Renal Tubular Acidosis

NEPHROLOGY
PHRAMONGKUTKLAO HOSPITAL

Asst. Prof. Naowanit Nata, MD
Nephrology Division, Department of Medicine
Phramongkutklao Hospital & College of Medicine

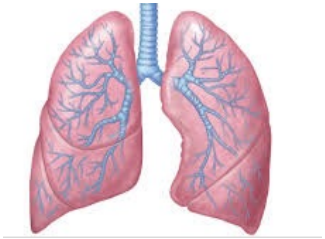
Outlines

- Kidney and acid-base homeostasis
- Proximal renal tubular acidosis
- Distal renal tubular acidosis

Daily Endogenous Acid Production

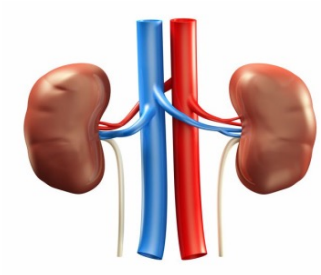
Volatile acid (CO_2)

- Carbohydrate metabolism
-15,000-20,000 mmol/day



Fixed acid 25-50 mEq/day (0.5-1 mEq/kg/day)

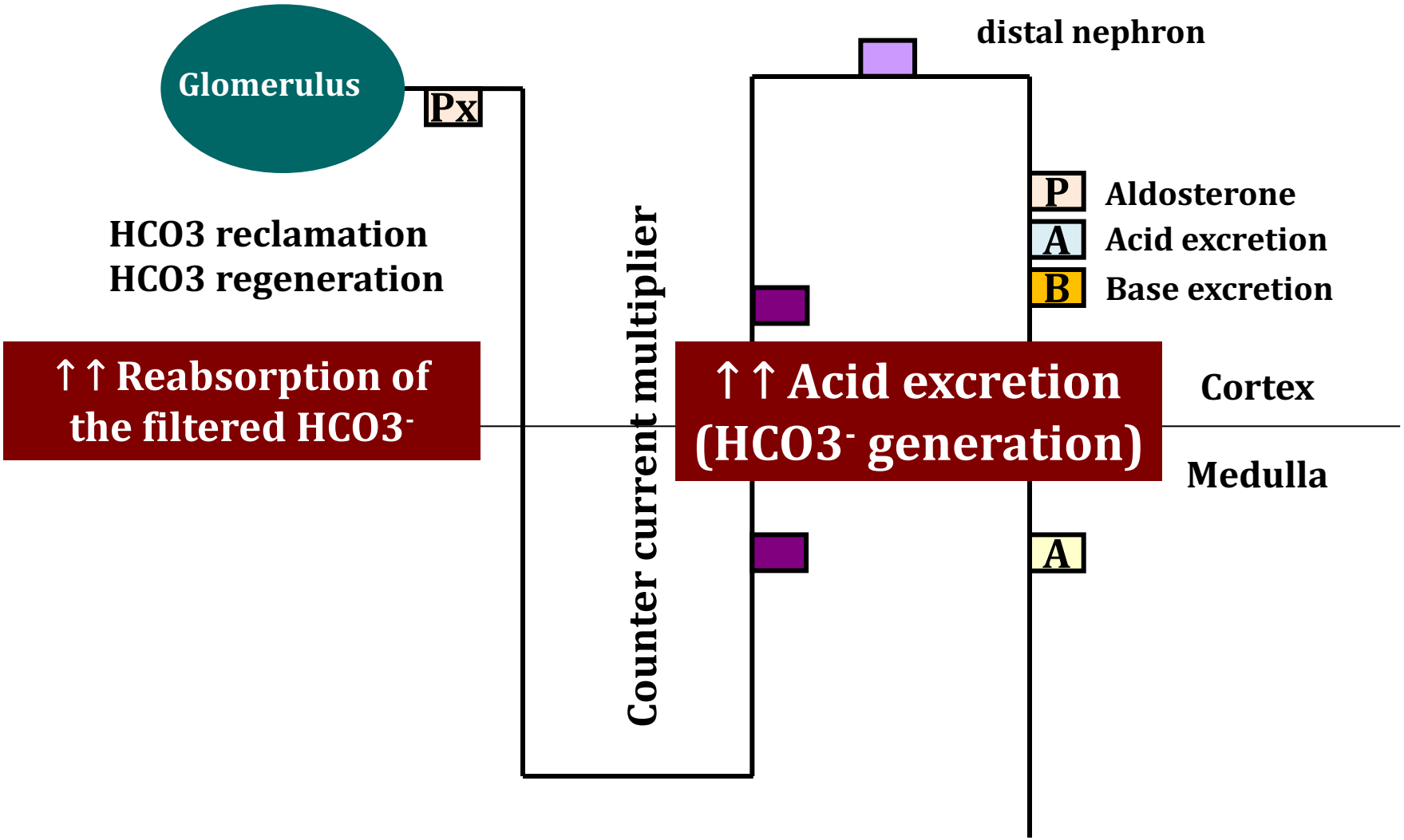
- **Normal dietary, metabolism**
  - **-Sulfuric acid (methionine, cysteine)**
  - **-Phosphoric acid (hydrolysis of P esterase)**
  - **-Organic acid**
  - **-Intermediary metabolites**



- **↑ Reabsorption of the filtered HCO_3^-**
- **↑ Acid excretion (HCO_3^- generation)**

Adapted from Brenner and Rector's The Kidney, 11th ed.

Nephron: Renal Tubules to Response to Acidemia



Px=proximal tubule, P=Principal cell, A=alpha-intercalated cell, B=beta-intercalated cell

$NH_3 + H^+ \leftrightarrow NH_4^+$

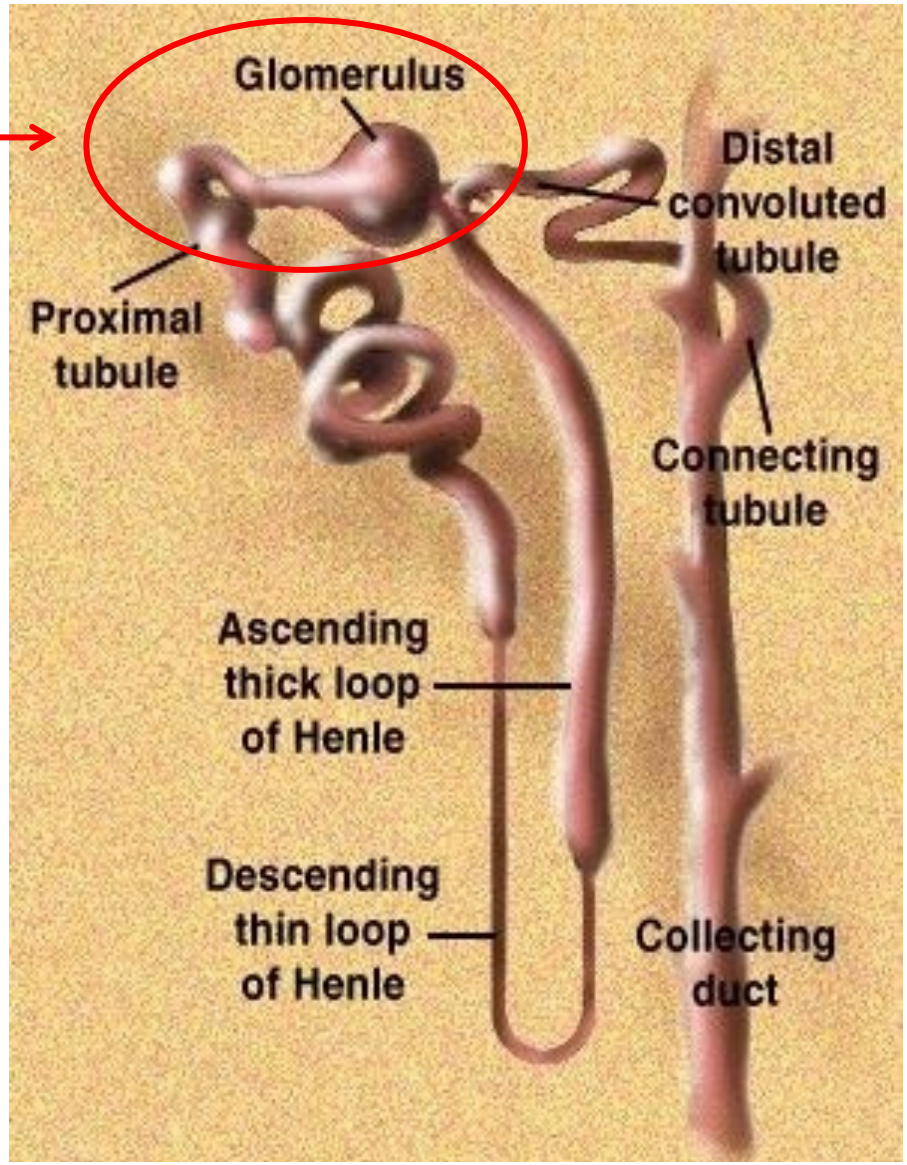
HCO_3^- Reclamation (Reabsorption)

Filtered HCO_3^-
4500-5000 mEq/day
(HCO_3 24 -31 mEq/L)
(RPF180 L/day)

