APCN2025_Taipei
Dec 6, 2025

Overview of Tubulopathies

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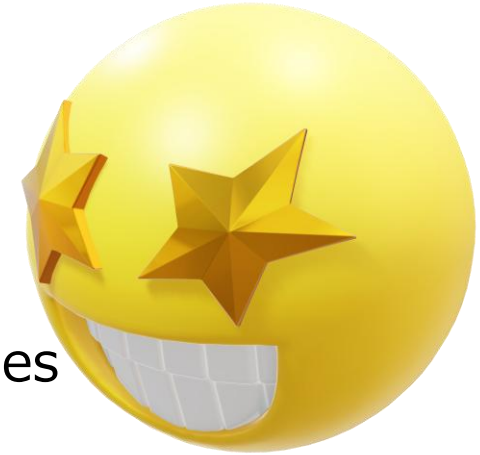
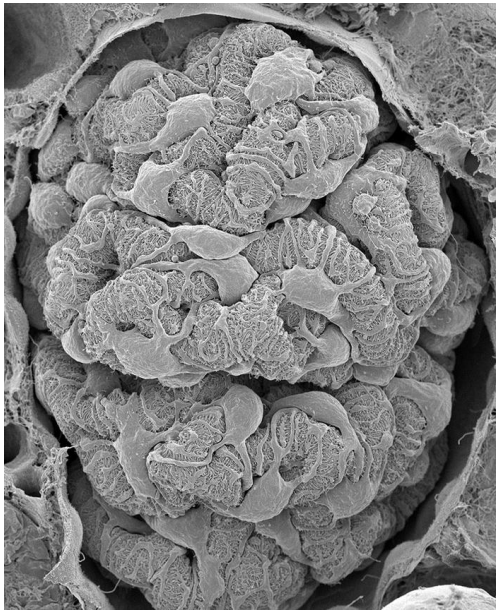
Agenda

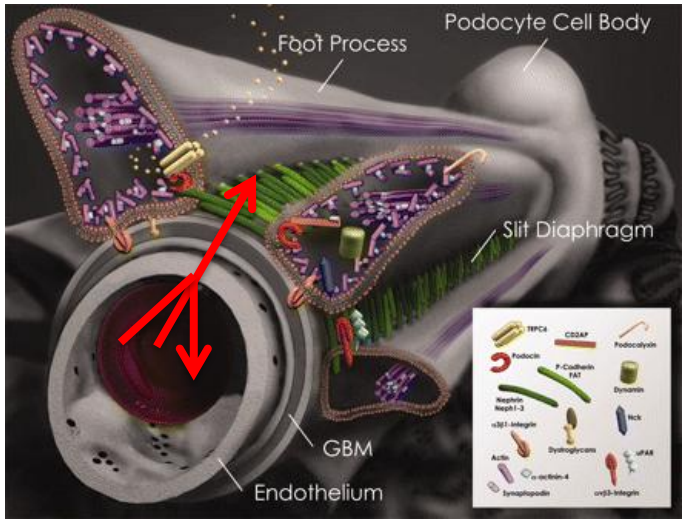


1. Structure and function of glomerulus and tubules
2. Primary Functions of the Proximal Tubule
3. Small molecular protein reabsorption from proximal tubule
4. Renal Tubular Acidosis
5. Diuretic effects

Barrier structure of the glomeruli



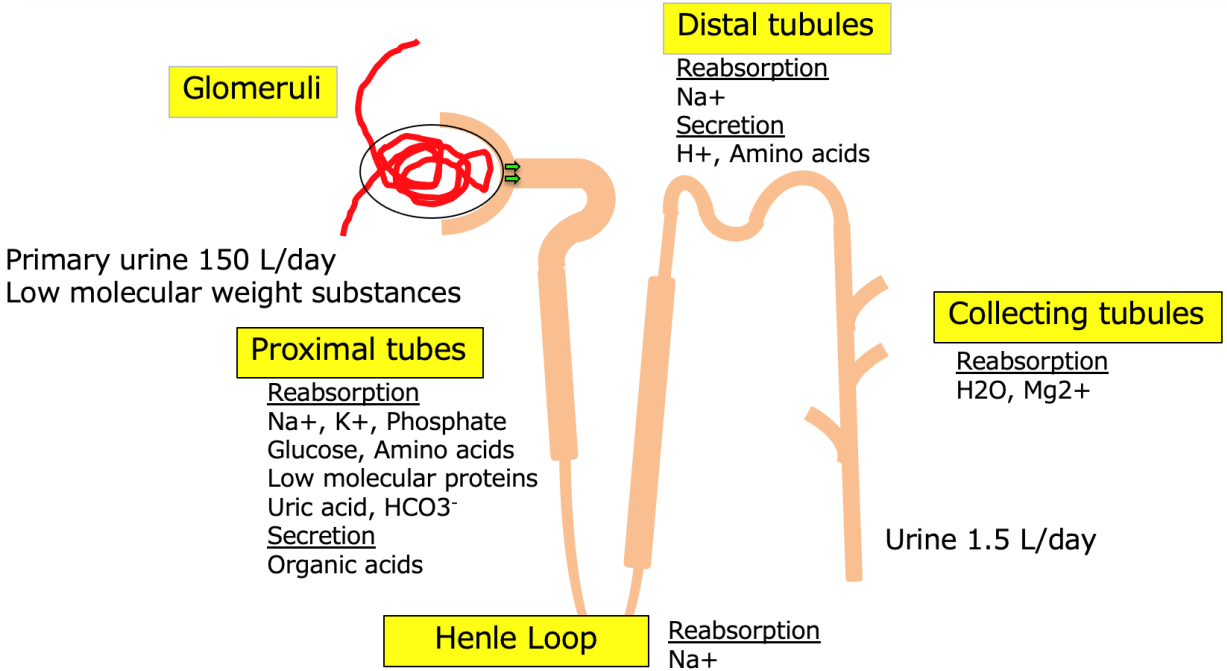
Miyaki T et al, Cell and Tissue Research **volume 379**, pages245–254(2020)



Reiser J et al, J Am Soc Nephrol 2009;950-953

Filters water and substances with a molecular weight of 3.5×10^4 or less (6.6×10^4 for albumin and 1.18×10^4 for B_2-MG) to filter blood waste and excrete it in urine

Structure and function of tubules



Roles

1. Regulating serum electrolyte levels.
2. Maintaining the blood pH between 7.35 and 7.45.
3. Reabsorbing small molecules that leak from the glomerulus.
4. Reabsorb approximately 99% of the water that leaks out during filtration.

