# RTA: AN OVERVIEW

# THE RTA SYNDROMES

| Syndrome | Locus | Defect |
|---|---|---|
| proximal | $S_1$- $S_3$ | ↓ $HCO_3$ threshold |
| hyperkalemic | CCD principal cell | ↓ $V_M$ (-) → ↓ $H^+$ secretion |
| gradient-limited | OMCD intercalated cells | three specific defects in $H^+$ secretion |

# CALCULATION OF VOLATILE ACID PRODUCTION

cellular respiration: $C_6H_{12}O_6 + O_2 \longrightarrow CO_2 + H_2O$

pulmonary exchange: $H_2O + CO_2 \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3$

Thus:

1) 1 mole metabolic $H_2O$ = 1 mole $H^+$

2) $\frac{\text{500 ml metabolic } H_2O}{\text{24 hrs}} \cdot \frac{\text{mol } H_2O}{\text{18 gm}} = \frac{\text{27 moles } H_2O}{\text{24 hrs}}$

3) $\frac{\text{500 ml metabolic } H_2O}{\text{24 hrs}} = \frac{\text{27,000 mEq } H^+}{\text{24 hrs}}$

# NON-VOLATILE ACID/BASE HOMEOSTASIS

## Acid Input

$$HA^* + NaHCO_3 \longrightarrow NaA^* + H_2CO_3$$

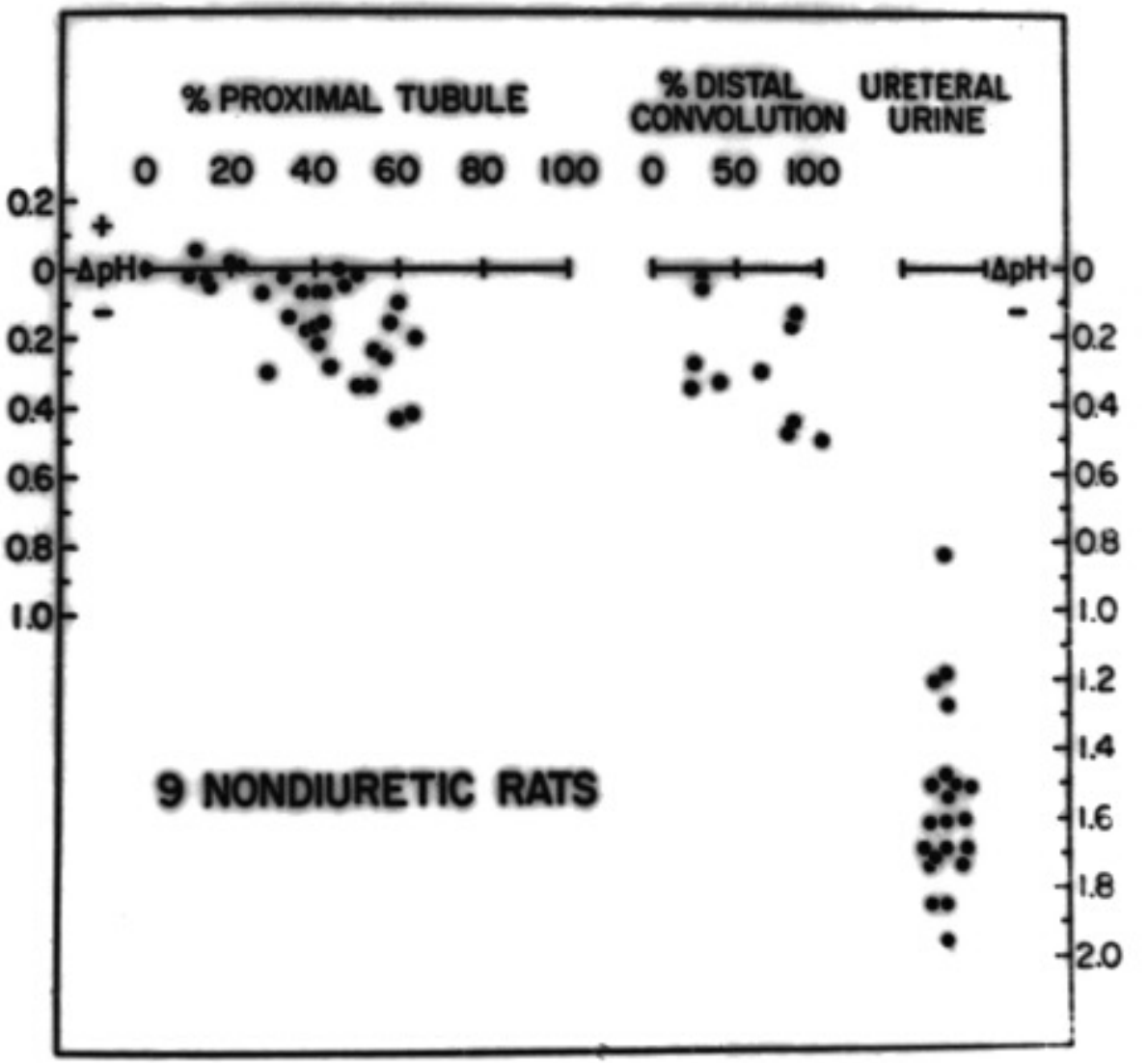
A* = non-volatile acid anion; 70 mEq/24 hrs.