Proximal tubule
80-85%

TALH
15%

Collecting duct
5%



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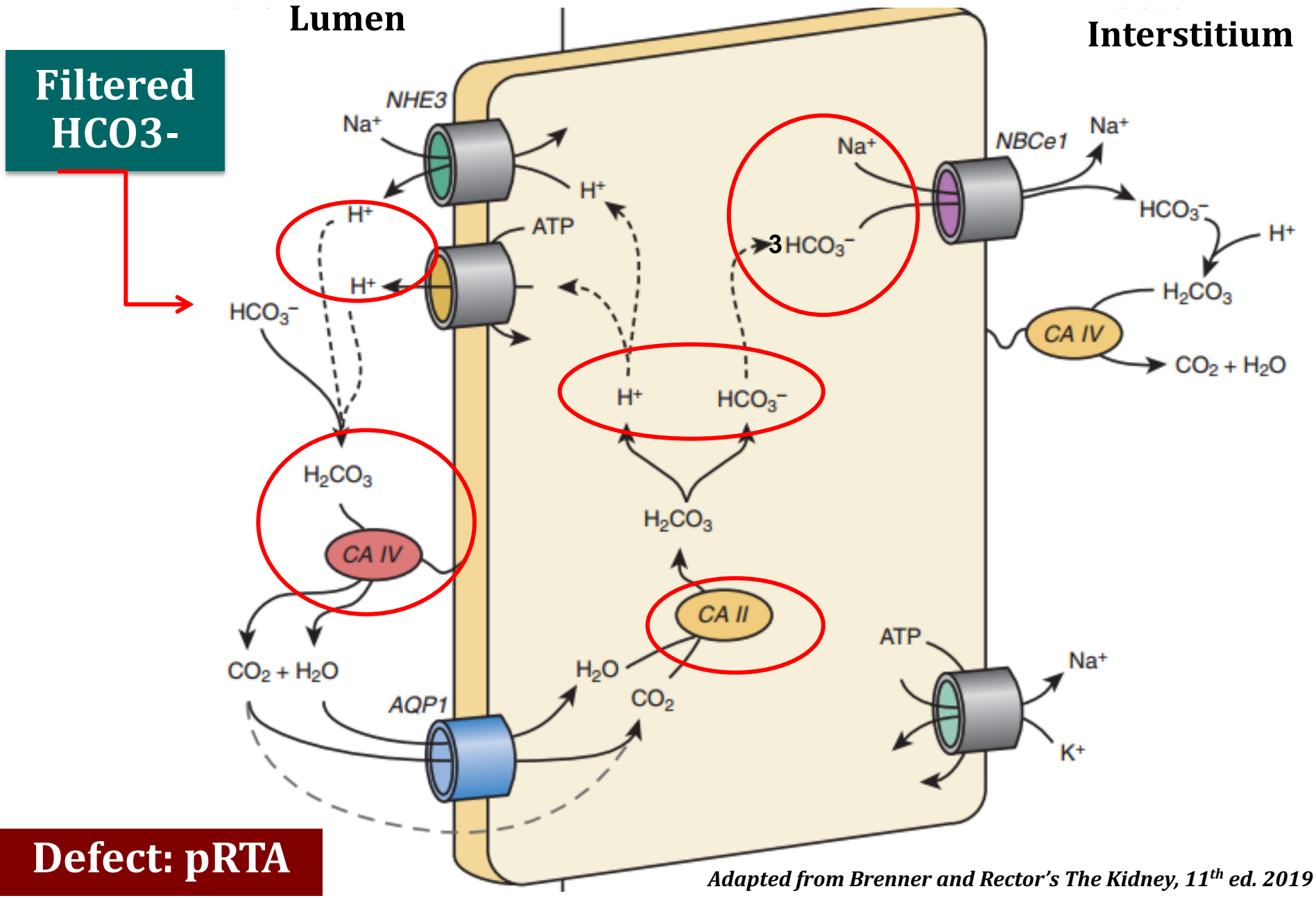
HCO_3^- Reclamation (Reabsorption) in Proximal tubule



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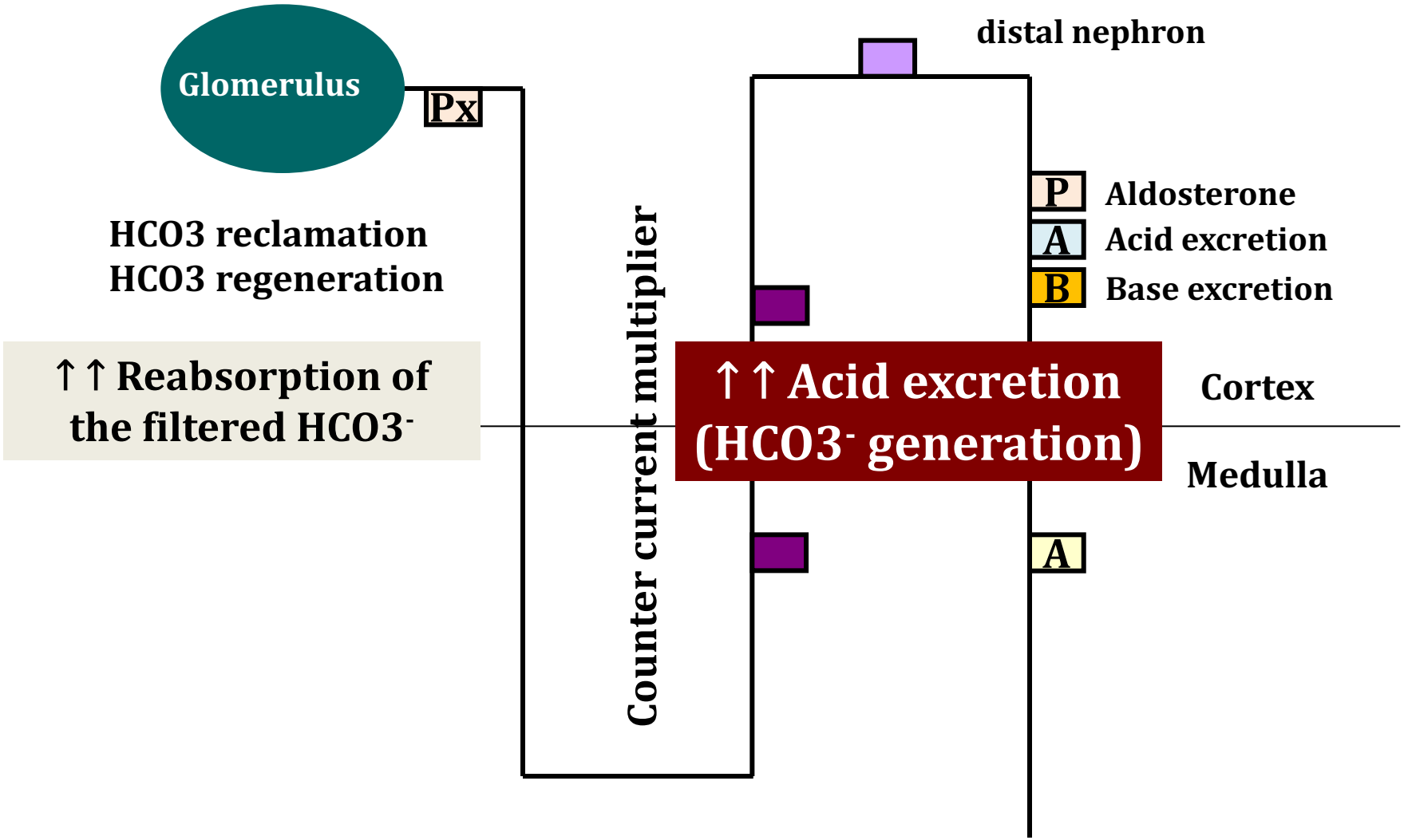
Nephron: Renal Tubules to Response to Acidemia



Px=proximal tubule, P=Principal cell, A=alpha-intercalated cell, B=beta-intercalated cell

$NH_3 + H^+ \leftrightarrow NH_4^+$

Normal Dietary H+ Generation
Fixed acid 26-52 meq/day (0.5-1 meq/kg/day)