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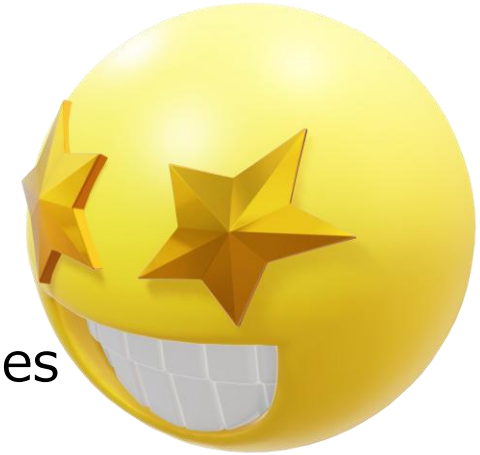

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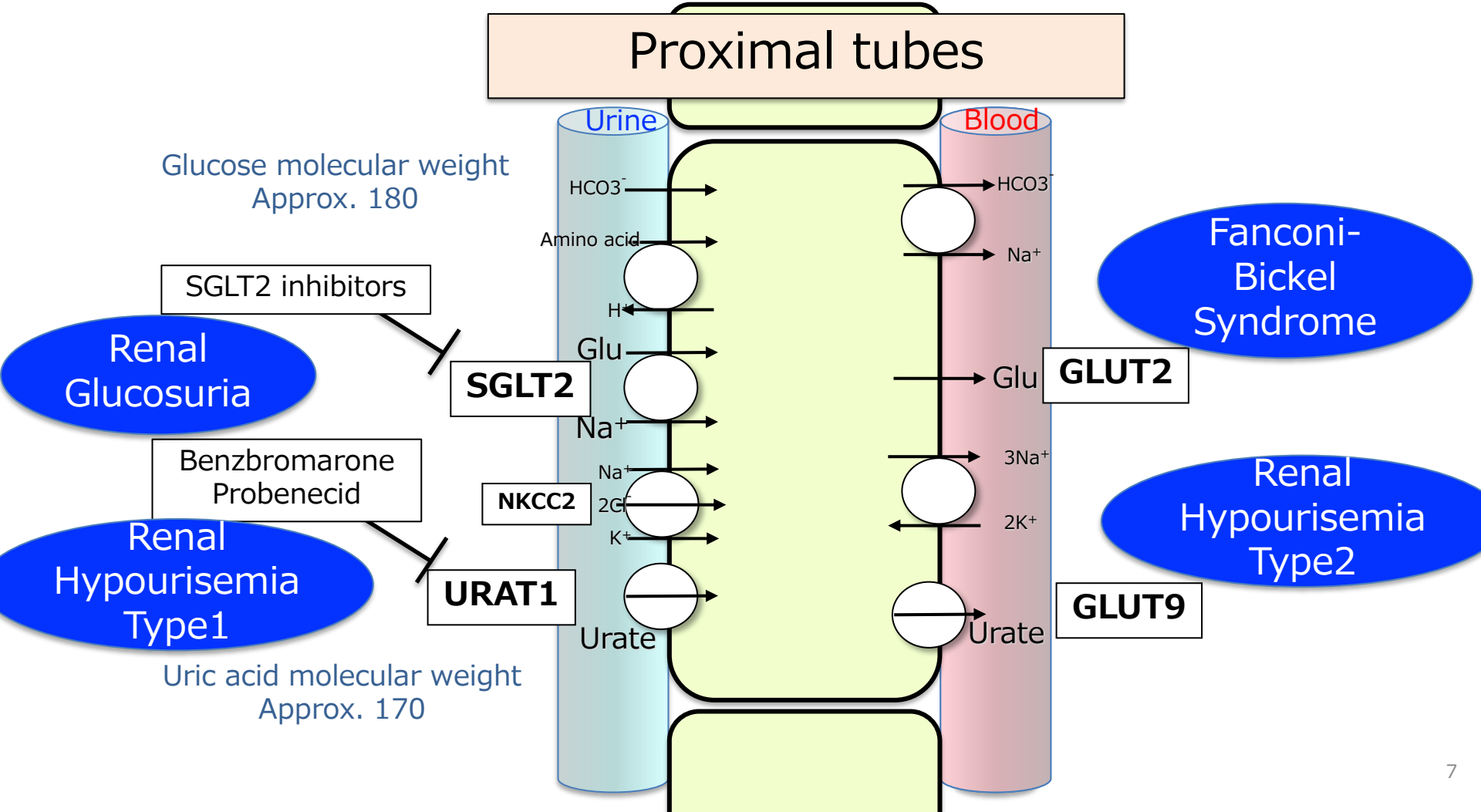
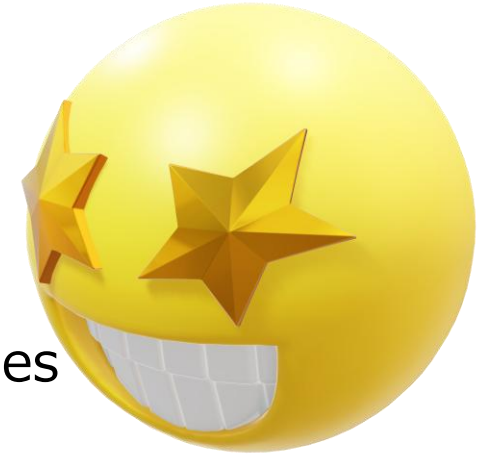
Structure and function of tubules

Question:
Can you explain the mechanism of action of SGLT2 inhibitors for the treatment of diabetes?


Proximal tubes
Urine
Blood
Glucose molecular weight
Approx. 180
HCO3-
Amino acid
H+
Glu
Na+
Na+
2Cl-
K+
Urate
HCO3-
Na+
Glu
3Na+
2K+
Urate
SGLT2 inhibitors
Renal Glucosuria
SGLT2
NKCC2
Benzbromarone
Probenecid
Renal Hypourisemia Type1
URAT1
Uric acid molecular weight
Approx. 170
Fanconi-Bickel Syndrome
GLUT2
Renal Hypourisemia Type2
GLUT9