## Renal Response

$HCO_3^-$ reclamation: proximal nephron; 4500 mEq/24 hrs

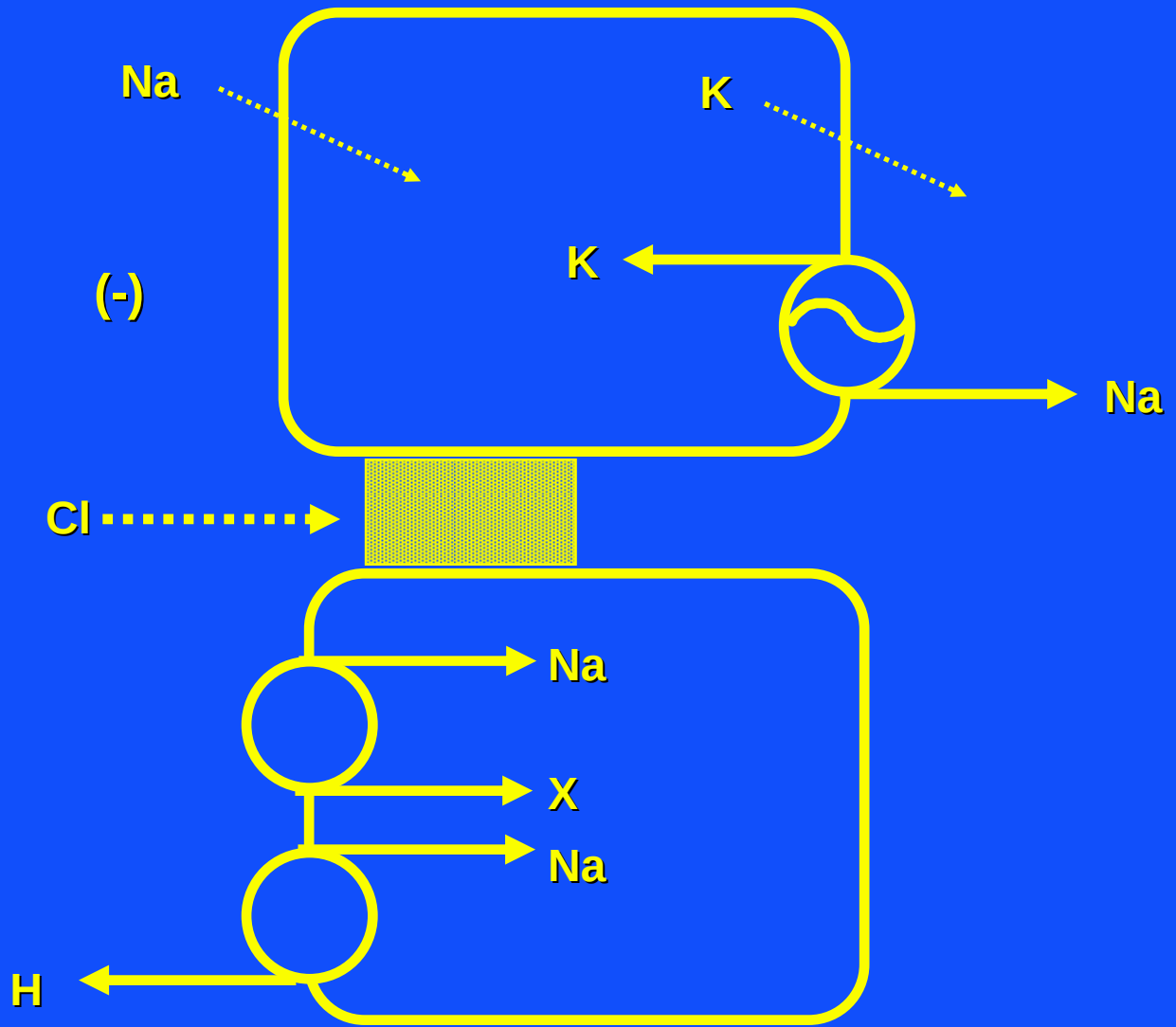
$HCO_3^-$ regeneration: distal nephron; 70 mEq/24 hrs

# TUBULAR FLUID pH CHANGES



# USSING, CRANE AND SKOU

## *How Epithelia Work*




**<u>Ussing</u> :**

- **Apical and basal membranes differ**
- **Asymmetrical pump**
- **Paracellular shunt**

**<u>Crane</u> :**

- **Co-transport**

**<u>Skou</u> :**

- **( Na + K ) - ATPase**

# THE RTA SYNDROMES

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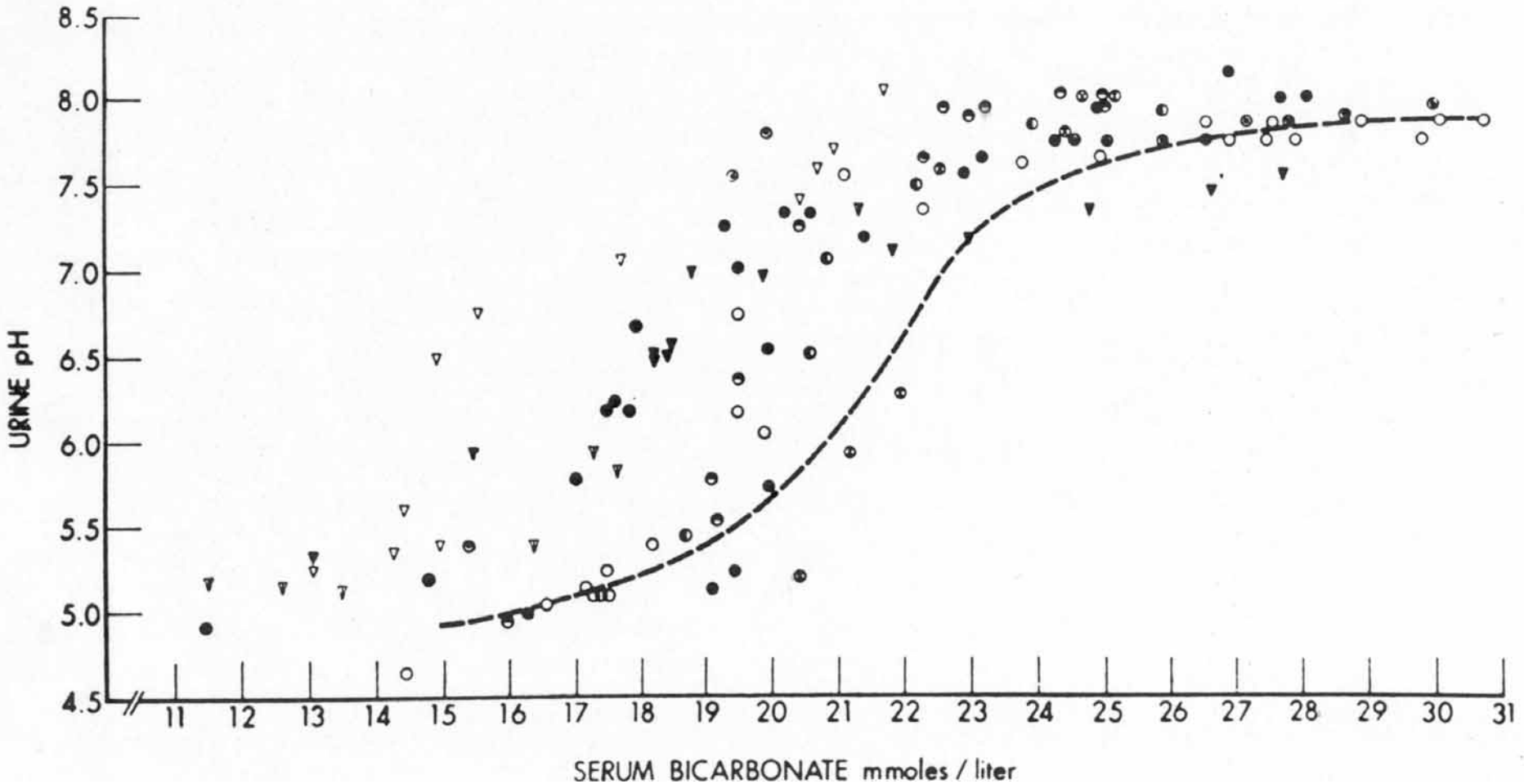
# BICARBONATE TITRATION CURVE IN PROXIMAL RTA