Renal Acid excretion

Free H^+

Low level

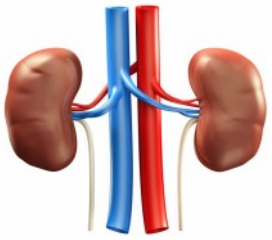
Titratable acid

$H^+ + HPO_4^{2-} \leftrightarrow H_2PO_4^-$

10-40 mEq/day

$NH_3 + H^+ \leftrightarrow NH_4^+$

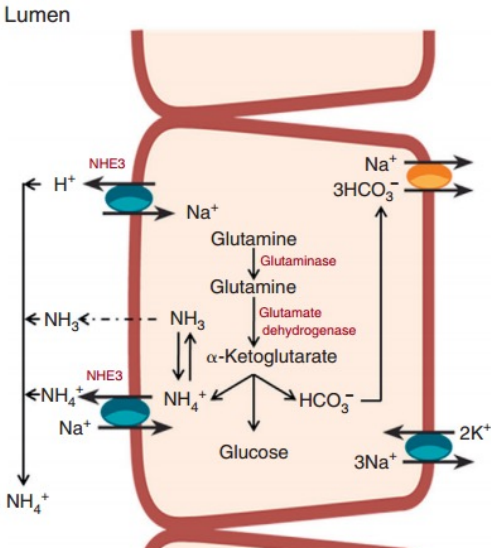
40 mEq/day

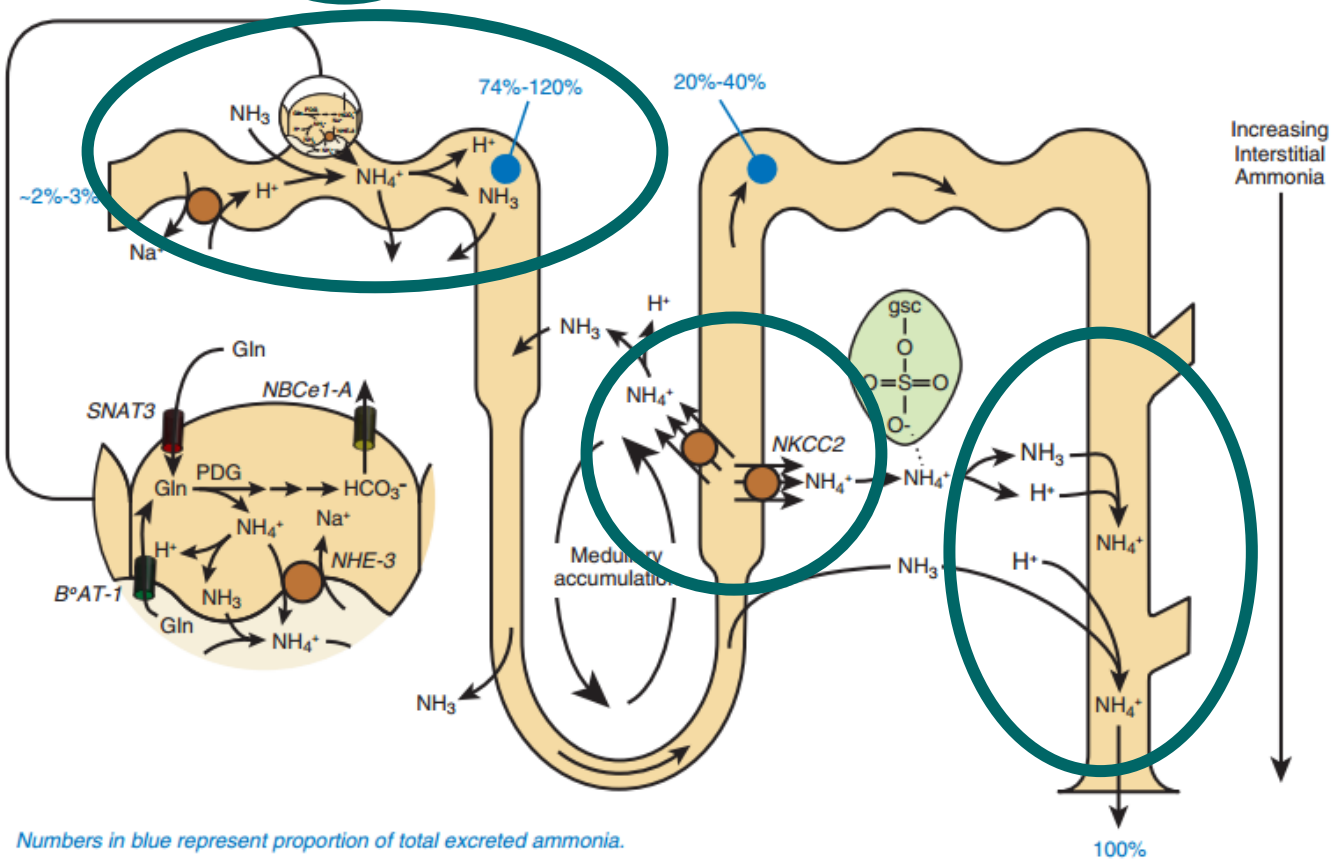


- *Adapted from Clin Soc 14:421;1955, Adapted from Kidney Int 24:670;1983,*
- *Adapted from Am J Physiol 253:F595;1987. Adapted from Brenner and Rector's The Kidney, 11th ed. 2019*

Integrated Overview of Renal Ammonia Metabolism

$$NH_3 + H^+ \leftrightarrow NH_4^+$$





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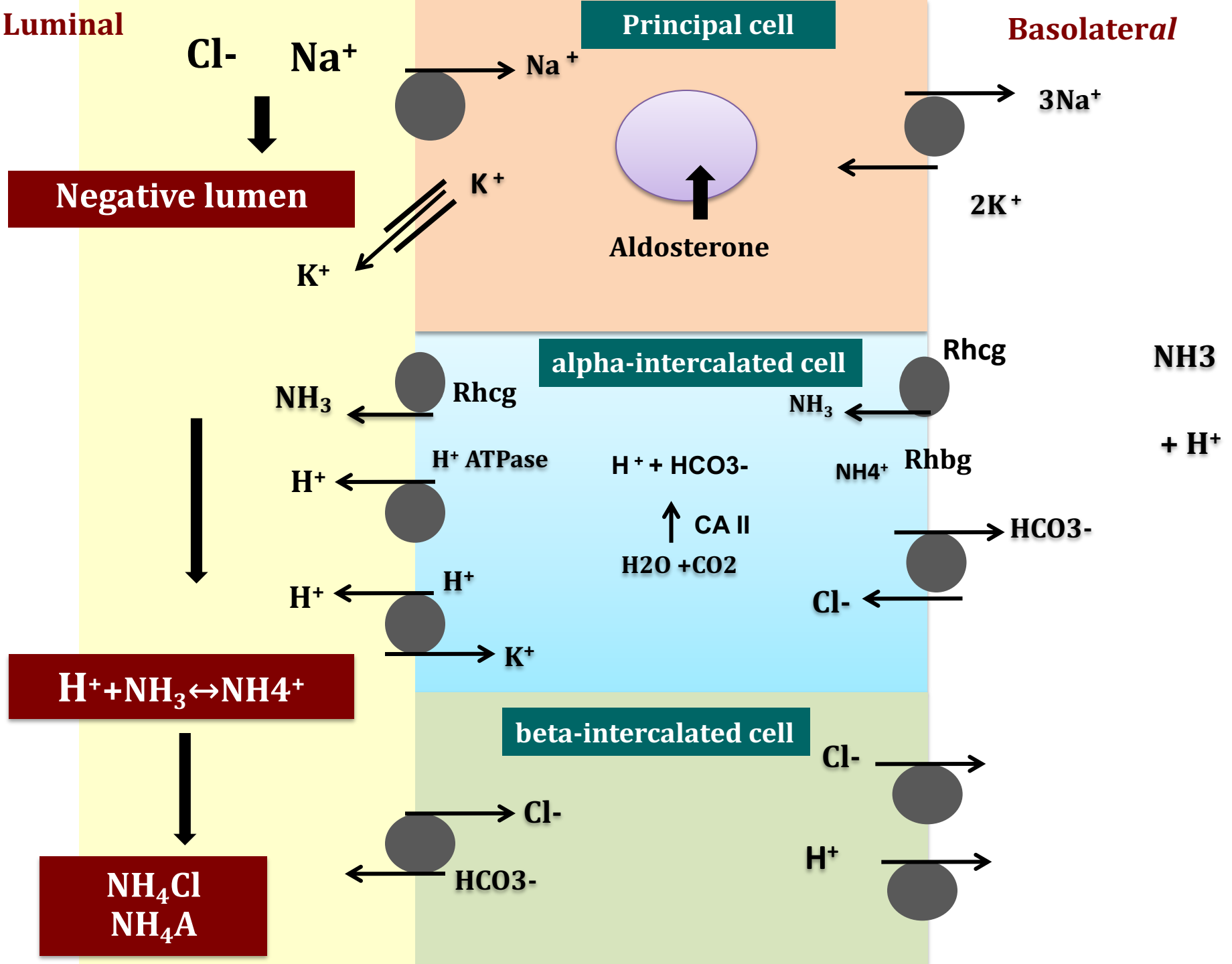
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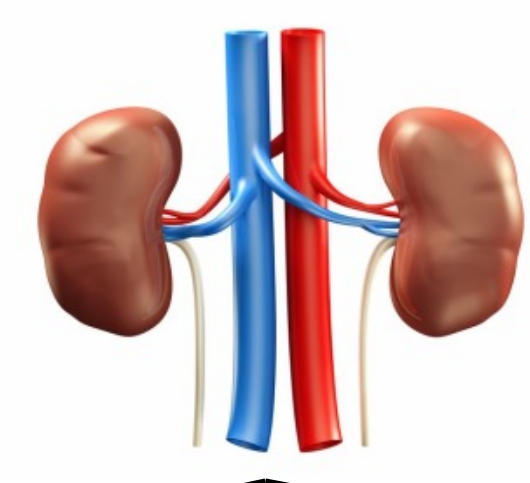
Na+
Principal cell
Basolateral
Na +
3Na+
Negative lumen
K +
2K +
Aldosterone
K+
alpha-intercalated cell
Rhcg
NH3
NH3
Rhcg
NH3
+ H+
H+ ATPase
H + + HCO3-
NH4+
Rhbg
H+
CA II
HCO3-
H2O +CO2
H+
H+
Cl-
K+
H+ + NH3 ↔ NH4+
beta-intercalated cell
Cl-
Cl-
H+
HCO3-
NH4Cl
NH4A

Kidney Metabolic Acidosis



Renal Tubular Acidosis (RTA)

Quantitative

↓↓↓ Nephron
GFR <15-20 mL/min

Qualitative

GFR >20 mL/min

Renal tubules: Impair response to acidemia

Approach

Type of RTA

Type 1 (dRTA)	**Distal RTA: Can't excretion of urine NH_4^+**
Type 2 (pRTA)	**Proximal RTA: Loss urine HCO_3**
Type 3	**Combine pRTA and dRTA**
Type 4	**Hypoaldosteronism or aldosterone resistant Can't excretion of urine NH_4^+**

Adapted from UpToDate 2022

Renal tubules: Impair response to acidemia

- Urine NH_4^+ <50-75 mEq/L
- Urine net charge (Positive)
- Urine osmolol gap <100-150

(GFR> 20 mL/min)

- **Defect of distal acidification in setting systemic acidosis (Urine pH >5.5)**

- Urine pH <5.3 (tubular cell secreted acid to urine)
- Urine pH >5.5 (tubular cell can't secrete acid)

- *Adapted from Brenner and Rector's The Kidney, 10th ed. 2016*
- *Adapted from Comprehensive Clinical Nephrology 6th ed,*

Calculated urine $NH4^+$ by Urine net charge (UNC) or Urine Anion Gap (UAG)