Agenda



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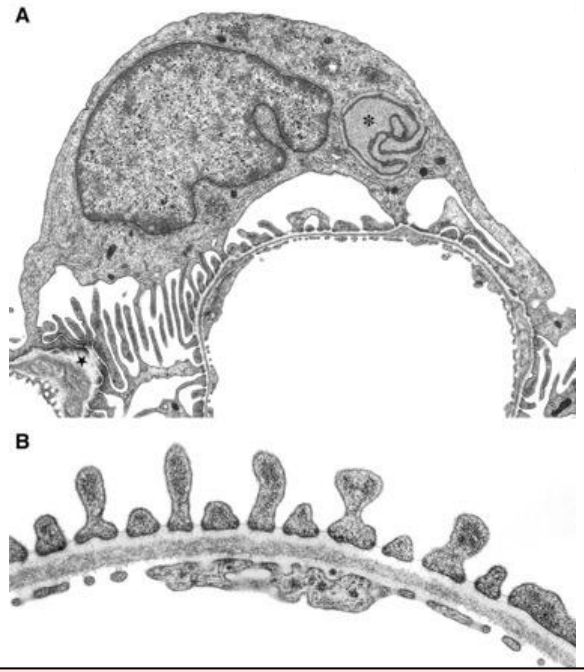
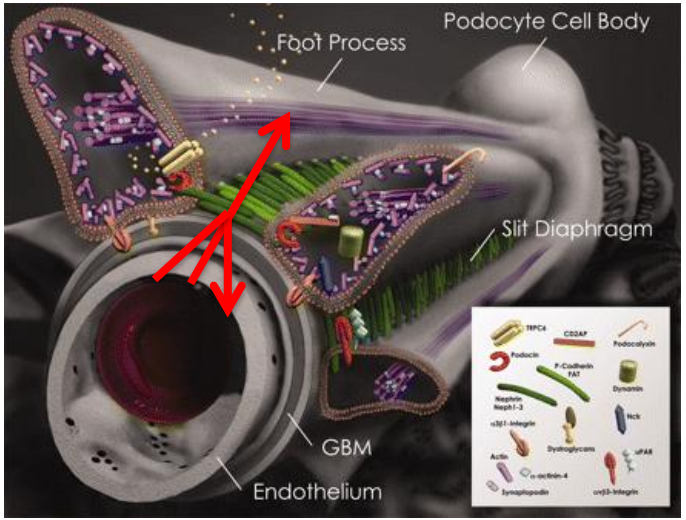
Structure and function of tubules

Question:
What are the indicators of high levels of urinary β2 microglobulin? How does it occur?

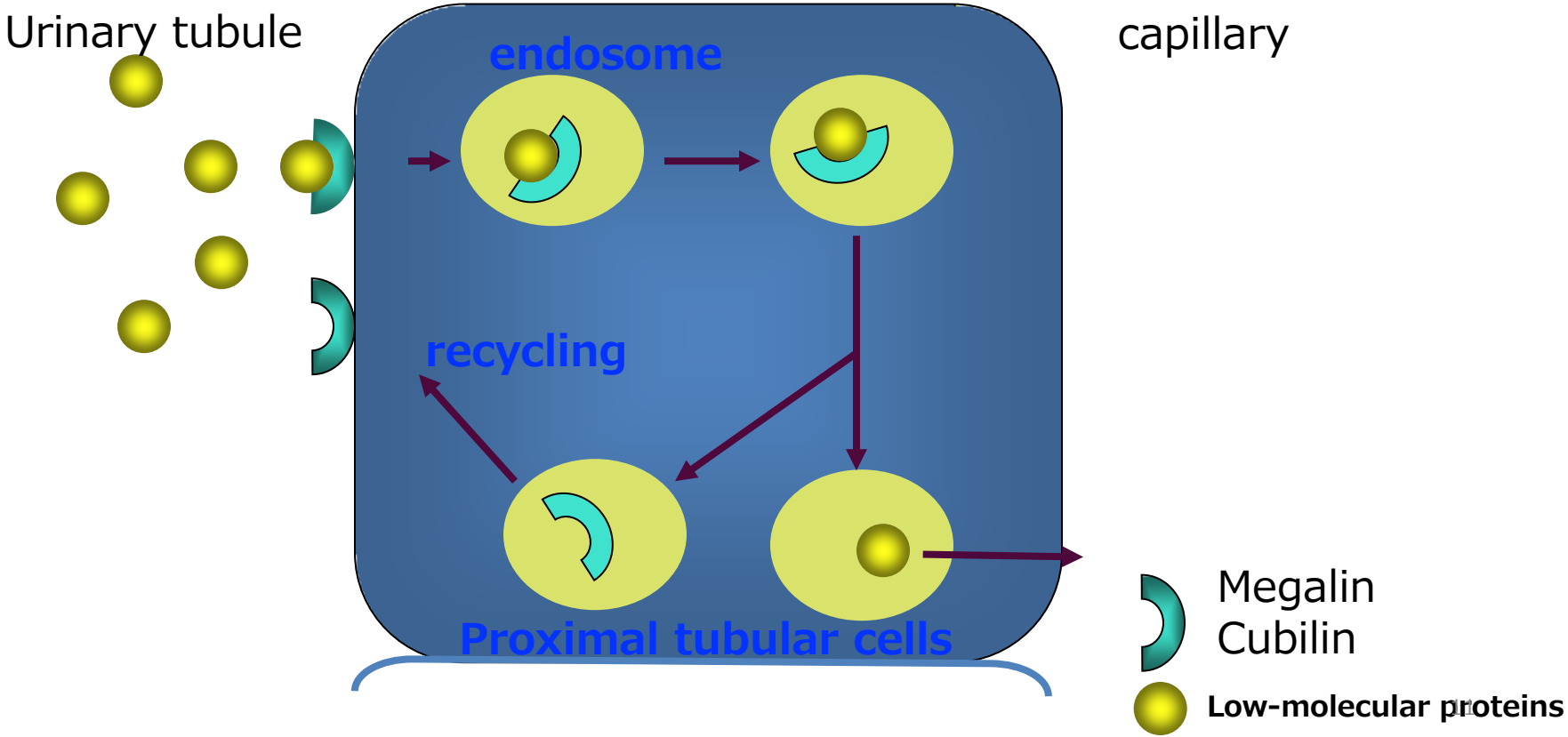
Barrier structure of the glomeruli





Filters water and substances with a molecular weight of 3.5 x 104 or less (6.6 x 104 for albumin and 1.18 x 104 for B2-MG) to filter blood waste and excrete it in urine