# PROXIMAL RTA/FANCONI SYNDROME

- Single pulse $HCO_3^-$ wasting:
  (25-20) = 5 mEq/L x 180 L/day = 900 mEq
- No $HCO_3^-$ loss for serum $HCO_3^-$ < $HCO_3^-$ threshold
- $HCO_3^-$ unresponsive acidosis
- $HCO_3^-$ Rx promotes kaliuresis
- Phosphaturia, glycosuria, amino aciduria
- No nephrocalcinosis

# FEATURES OF PROXIMAL $Na^+$ ABSORPTION

- GTB: fractional rather than absolute $Na^+$ absorption rates
- Modulated by tubulo-glomerular feedback (TGF)
- Isotonic fluid absorption
- Principal locus for $HCO_3^-$ absorption and organic solute processing
- Axial heterogeneity

# MODULATION OF PROXIMAL $Na^+$ ABSORPTION

**Increase**

Volume contraction

**Suppress**

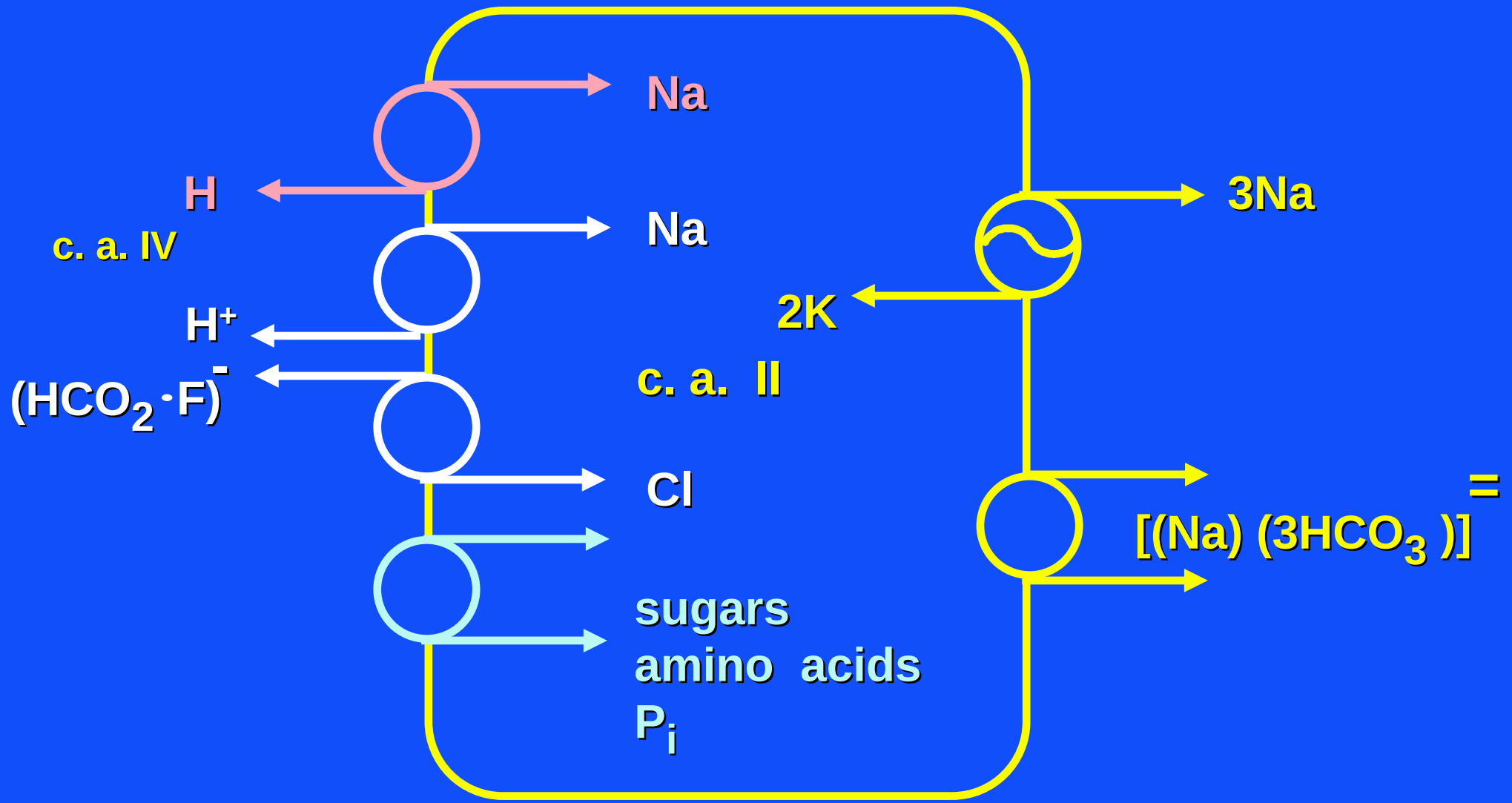
Volume expansion

GTB
(peritubular oncotic pressure)