UNC = [urine Na^+ + urine K^+] – urine Cl^-

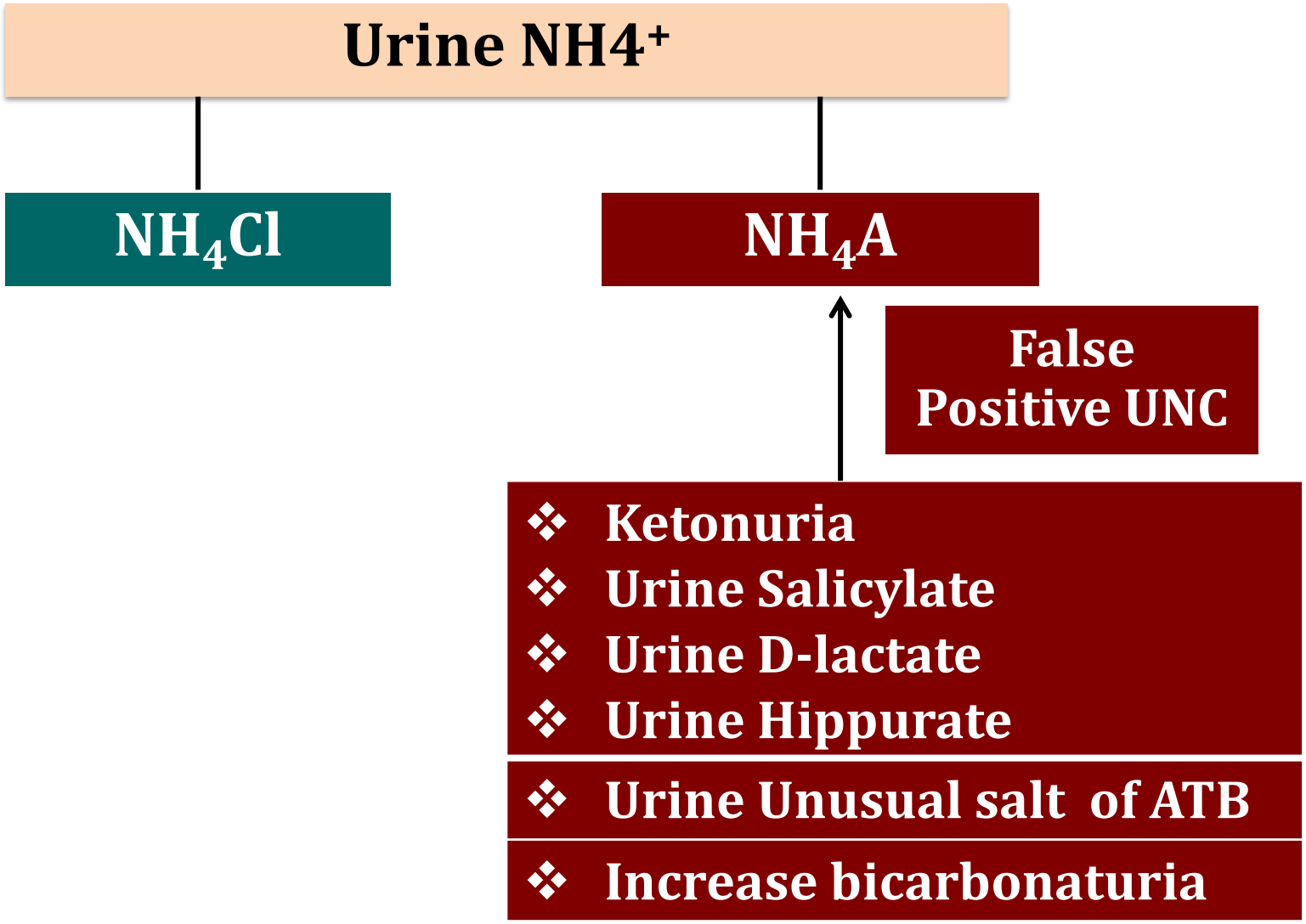
Negative UNC

Can secrete acid NH_4Cl to urine

Positive UNC

Can't secrete acid NH_4Cl to urine

Pitfall: Urine net charge (Indicated: NH_4Cl)



Urine Osmolal Gap

Urine osmolal gap = Measured urine osmolality – calculated urine osmolality

Calculated urine osmolality = [2x(urine Na + urine K)]+ Urine urea ÷ 2.8 + Urine glucose ÷18

Measured urine osmolality
NaSalt
KSalt
Urea
Glucose
NH4salt

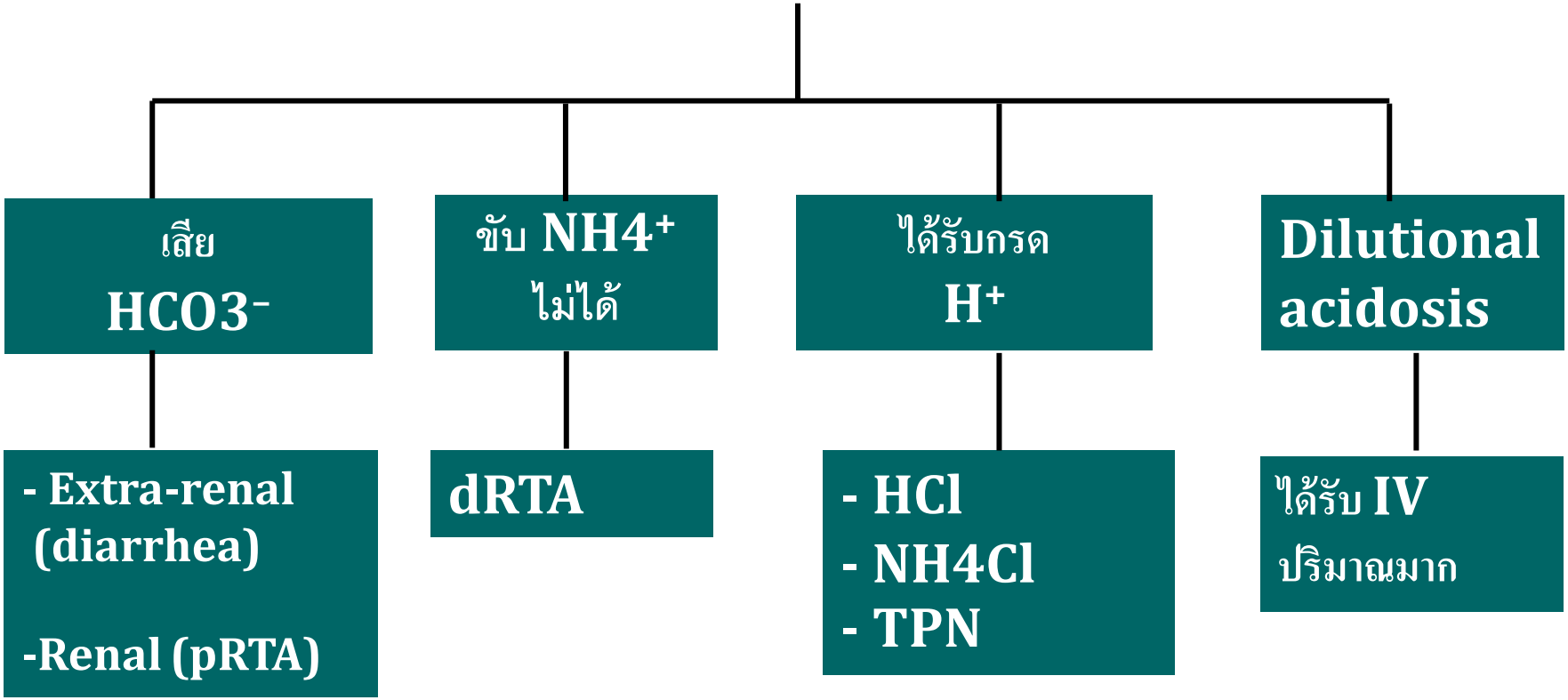
−

Calculated urine osmolality
NaSalt
KSalt
Urea
Glucose

Lab: Can't secreted acid to urine

Can't secreted acid to urine
1. Direct measurement: Urine NH_4^+ <50-75 mEq/L
2. Calculated urine NH_4^+ by Urine net charge (UNC) or urine anion gap (UAG): Positive
3. Calculated urine NH_4^+ by Urine osmolal gap: <100-150

Differential Cause of Normal AG metabolic acidosis



Normal AG metabolic acidosis

UNC (while ABG: pH <7.35)

Negative

1. GI loss $HCO3^{-}$-
- **Diarrhea**
- **Ostomy**

Positive

Fluid and electrolytes in Body fluid

Body fluid	Na	K	HCO3	H	Cl	pH	Volume/24 h (L)
Sweat	30-50	5	-	-	45-55	-	0.5
Saliva	45	20	60	-	44	7	0.5-1.5
Gastric	40-65	10	-	90	100-140	2	2-4
Pancreas	135-155	5	70-90	-	55-75	8	1.0
Bile	135-155	5	35-50	-	80-110	7	1.5
Jejunum/ileostomy	100-120	10	50-70	-	50-60	7	1.8
Colon		90					
Diarrhea	25-50	35-60	30-45	-	20-40	-	
Normal stool	5	10	-	-	10	-	0.1

Parrish CR. Pract Gastro.2005; 29: 67.

Normal AG metabolic acidosis

UNC (while ABG: pH <7.35)

Negative

1. GI loss HCO_3^--
   - Diarrhea
   - Ostomy

   Low urine K

2. pRTA

   High urine K

3. HCl, NH_4Cl

4. Dilutional acidosis

Positive → dRTA

Urine osmolal gap

- **< 100** → dRTA
- **> 100**
  - ❖ Urine Hipurate
  - ❖ Urine D-lactate
  - ❖ Urine Ketoacids
  - ❖ Urine Salicylate
  - ❖ Urine unusual salt
  - ❖ Bicarbonaturia

Outlines

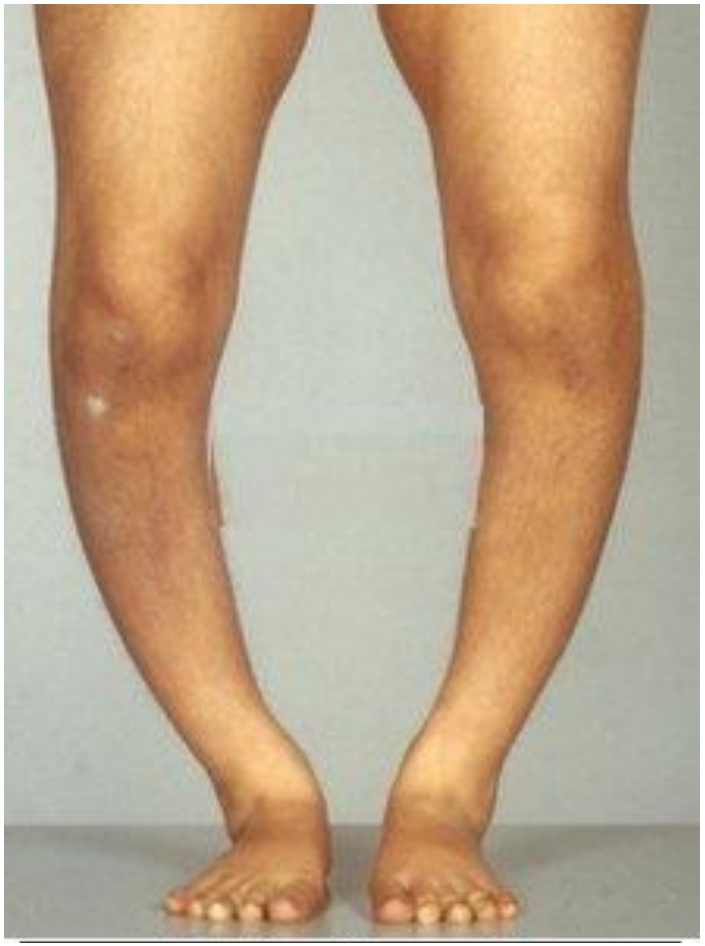
- Kidney and acid-base homeostasis
- **Proximal renal tubular acidosis**
- Distal renal tubular acidosis