Reabsorption of low molecular weight proteins by megalin and cubillin



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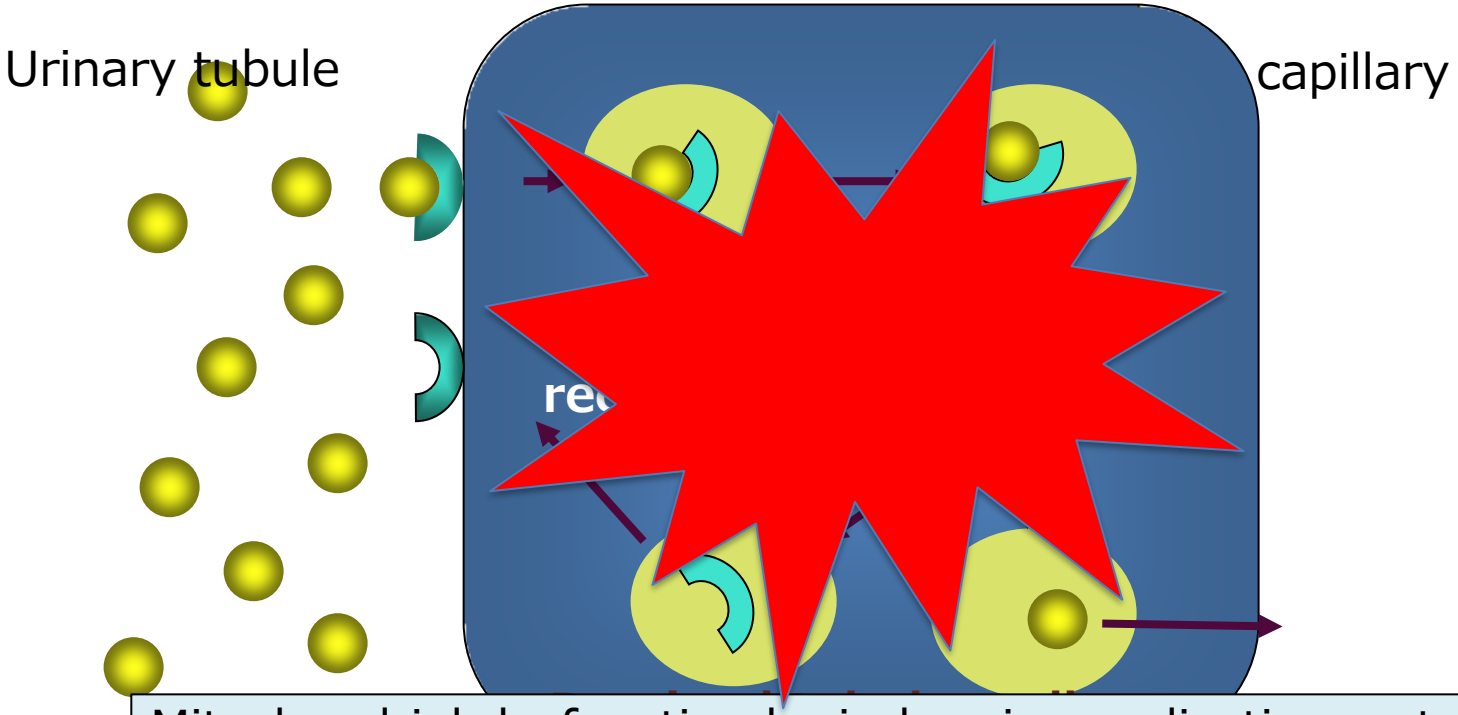

Mitochondrial dysfunction by ischemia, medications, etc.
→ proximal tubular disorders→ high urinary BMG

Reabsorption of low molecular weight proteins by megalin and cubillin

Megalin dysfunction

Primary: Donnai-Barrow syndrome
(craniofacial features, hearing loss, Low-molecular proteinuria)
Secondary: Dent-disease 1 (CLCN5), Dent-disease 2 (OCRL)

Cubilin dysfunction

CUBN-related Nephropathy (Chronic Benign Proteinuria)
Imerslund-Grasbeck Syndrome (Vit B12 deficiency)

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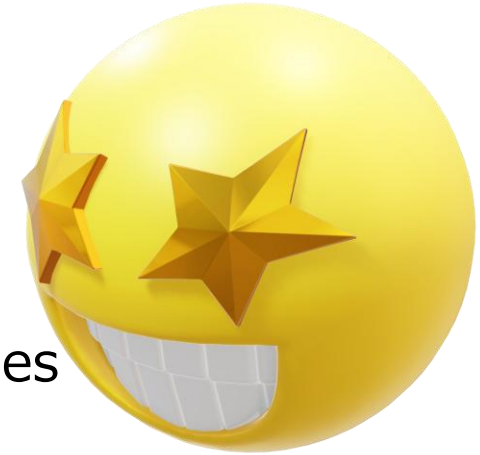

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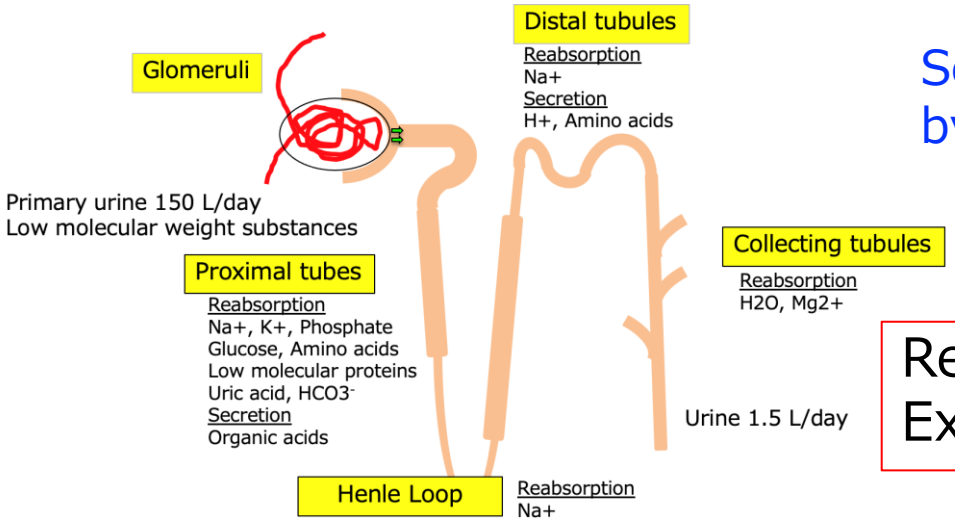
Structure and function of tubules

Question:
Can you explain the onset mechanisms of tubular acidosis to your students?