renal nerve stimulation
A- II
$pCO_2$ increases
↓ cytosolic $K^+$

PTH
NHERF
TGF

# GENERAL MODEL FOR PROXIMAL TRANSPORT



# ROLE OF $P_i$ DEPLETION IN PROXIMAL RTA

**Hereditary Fructose Intolerance**

Fructose ⟶ F - I - P ⟶// triose phosphate aldolase

↓ cellular { adenine nucleotides; ATP; $P_i$

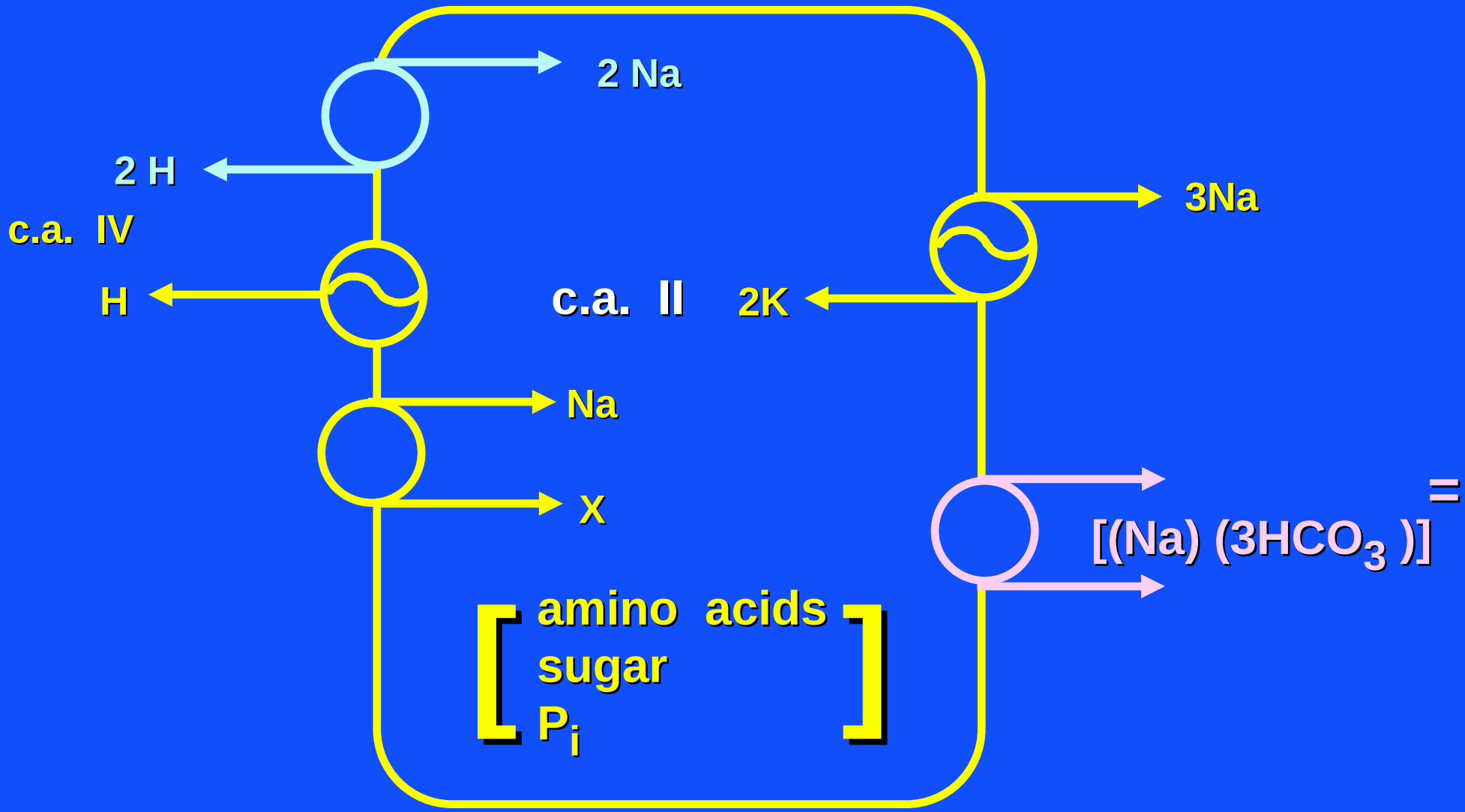
reversal by $P_i$ loading

**Hypocalcemia and/or Hyperparathyroidism**

_____$P_i$ wasting and RTA

_____syndrome reproduced by $P_i$ depletion

# PROXIMAL RTA: THREE SPECIFIC DEFECTS



# PROXIMAL RTA: MOLECULAR ORIGINS

- *SLC9A3* gene → encodes $NHE_3$
  candidate gene: isolated RTA

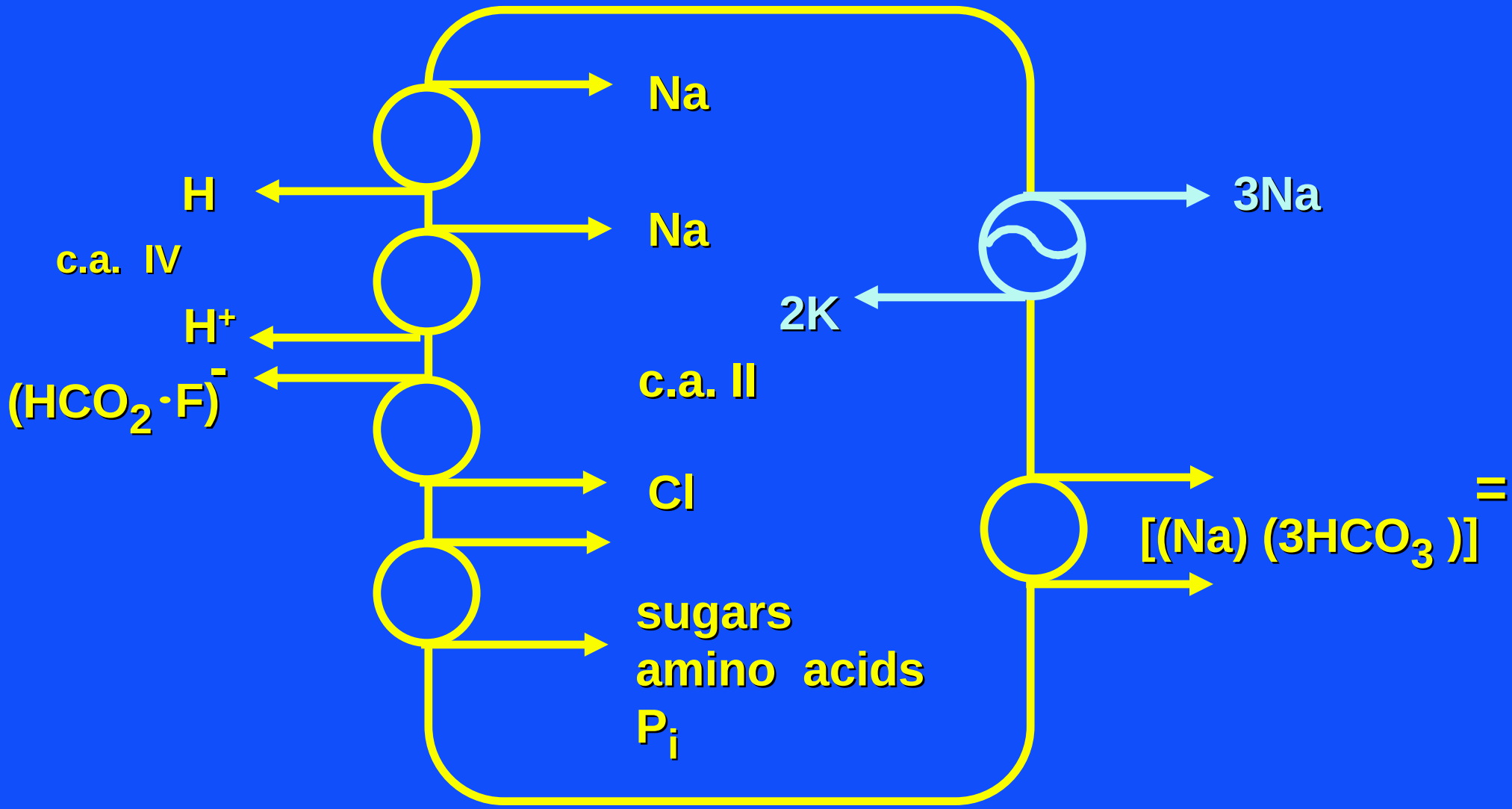
- *SLC4A4* gene → encodes (Na) ($3HCO_3$)
  proximal RTA
  ocular abnormalities

- Proximal RTA due to CA II abnormalities
  osteoporosis
  5 mutations identified to date

*J. Neph.*
15:S135, 2002

# PROXIMAL TUBULAR DISORDERS

## *GENERALIZED FANCONI SYNDROME*



# PROXIMAL RTA: CLINICAL SPECTRUM

- Infantile
- Genetic disorders:
  cystinosis, HFI, Wilson's disease
- Hyperparathyroidism
  primary
  secondary: chronic hypocalcemia
- Gammopathies, especially light chain disease
- Drugs
- Renal transplantation

# PROXIMAL RTA: TREATMENT

- $Na^+$ restriction: ↑ proximal rates of fluid absorption
- $K^+$ supplementation

