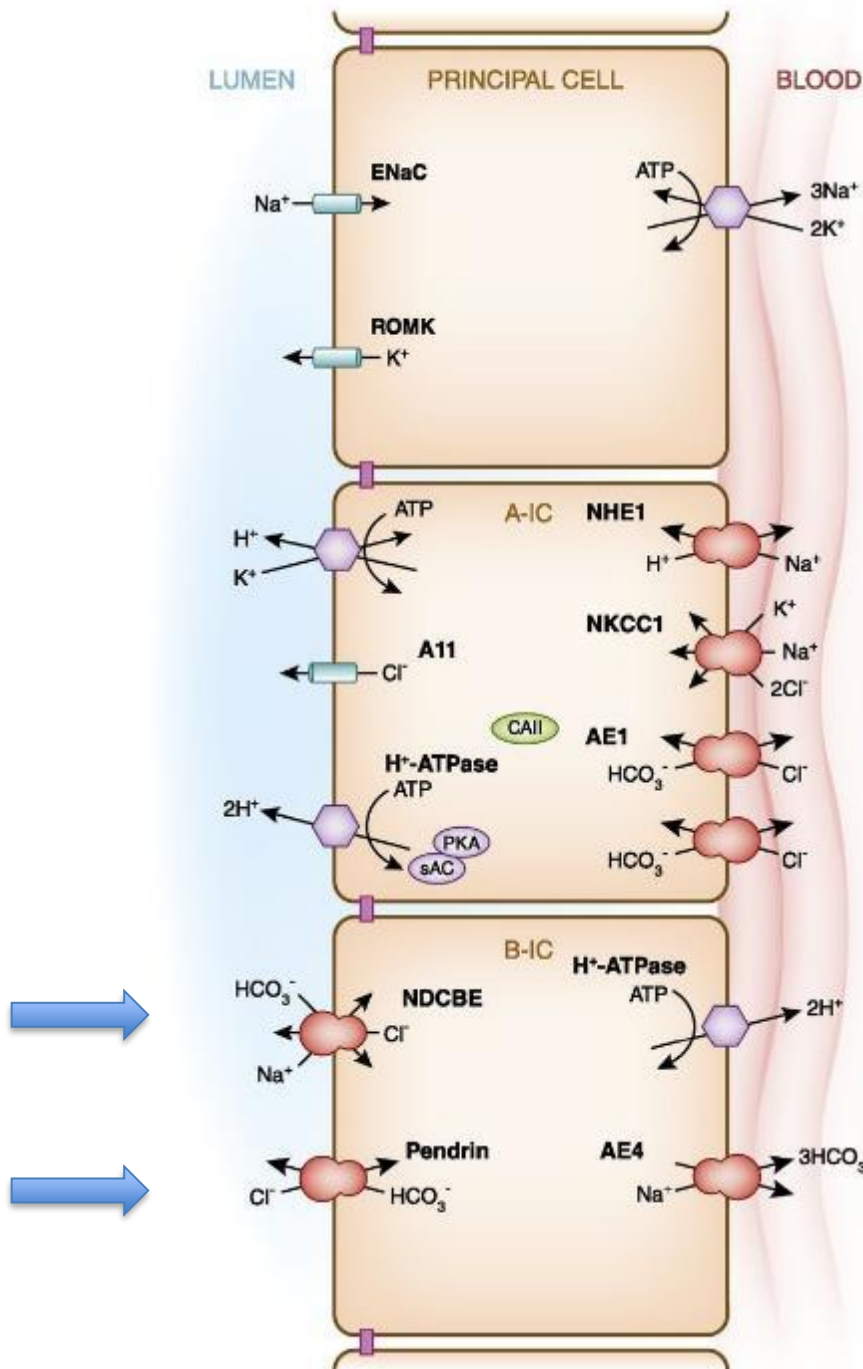