Basic knowledge of tubular acidosis

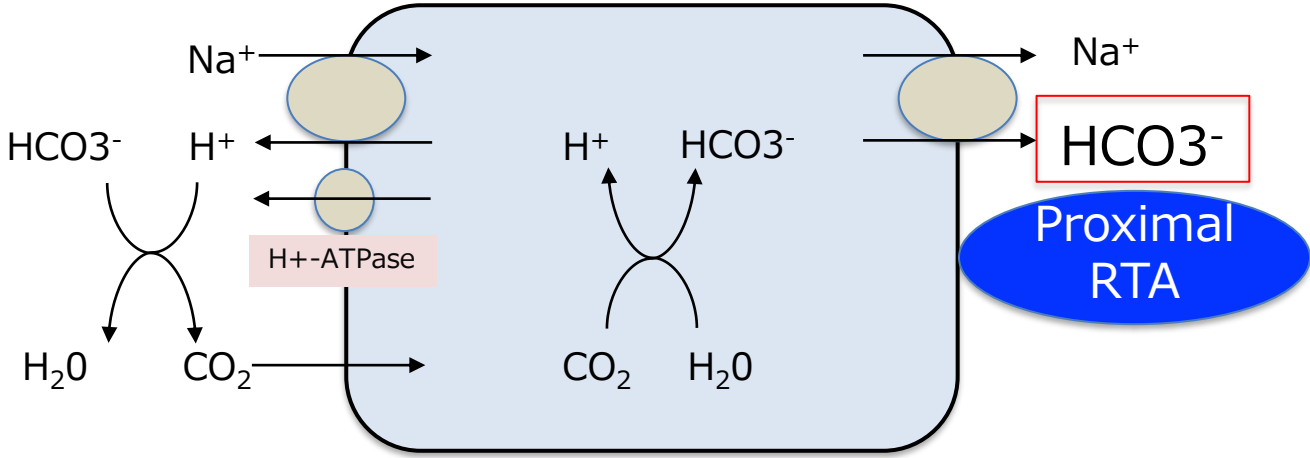


Serum pH to 7.35-7.45 is controlled by the kidney tubules

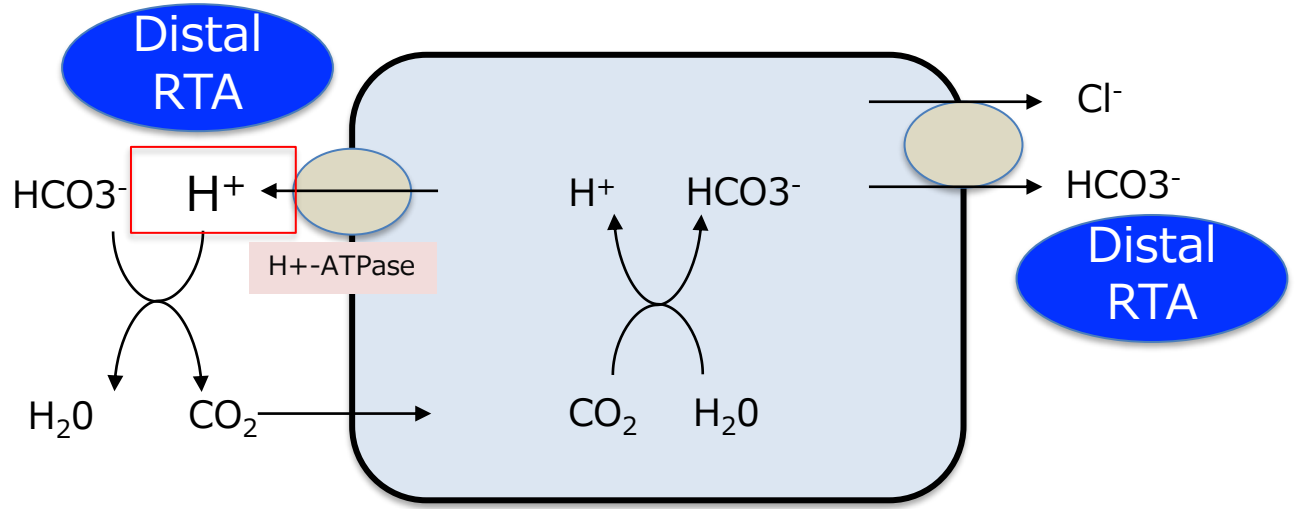
Reabsorb HCO_3^- → proximal tubules
Excretion of H^+ → distal tubules

Proximal tubular acidosis → inability to reabsorb (lose) HCO_3^-
Distal tubular acidosis → inability to excrete H^+ (accumulation)

Proximal tubules



Distal tubules



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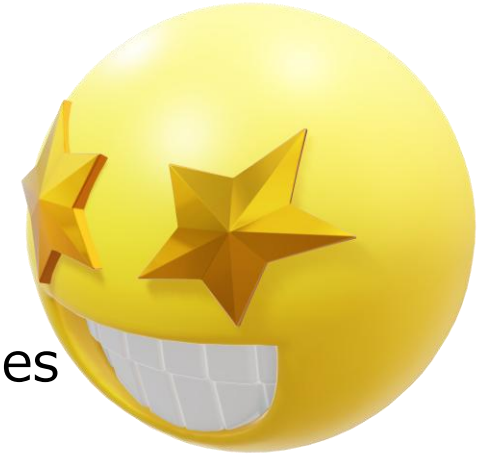

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Structure and function of tubules

Question:
Why do furosemide and thiazide have a diuretic effect? Can you explain it correctly?

Reabsorption of water in the tubules

Glomeruli

Primary urine 150 L/day

Distal tubules

10%

Active transport with AVP-AQP2

Collecting tubules

15%

Proximal tubes

65%

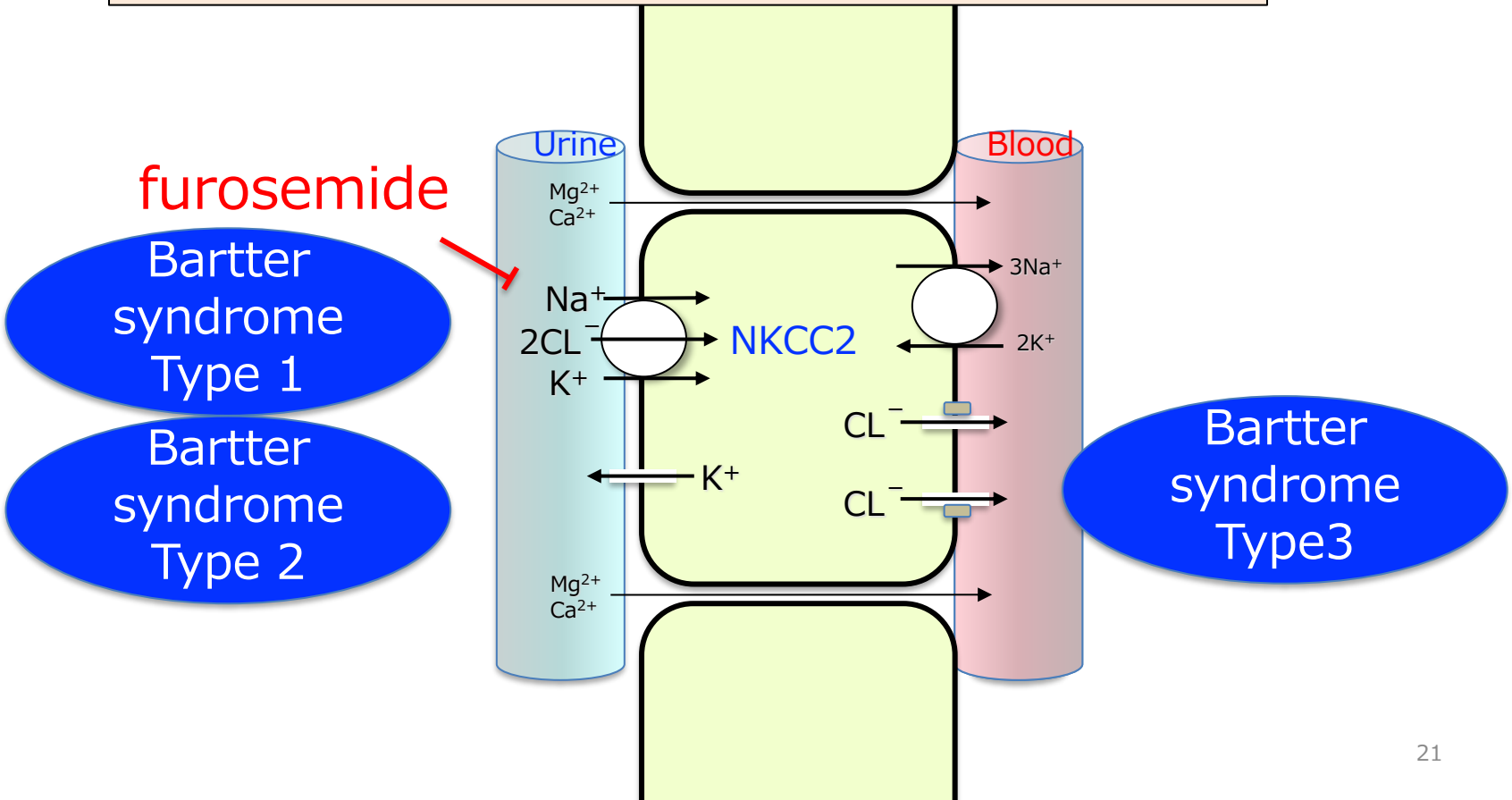
Passive transport associated with Na reabsorption