Clinical Presentation of pRTA

pRTA

↓

- **Symptoms: Cause**
- **HCMA**
- **Hypokalemia/normal**
- **Growth retardation**
- **Bone disease**



Type 2 RTA: Proximal RTA (pRTA)

- Defect of HCO_3^- reabsorption at Proximal tubule (decrease renal threshold)
- Loss HCO_3^- in urine (FE HCO_3^- >10-15 %)
- Urine net charge (Negative or positive)
  UNC = Urine (Na + K)- urine Cl
- Serum potassium: ↓ serum K^+ or K^+↔
- Normal distal acidification (Urine pH<5.3)
- High urine citrate

Type of Proximal RTA

- **Isolated pRTA**
  - **Loss HCO_3^- alone**
- **Fanconi Syndrome**
  - **Bicarbonaturia**
  - **Glycosuria**
  - **Amino aciduria**
  - **Hyperuricosuria**
  - **Hyperphosphaturia***

- *Adapted from Brenner and Rector's The Kidney, 10th ed. 2016*
- *Adapted from Comprehensive Clinical Nephrology 6th ed, 2019.*

Cause of proximal RTA

Isolated pRTA

❖ Congenital
- CA II deficiency
- NBC defect

❖ Acquire
- Acetazolamide
- Topiramate

Fanconi syndrome

❖ *Genetic:*
Wilson's dz
Cystinosis

❖ *Dysproteinemia:*
MM
Amyloidosis

❖ *Autoimmune:*
Sjogren
SLE

❖ Drugs and toxin:
Tenofovir
Aminoglycoside
Outdate
tetracycline
Ifosfamide
Glue
Lead
Mercury

Treatment Proximal RTA

❖ **Correct Cause of pRTA**

Alkaline supplement

Children

1. Keep normal HCO_3^-
2. $NaHCO_3$/Na citrate (5-15 mEq/kg/day)
3. K^+ supplement

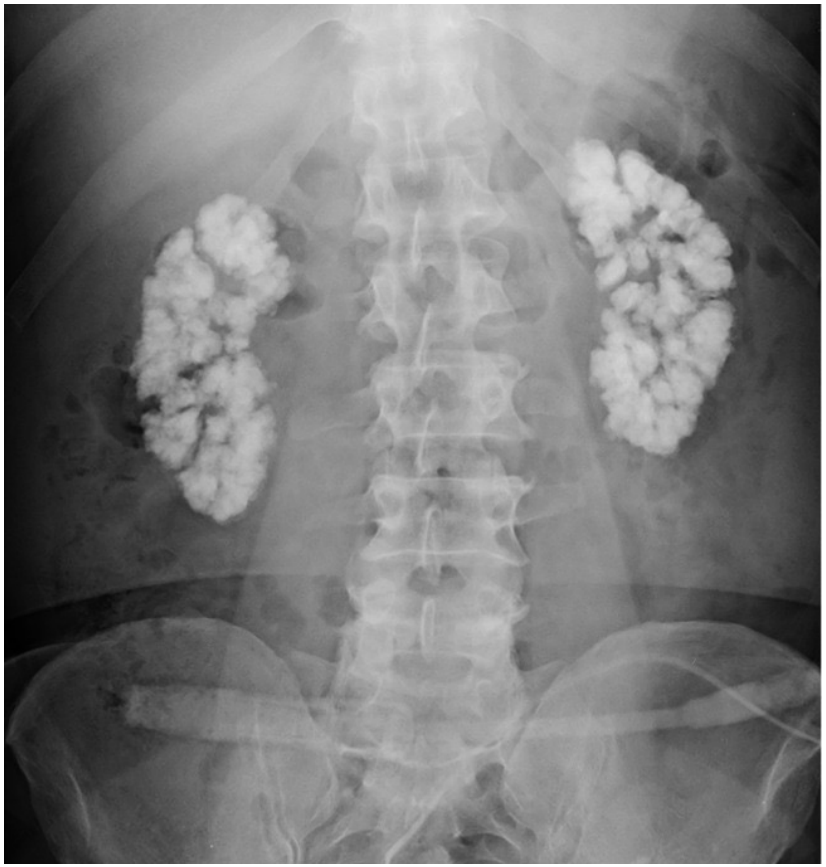
Adult

1. Keep HCO_3^- >18 mEq/L
2. $NaHCO_3$/Na citrate
3. K^+ supplement

Outlines

- Kidney and acid-base homeostasis
- Proximal renal tubular acidosis
- **Distal renal tubular acidosis**

Clinical presentation dRTA



dRTA

Symptoms: Cause

HCMA

Hypo/hyper K^+

Growth retardation

Bone disease

Stone/Nephrocalcinosis

Stone: dRTA

1. Hypercalciuria >> (30%)

- Bone resorption: Due to more acidosis

- Decrease renal Ca^{+} reabsorption due to more MA

2. Decrease urine citrate excretion (30%)

3. High urine pH precipitate stone formation (calcium phosphate)

Normal AG metabolic acidosis

UNC (while ABG: pH <7.35)

Negative

1. GI loss HCO_3^-
   - Diarrhea
   - Ostomy
2. pRTA
3. HCl, NH_4Cl
4. Dilutional acidosis

Positive → dRTA

Urine osmolal gap

< 100

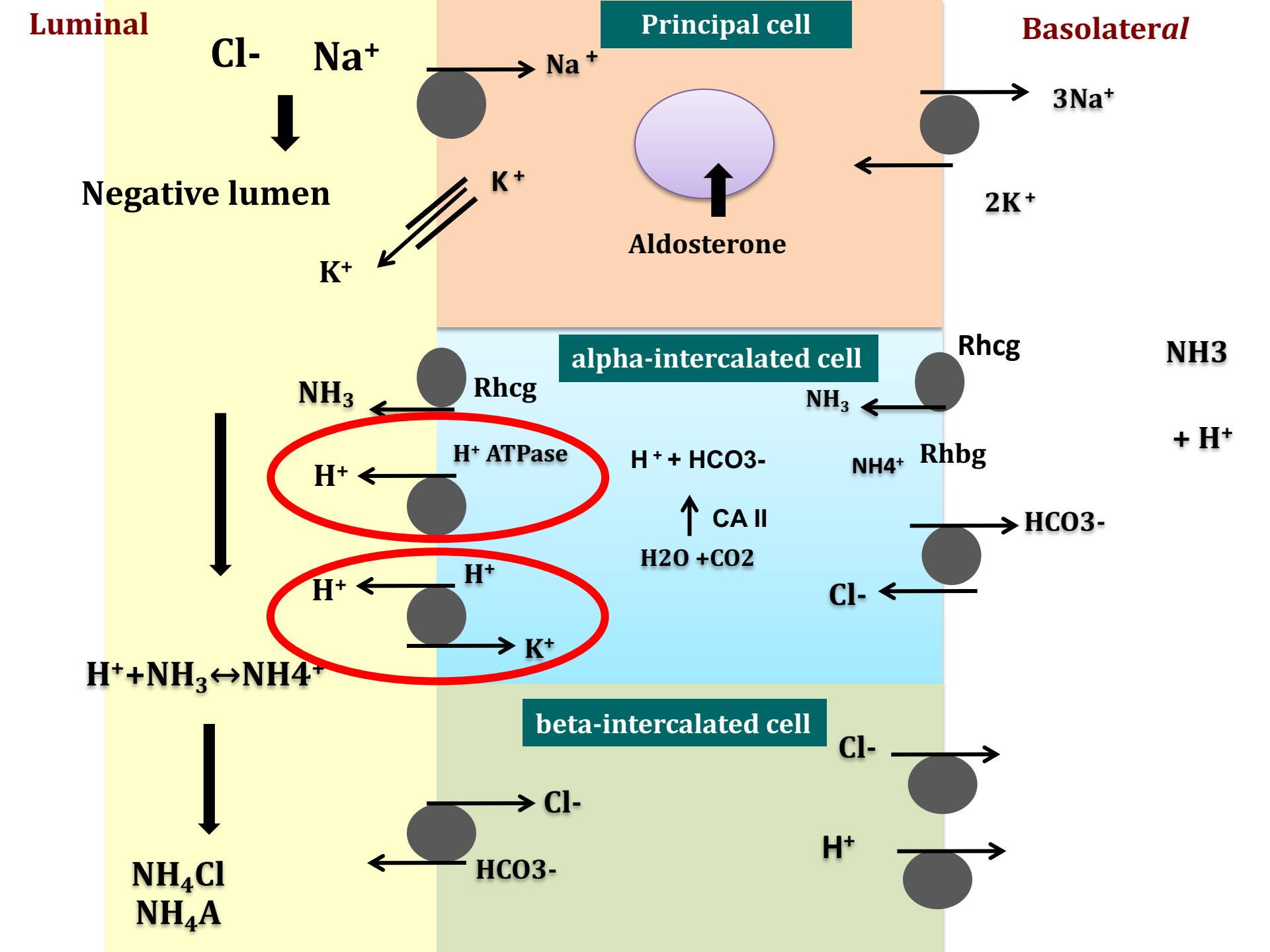
dRTA
Or
Type 4 RTA

> 100

- Urine Hipurate
- Urine D-lactate
- Urine Ketoacids
- Urine Salicylate
- Urine unusual salt
- Bicarbonaturia