# THE RTA SYNDROMES

| Syndrome | Locus | Defect |
|---|---|---|
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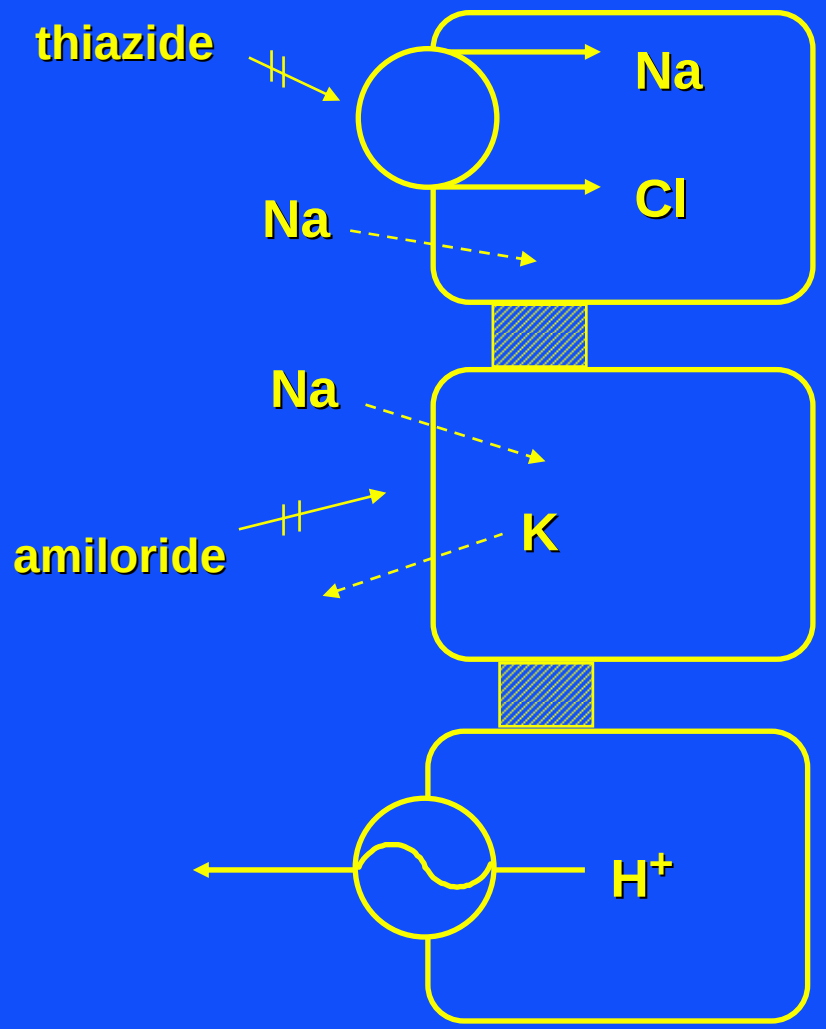
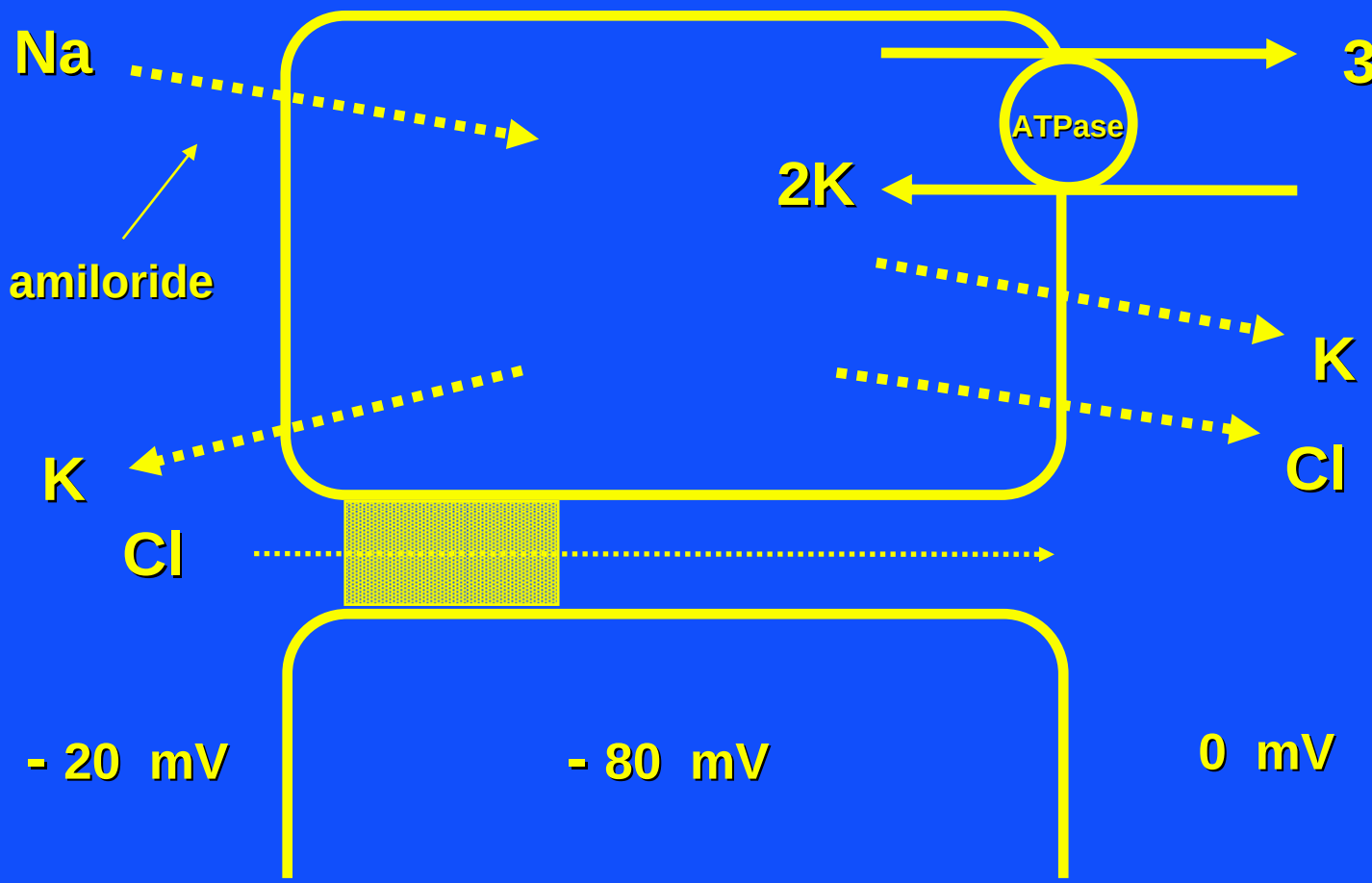
| hyperkalemic | CCD<br>principal<br>cell | ↓ $V_M$ (-) ⟶ ↓ $H^+$ secretion |
| gradient-limited | OMCD<br>intercalated<br>cells | three specific defects in $H^+$ secretion |