Henle Loop

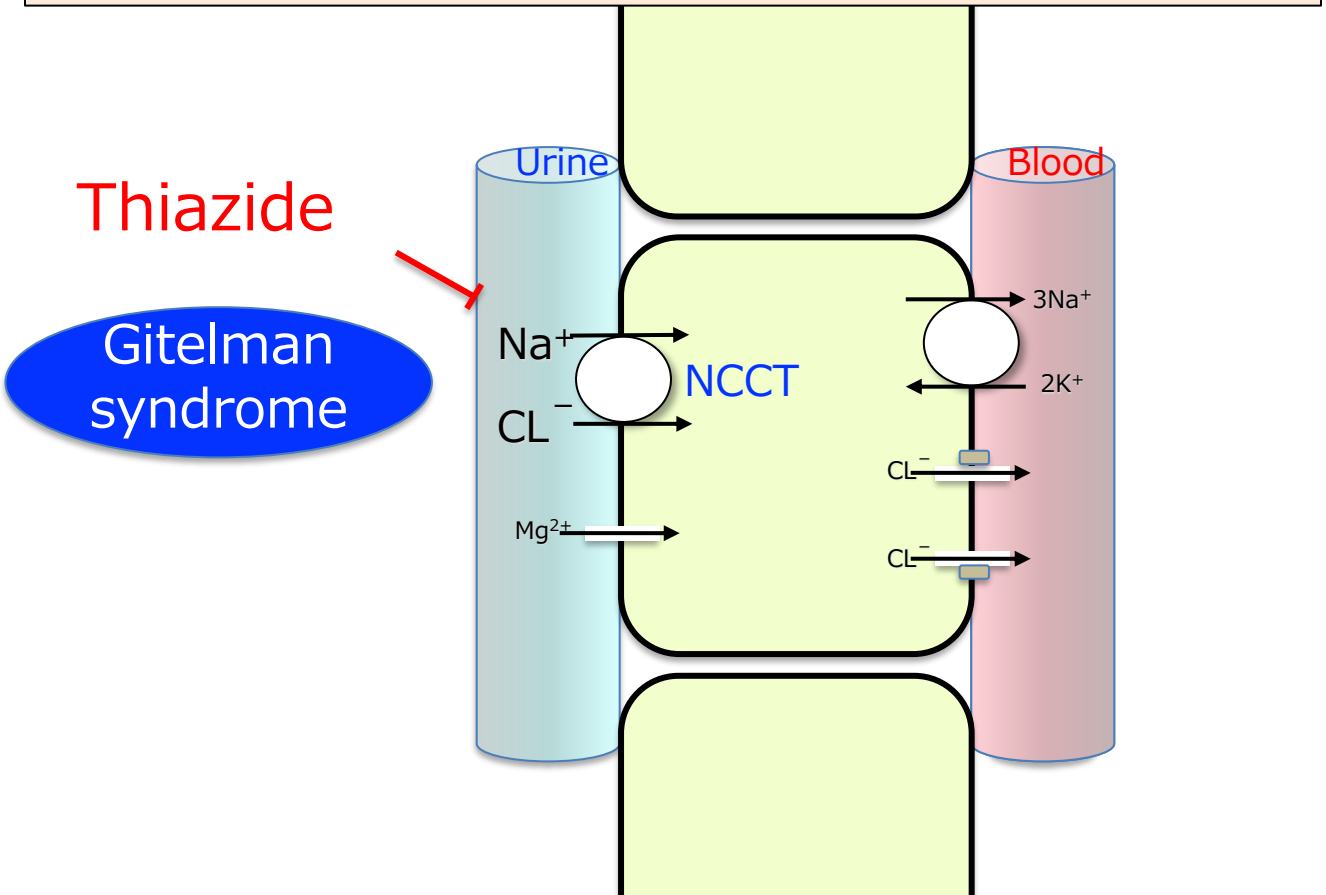
10%

Urine 1.5L/day

Henle Loop


furosemide
Bartter syndrome Type 1
Bartter syndrome Type 2
Urine
Blood
Mg2+
Ca2+
Na+
2CL−
K+
NKCC2
3Na+
2K+
CL−
CL−
K+
Mg2+
Ca2+
Bartter syndrome Type3

Distal tubules



Reabsorption of water in the tubules

Question:
Wasn't there another important diuretic?