Type dRTA or type 4 RTA: Plasma K^+

- Hypo K^+ or normo K^+
  - 1st Urine pH
    - >5.5
      - ❖ Classical dRTA (secretory defect)
- Hyper K^+


Luminal
Principal cell
Basolateral
Cl-
Na+
Na +
3Na+
Negative lumen
K +
2K +
K+
Aldosterone
alpha-intercalated cell
Rhcg
NH3
NH3
Rhcg
NH3
+ H+
H+ ATPase
H+
H + + HCO3-
NH4+
Rhbg
CA II
HCO3-
H2O +CO2
H+
H+
Cl-
K+
H+ + NH3 ↔ NH4+
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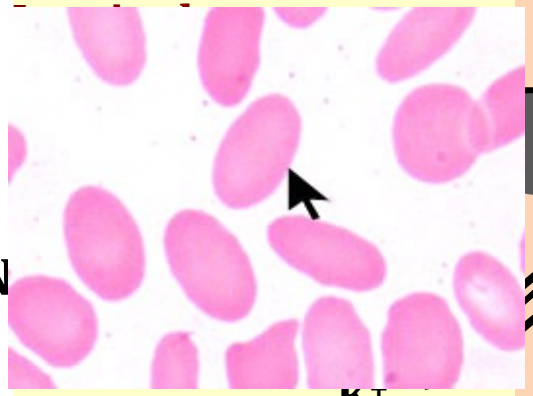
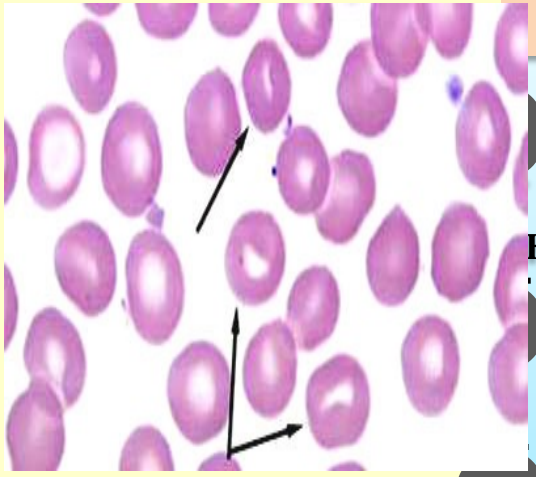
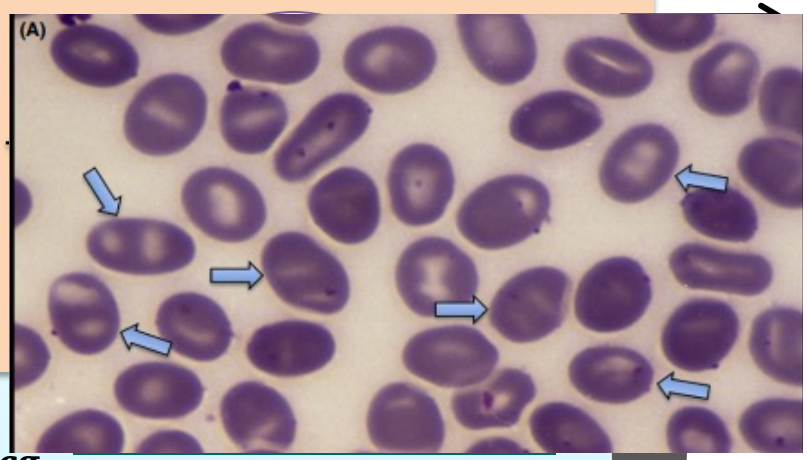
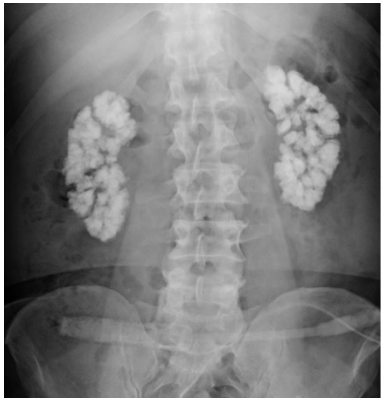
H+
HCO3-
NH4Cl
NH4A