# AXIAL HETEROGENEITY OF THE DISTAL NEPHRON

| Cell | Lumen Voltage |
|---|---|
| DCT | - |
| CCT | - |
| OMCD | + |

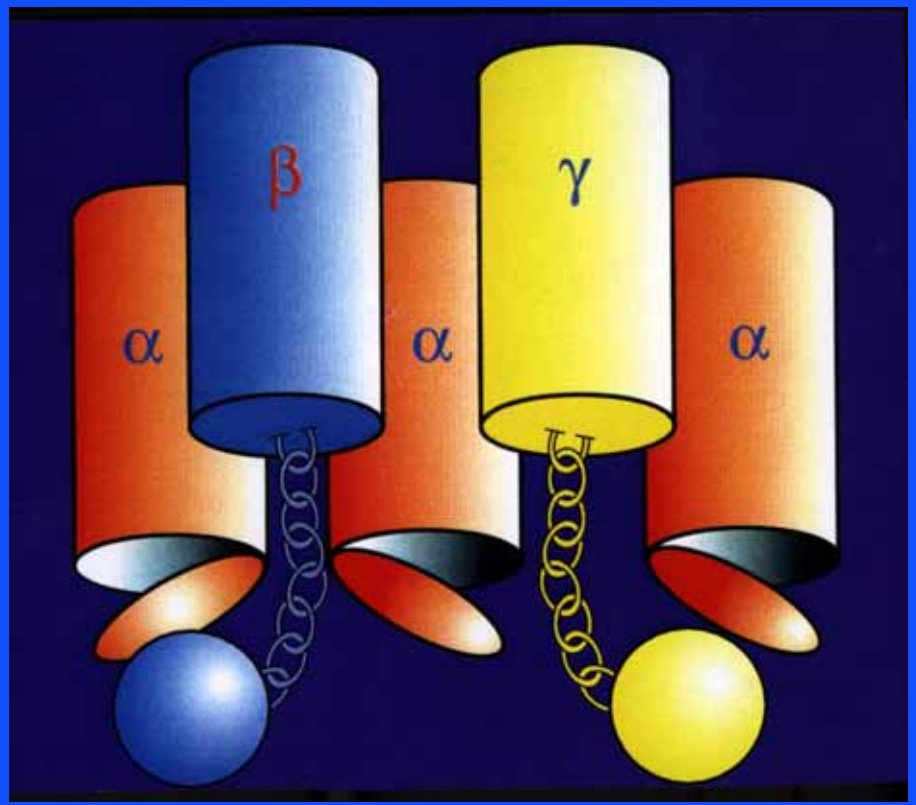


# THE CCD PRINCIPAL CELL




- Predominant in late DCT and CCT
- Aldosterone-responsive
- Sensitive to:
  - amiloride
  - triamterene
  - spironolactone