Reabsorption of water in the tubules

Glomeruli

Primary urine 150 L/day

Distal tubules

10%

Active transport with AVP-AQP2

Collecting tubules

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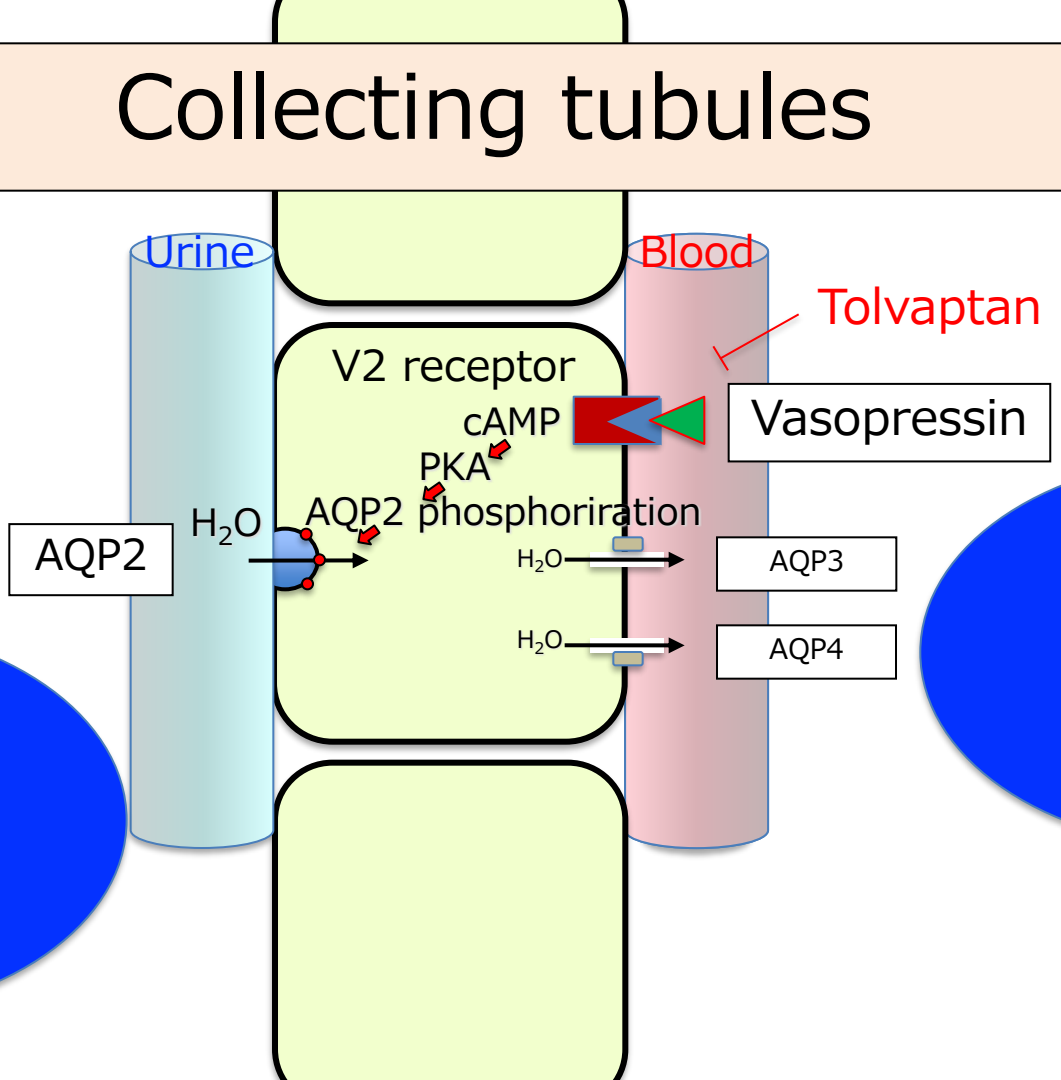
Urine 1.5 L/day

Collecting tubules

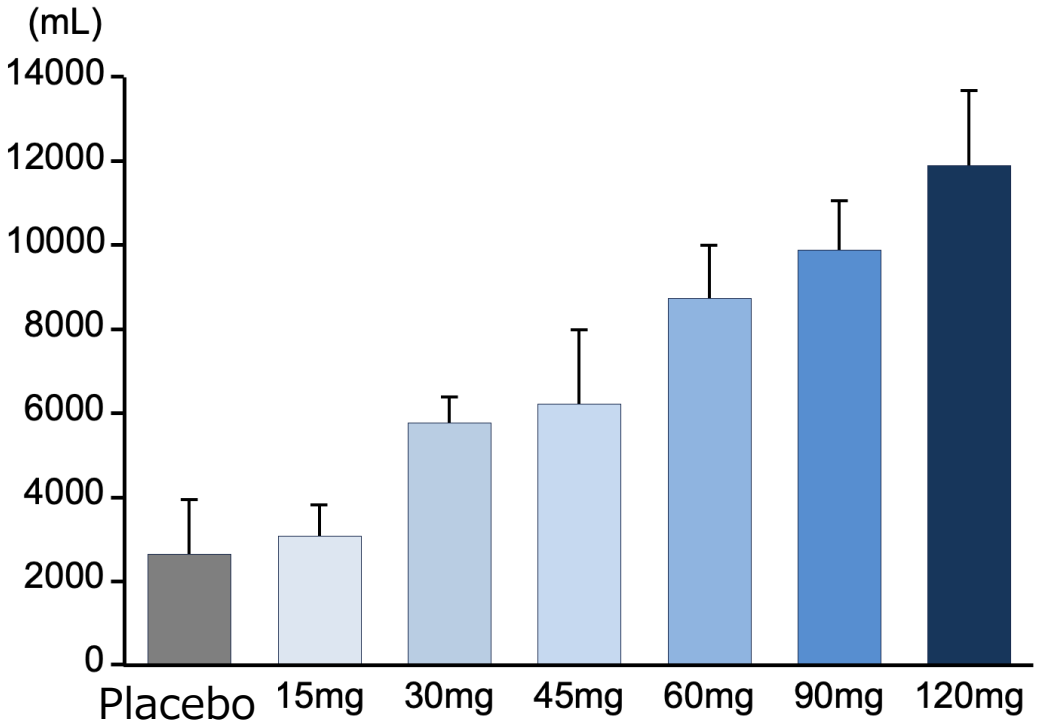


Nephrogenic Diabetes Insipidus (Arginine Vasopressin Resistance)

Nephrogenic Diabetes Insipidus (Arginine Vasopressin Resistance)