Principal cell

Basolateral

Na^+

$3Na^+$

K^+

Rhcg

NH_3

H^+ ATPase

$H^+ + HCO3^-$

$NH4^+$

Rhbg

$+ H^+$

CA II

$H2O + CO2$

$HCO3^-$

Cl^-

H^+

K^+

$H^+ + NH_3 \leftrightarrow NH4^+$

NH_4Cl

NH_4A

beta-intercalated cell

Cl^-

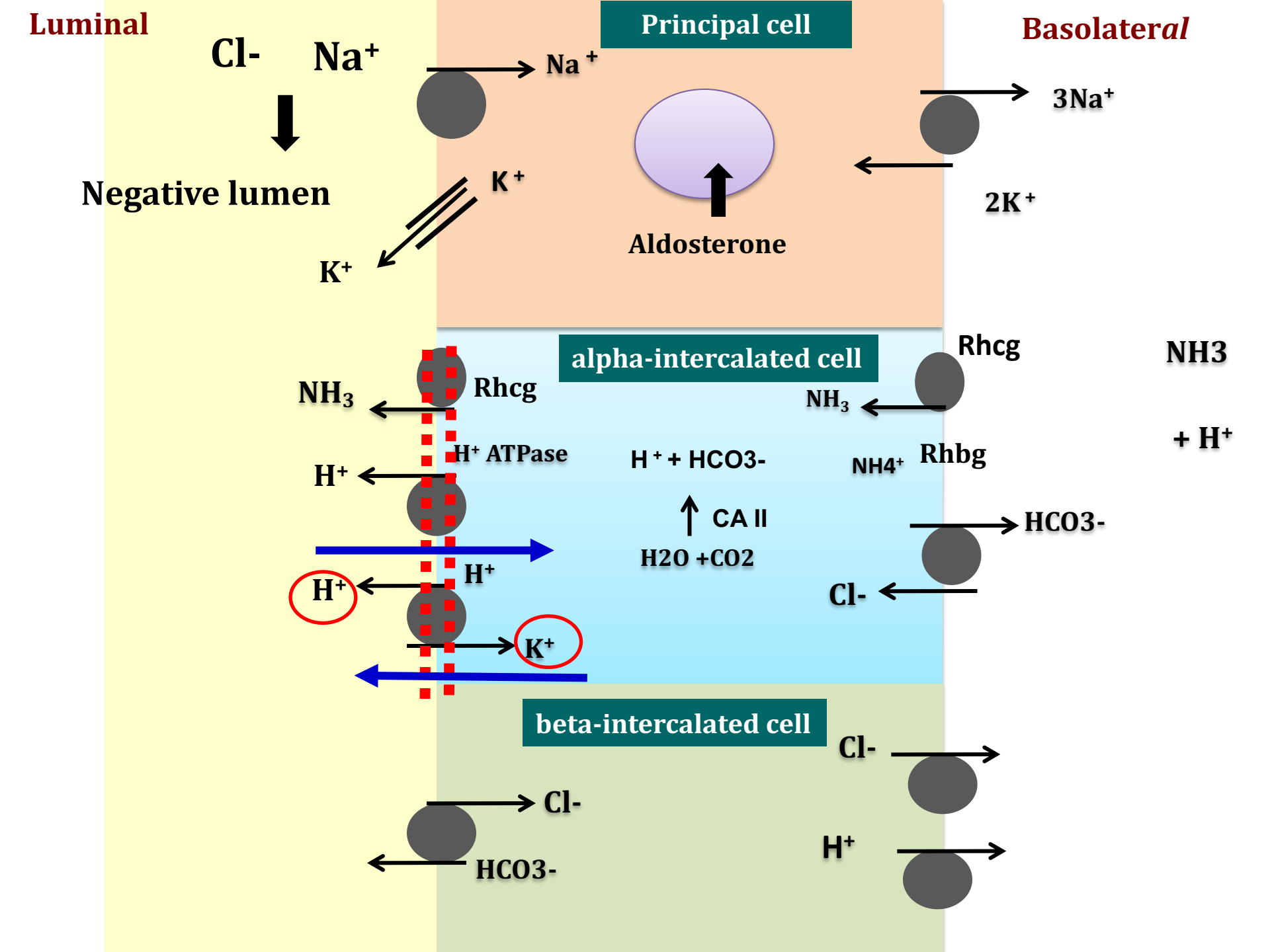
Cl^-

$HCO3^-$

H^+

Type dRTA or type 4 RTA: Plasma K^+

- Hypo K^+ or normo K^+
  - 1st Urine pH
    - >5.5
      - ❖ Classical dRTA (secretory defect)
      - ❖ Backleak (permeability defect)
- Hyper K^+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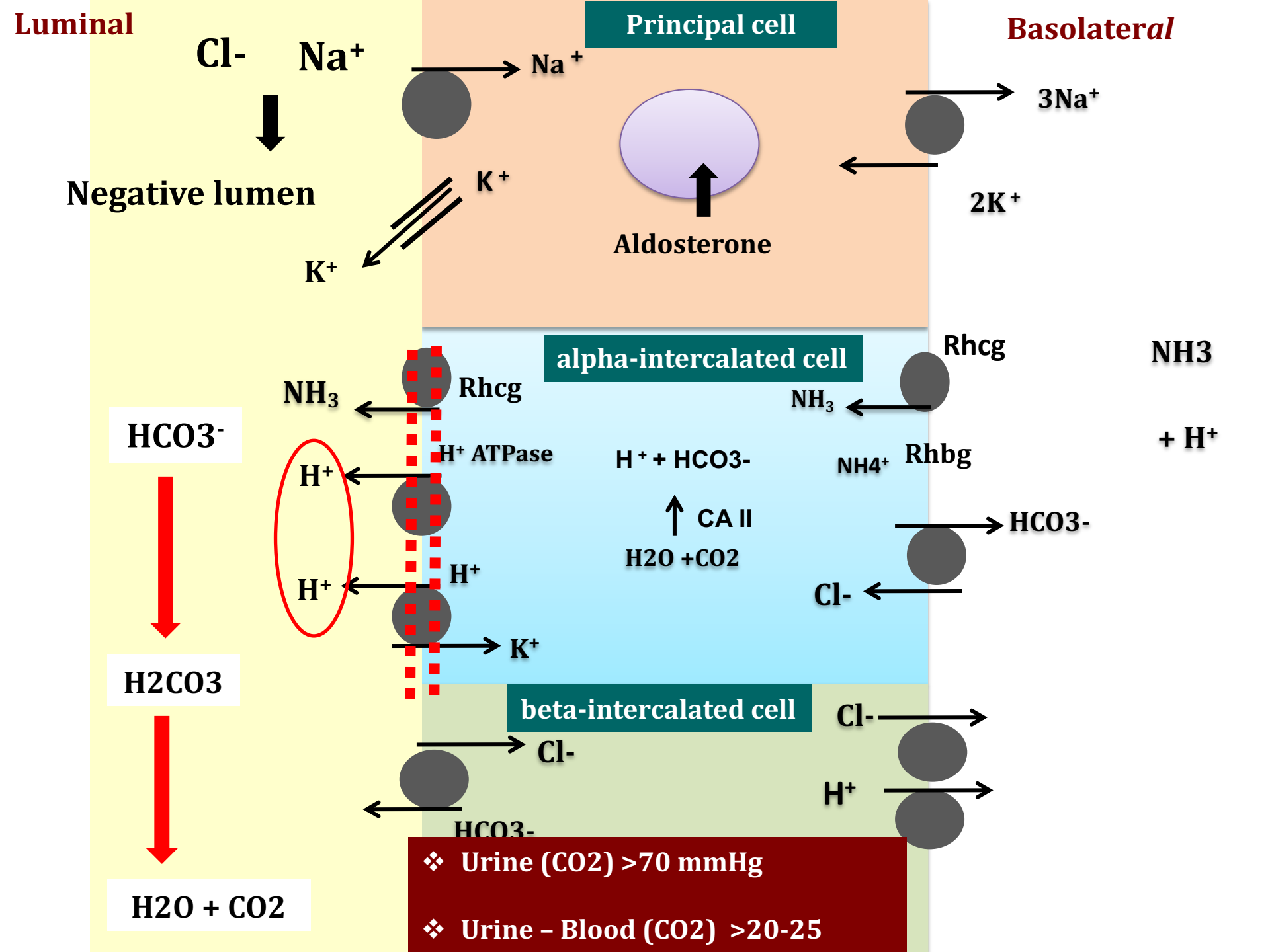
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H+ + HCO3-
NH4+
Rhbg
H+
CA II
HCO3-
H2O +CO2
H+
Cl-
H+
K+
beta-intercalated cell
Cl-
Cl-
H+
HCO3-
H2CO3
H2O + CO2
❖ Urine (CO2) >70 mmHg
❖ Urine – Blood (CO2) >20-25

Cause dRTA with Hypokalemia

Autoimmune

- SLE, Sjogren's syndrome
- Thyroiditis
- Primary billiary cirrhosis
- Chronic active hepatitis
- Pulmonary fibrosis

Drug and toxin

- Amphotericin B
- Toluine
- Ifosfamide
- Balkan nephropathy
- Analgesic nephropathy
- Chemotherapy

Genetic with systemic disorder

- Southeast asian ovalocytosis
- Hereditary elliptocytosis
- Sickle cell anemia
- Wilson's disease
- Ehlers-Danlos syndrome
- Marfan syndrome
- Osteopetrosis with CA II deficiency
- Medullary cystic disease

Dysproteinemia

- Multiple myeloma
- Amyloidosis
- Cryoglobulinemia

Primary

- Idiopathic, sporadic

Tubulointerstial disease

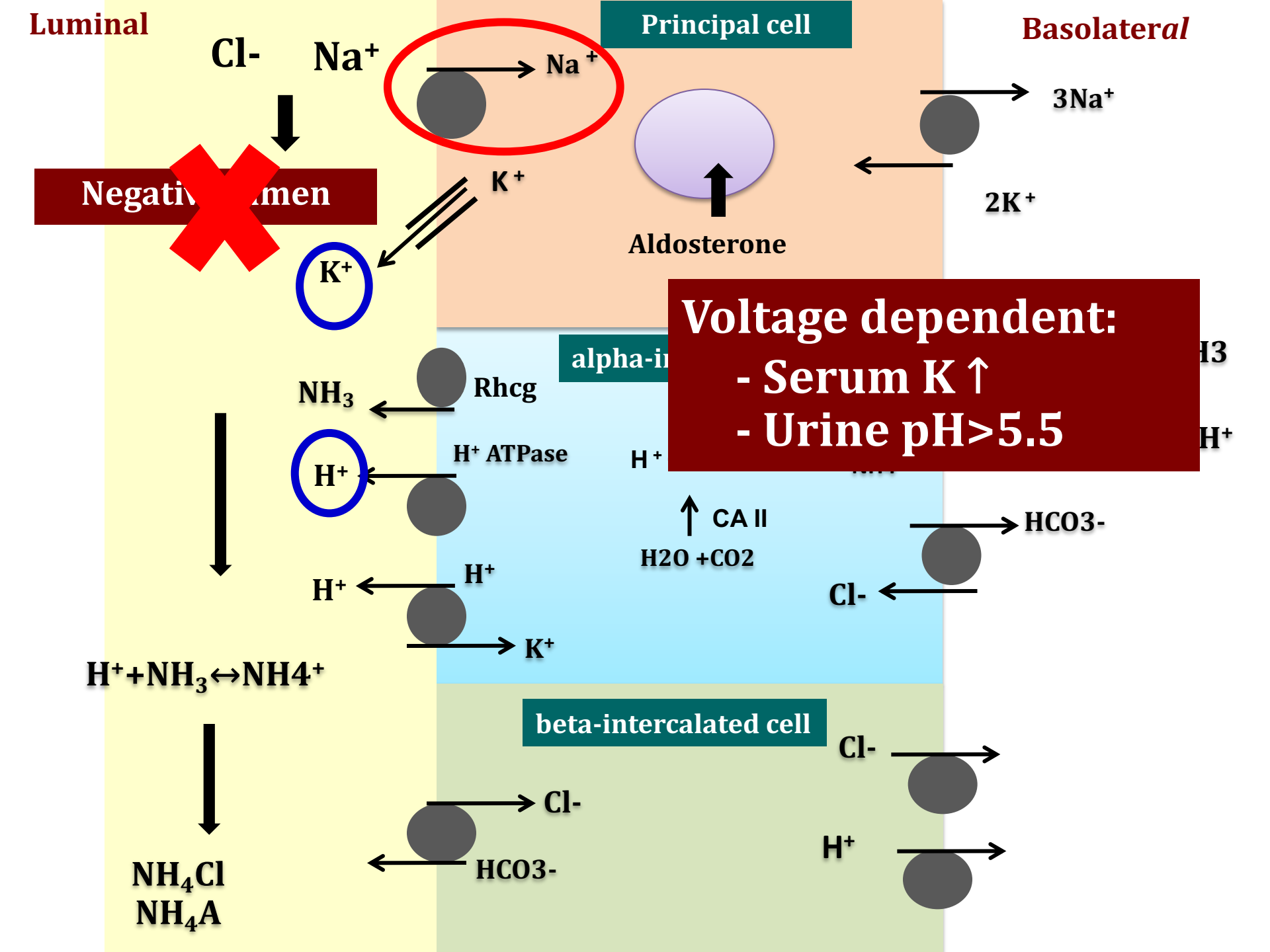
- Chronic pyelonephritis
- Myelomonoblastic leukemia
- Leprosy
- Renal transplant

Disease asociated with nephrocalcinosis

- Hyperparathyroidism
- Hyperthyroid
- Hyperoxaluria
- Medullary sponge kidney

Type dRTA or type 4 RTA: Plasma K^+

- **Hypo K^+ or normo K^+**
  - **1st Urine pH**
    - **>5.5**
      - ❖ Classical (secretory)
      - ❖ Backleak (permeability defect)
- **Hyper K^+**
  - **1st Urine pH**
    - **<5.5**
      - ❖ Hypoaldo-steronism
      - ❖ Pseudohypo aldosteronism
    - **>5.5**
      - ❖ Voltage dependent
      - ❖ Pseudohypo aldosteronism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Na+
Na+
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K+
Aldosterone
K+
Voltage dependent:
- Serum K ↑
- Urine pH>5.5
alpha-i
NH3
Rhcg
H+
H+ ATPase
H+
CA II
H2O +CO2
HCO3-
Cl-
H+
H+
K+
H+ + NH3 ↔ NH4+
beta-intercalated cell
Cl-
Cl-
HCO3-
H+
NH4Cl
NH4A

Cause of Voltage-dependent dRTA

1. Drugs which block Na^+ channel:

- **Amiloride**
- **Triamterene**
- **Trimethoprim (usually in high doses)**
- **Pentamidine**

2. Drugs: Competition to entry Na^+ channel:

- **Lithium (competition)**

3. Tubulointerstitial disease:

- **Partial obstructive uropathy**

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      - ❖ Classical (secretory)
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- **Hyper K^+**
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      - ❖ Pseudohypo aldosteronism
    - **>5.5**
      - ❖ Voltage dependent
      - ❖ Pseudohypo aldosteronism

Cause Type 4 RTA (hyperkalemia)

Aldosterone deficiency

1. Primary hypoaldosteronism

- Addison's disease
- CAH 21-hydroxylase deficiency
- Aldosterone synthase deficiency
- Heparin and LMWH