# ENaC
## *Epithelial Na Channel*




- Each α subunit :
  *amiloride-sensitive Na channel*
- β and γ subunits:
  ↑ *surface delivery of ENaC*
- Liddle's syndrome:
  *β subunit mutation*
- pseudohypoaldo I:
  *α or β subunit mutation*
- ARDS
  *α subunit mutation*

*News in Physiol. Sci.*
12:55, 1997

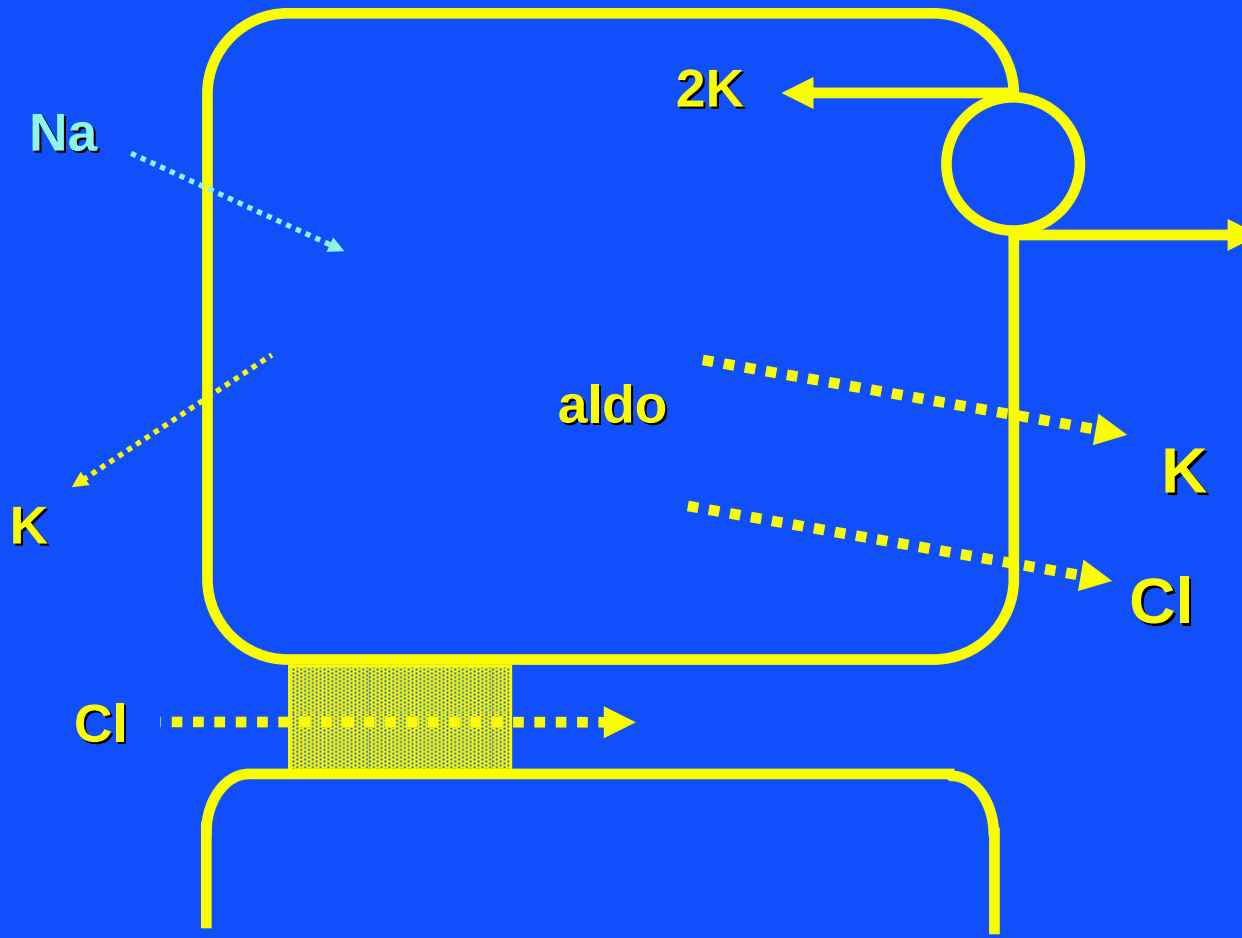
# HYPERKALEMIC RTA SYNDROMES

## *PRINCIPAL CELL DISORDERS*

| DISORDER | PRINCIPAL DEFECT | PRINCIPAL FEATURES |
|---|---|---|
| Pseudohypoaldosteronism I | Closed $Na^+$ channel | ↑ $K^+$; $Na^+$ wasting; RTA |
| Gordon's syndrome | CCT: ↑ $Cl^-$ shunt and DCT: WNK activation of NCC | ↑ $K^+$; $Na^+$ avidity; RTA |
| Interstitial disease | Hyporeninemic hypoaldosteronism | ↑ $K^+$; $Na^+$ wasting; RTA |