Tolvaptan Single Dose Study in Healthy Adults

24-hour urine output



Kim. S. R. et al. : Cardiovasc Drugs Ther. 25(Suppl 1): S5-S17, 2011

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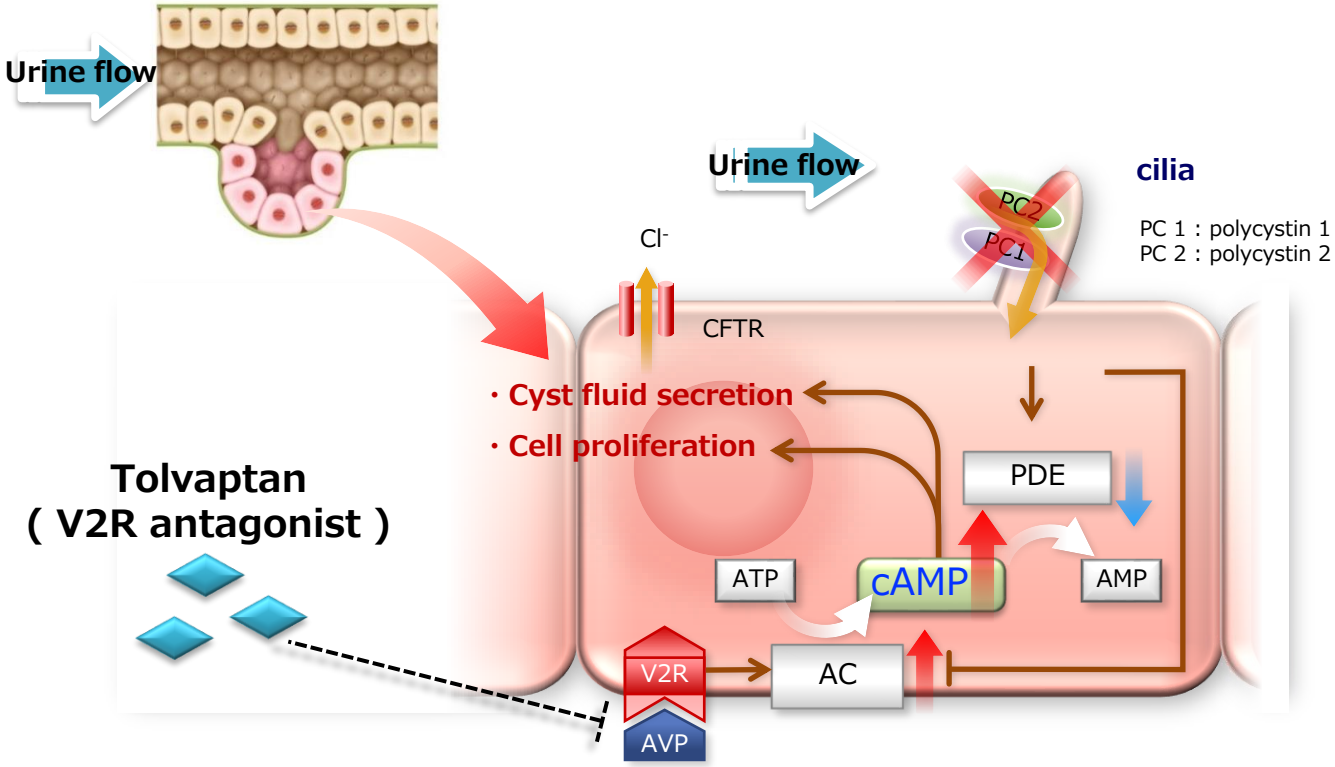
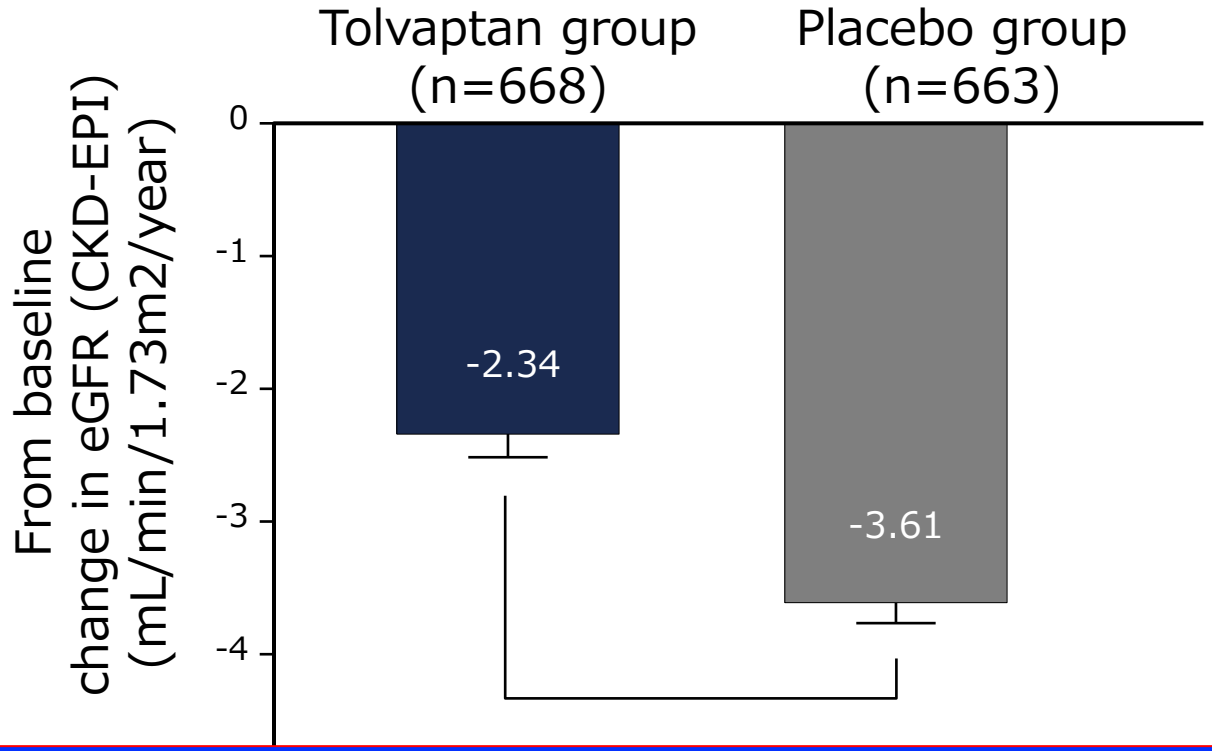
Tolvaptan, which was originally developed as a diuretic, has an unexpected effect...

Molecular mechanism of cyst formation in polycystic kidney disease (ADPKD)



Amount of change in eGFR from pre-dose baseline



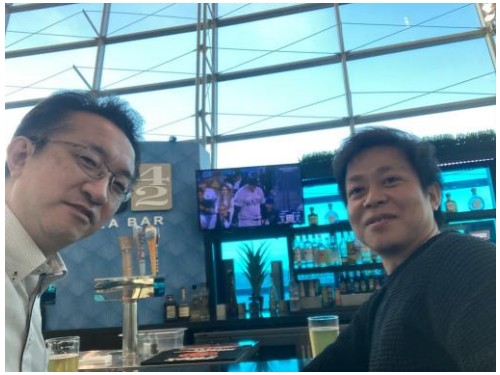
Tolvaptan is now used all over the world as a silver bullet for ADPKD!

Torres VE., et al.: N Engl J Med., 2017

Take Home Message

1. The function and structure of the kidneys, which may seem complicated, are actually quite simple.
2. By carefully examining each channel and transporter, we can elucidate the molecular mechanisms underlying kidney function.
3. Furthermore, understanding that many drugs exert their effects by blocking these transporters enables us to use these medications more effectively.
4. By enjoying the study of kidney biology, you can gain a deeper understanding of your patients, so I encourage you to continue learning about these molecular mechanisms.

Pediatrics, Nephrology Group, Kobe University



The Department of Pediatrics at Kobe University accepts Japanese government-sponsored international students from ASEAN countries. Don't hesitate to get in touch with me if you are interested!

kandainozu@gmail.com