2. Hyporeninemic ypoaldosteronism

- DM
- Tubulointerstitial
- Volume expansion
- ACEI, ARB, NSAID, CNI
- AIDS

Aldosterone resistance

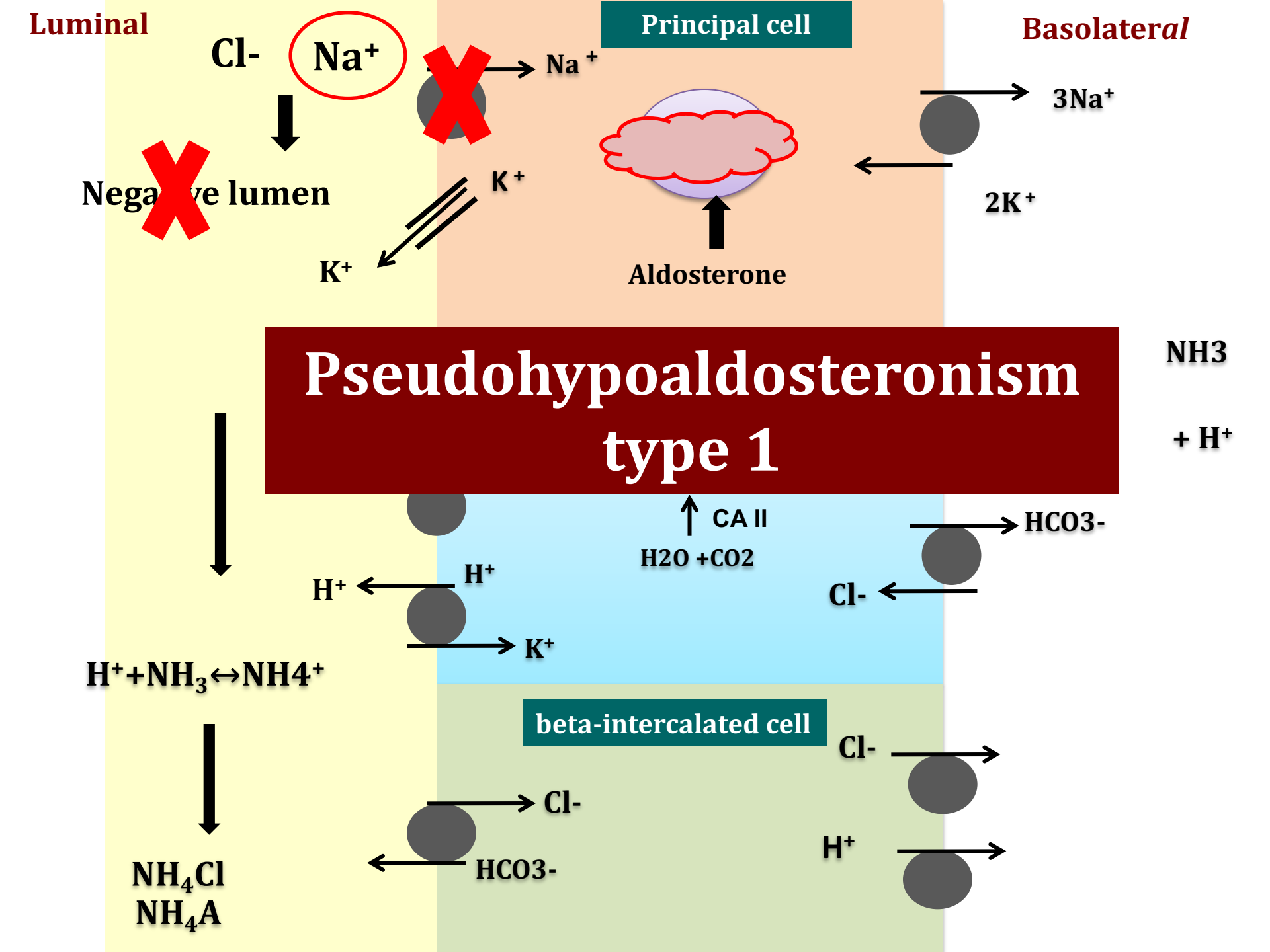
Cause Type 4 RTA (hyperkalemia)

Aldosterone deficiency

- Primary hypoaldosteronism
- Hyporeninemic hypoaldosteronism

Aldosterone resistance

- Pseudohypoaldosteronism type 1
- Pseudohypoaldosteronism type 2
- Pseudohypoaldosteronism type 3


Luminal
Principal cell
Basolateral
Cl-
Na+
Na+
3Na+
2K+
Negative lumen
K+
K+
Aldosterone
Pseudohypoaldosteronism type 1
NH3
+ H+
CA II
H2O +CO2
HCO3-
H+
H+
Cl-
K+
H+ + NH3 ↔ NH4+
beta-intercalated cell
Cl-
Cl-
H+
HCO3-
NH4Cl
NH4A

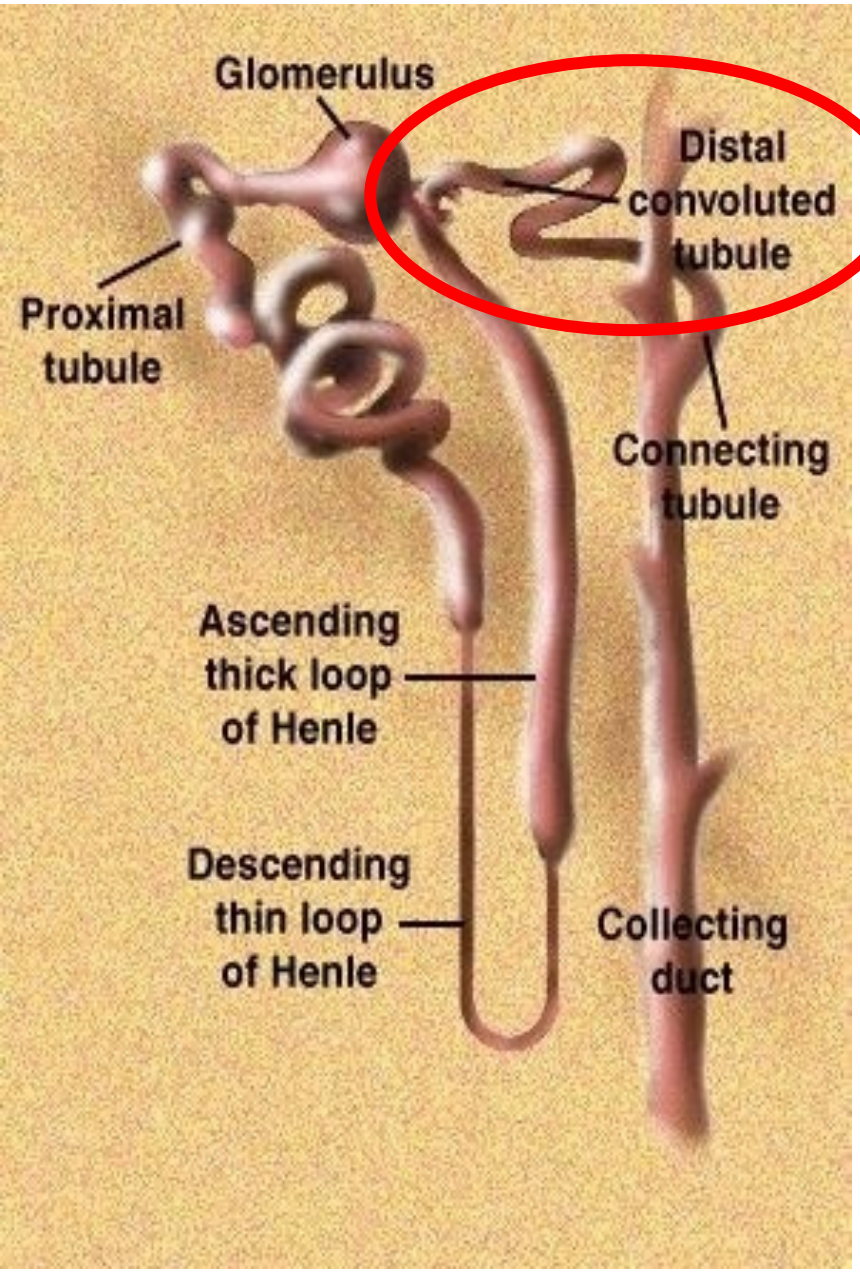
Cause Type 4 RTA (hyperkalemia)

Aldosterone deficiency

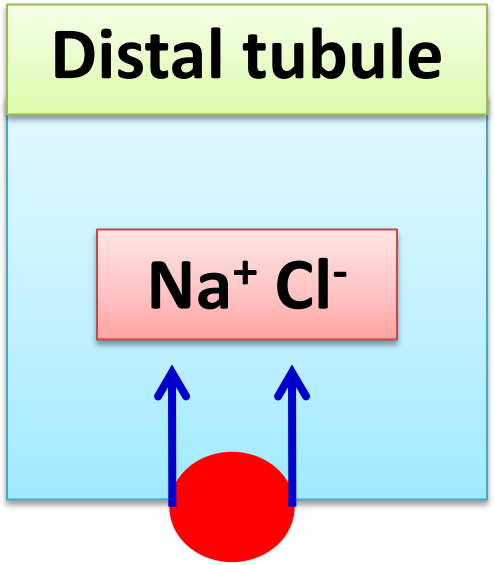
- Primary hypoaldosteronism
- Hyporeninemic hypoaldosteronism

Aldosterone resistance

- Pseudohypoaldosteronism type 1
  - Low BP
- Pseudohypoaldosteronism type 2
  - High BP
- Pseudohypoaldosteronism type 3



Pseudohypoaldosteronism type 2 (Gordon syndrome)



Gain of function of NaCl channel

Treatment dRTA

1. **Find out Cause and Treat cause**

2. **Alkaline supplement:**

3. **K^+ supplement**

Outlines

- Kidney and acid-base homeostasis
- Proximal renal tubular acidosis
- Distal renal tubular acidosis

Thank You for Your Attention

NEPHROLOGY
PHRAMONGKUTKLAO HOSPITAL

Asst. Prof. Naowanit Nata, MD
Nephrology Division, Department of Medicine
Phramongkutklao Hospital & College of Medicine