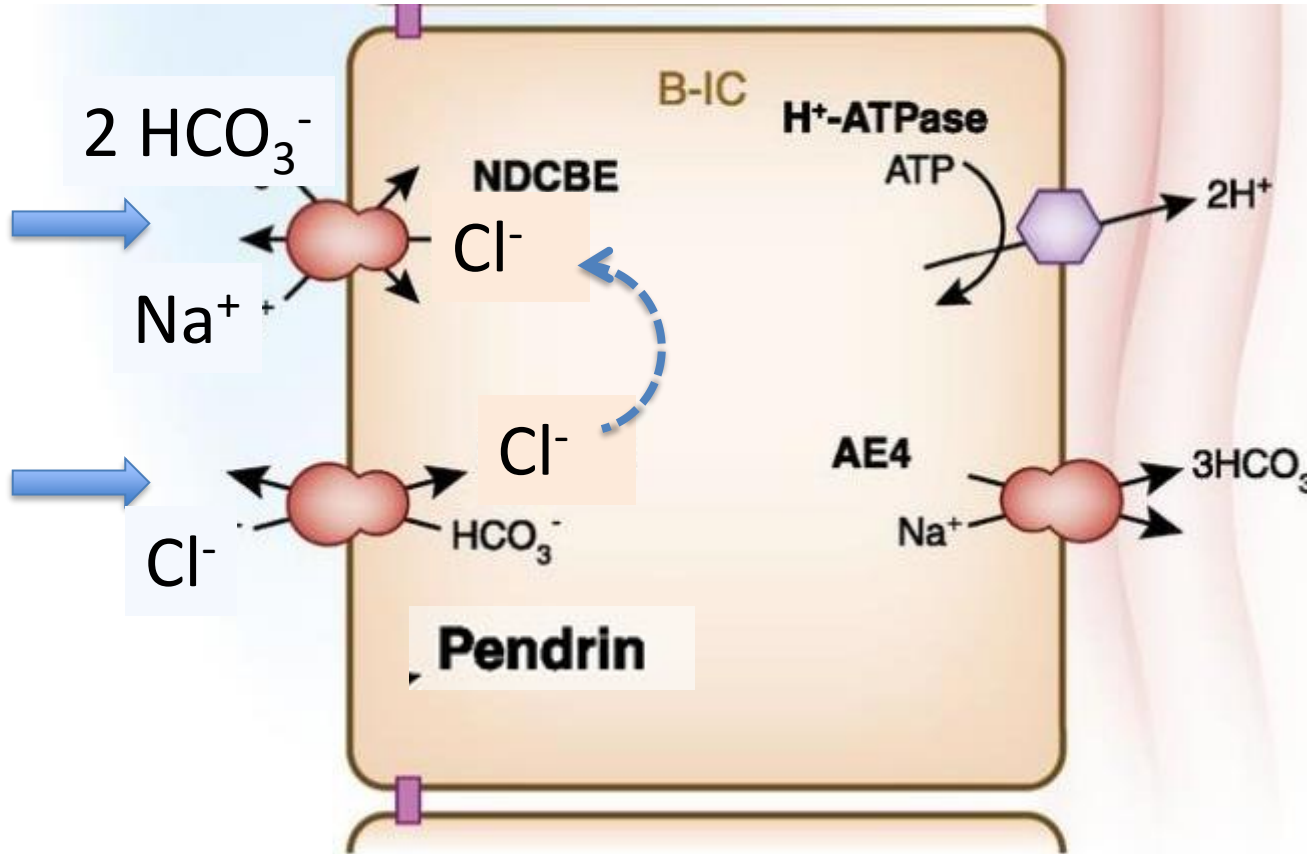


Image from Roy A et al CJASN 2015
Explanation from Emmett M CJASN 2022

NDCBE- sodium driven bicarbonate chloride exchanger



Net effect of 2 Pendrin cycles (2 HCO_3^- ions enter lumen in exchange for 2 Cl^-)

And

one NDBCE cycle (2 HCO_3^- and one Na^+ enter cell and one Cl^- enters lumen)

→ Is reabsorption of one NaCl

Pendred syndrome – salt depletion and alkalosis with thiazides (and sensorineural hearing loss and goiter)

Image from Roy A et al CJASN 2015

Explanation from Emmett M CJASN 2022

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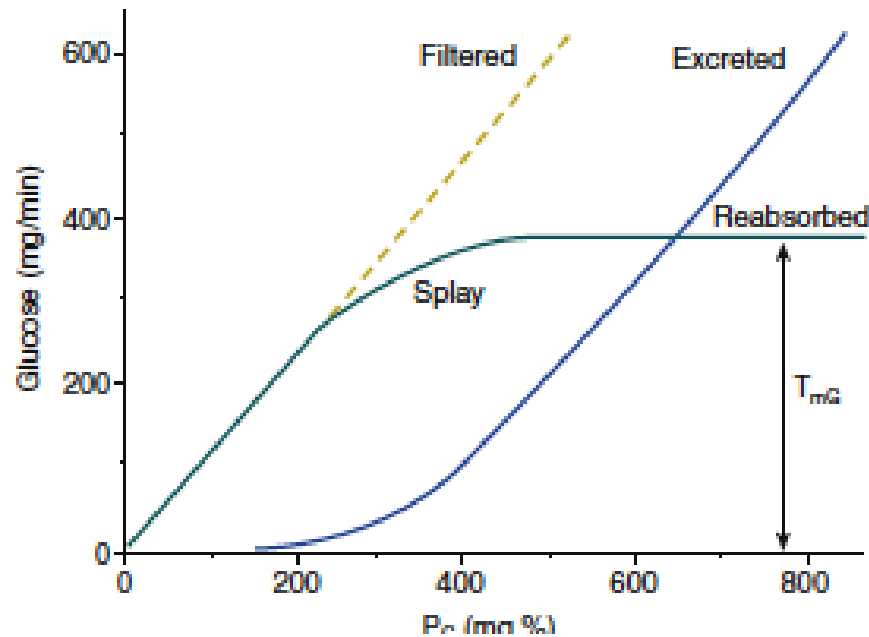
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extra

9. A 45-year-old woman with a history of type 2 diabetes mellitus is seen in clinic for further care. Recently, she received an injection of corticosteroids for back pain, and this led to worsening of her usual glycemic control such that her sugars have been between 280 and 370 mg/dl. Urinalysis in clinic today shows no glucose on the urine dipstick. The reason for the discordance in her report of her serum glucose values and this urinary finding is:

- a. Decreased glomerular filtration
- b. Decreased resistance to insulin
- c. Increased endogenous insulin
- d. Increased glomerular pressure
- e. Increased resorptive threshold for glucose

Typical filtration curve for renal glucose reabsorption



When the filtered load of glucose is low, all of the glucose is reabsorbed, and none is excreted. When the filtered glucose rises above the maximum tubular capacity (TM), glucose appears in the urine. "Splay" is the difference between the theoretical curve and actual observations.

extra

A 45-year-old woman with a history of type 2 diabetes mellitus is seen in clinic for further care. Recently, she received an injection of corticosteroids for back pain, and this led to worsening of her usual glycemic control such that her sugars have been between 280 and 370 mg/dl. Urinalysis in clinic today shows no glucose on the urine dipstick. The reason for the discordance in her report of her serum glucose values and this urinary finding is:

- a. Decreased glomerular filtration
- b. Decreased resistance to insulin
- c. Increased endogenous insulin
- d. Increased glomerular pressure
- e. **Increased resorptive threshold for glucose**

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A chapter by chapter recap of Burton Rose's classic, *The Clinical Physiology of Acid Base and Electrolyte Disorders*



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- Knowledge of physiology helps with diagnosis and treatment of kidney disorders

Further reading

- <https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-arv/drug-characteristics-tables#table12> (accessed 6/28/26)
- Alicic RZ, Rooney MT and Tuttle KR. Diabetic Kidney Disease CJASN 2017. PMID: [28522654](#)
- Ellison D, Terker AS, and Gamba G. Potassium and its discontents JASN 2016 PMID: [26510885](#)
- Emmet M. metabolic alkalosis. A brief physiological review. CJASN 2020 PMID: [32586924](#)
- **Hoening MP** and Hladik G. Overview of Kidney Structure and Function. In: Primer on Kidney Diseases 8th edition. Gilbert S and Weiner DE. 2022. Elsevier.
- **Hoening MP**, Zeidel ML. Homeostasis, the milieu intérieur, and the wisdom of the nephron. CJASN 2014 PMID: [24789550](#).
- Palmer BF and Clegg DJ. Physiology and Pathophysiology of Potassium Homeostasis: Core Curriculum AJKD 2019 PMID: 31227226
- Roy A, Al-bataineh MM, and Pastor-Soler NM. Collecting Duct Intercalated cell function and regulation. CJASN 2015; 10(2): 305-324. PMID: [25632105](#)
- Wang W and Lin D. Inwardly rectifying K⁺ channels 4.1 and 5.1 in the renal distal nephron. Am J Physiol. PMID: [35759440](#)
- Welling P. the Aldosterone Paradox and the Potassium Switch @PAWellingMD Tweetorial