# PRINCIPAL CELL DISEASES

## *$Na^+$ CHANNEL BLOCKADE (PSEUDOHYPOALDOSTERONISM I)*

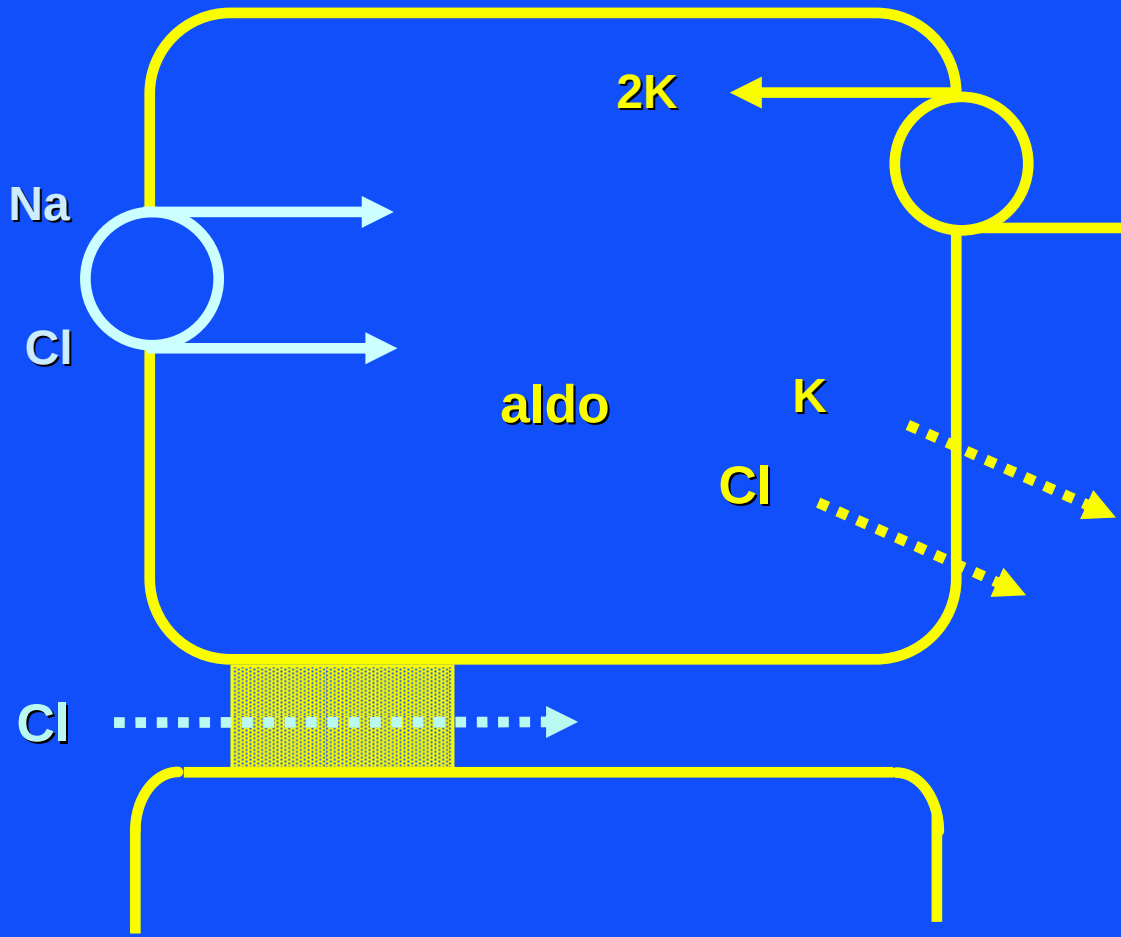



**<u>Na Channel Blockade</u>:**

- Prototype: amiloride Rx
- Na wasting
- ↓ $V_M$
- ↓ K, H secretion
- Aldosterone unresponsive
- $\alpha$ or $\beta$ subunit mutations in ENaC

# DISTAL CONVOLUTED TUBULE DISEASE

## *GORDON'S SYNDROME (PSEUDOHYPOALDOSTERONISM II)*

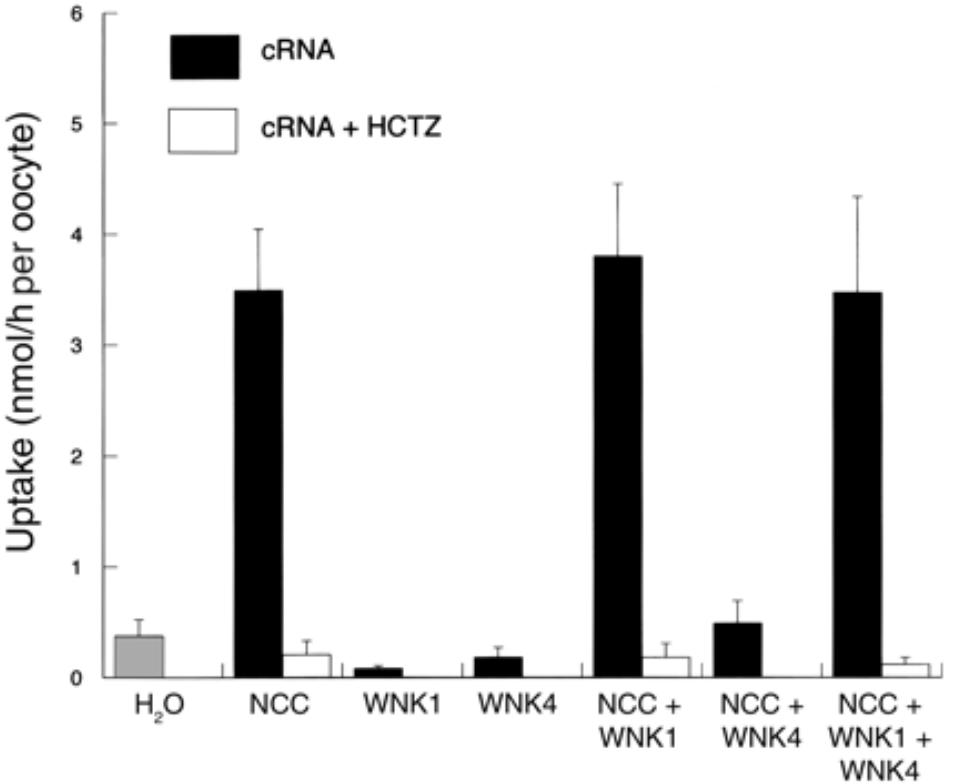



**WNK 1, 4 mutations activate thiazide-sensitive NaCl transporter**

- ↑ shunt Cl permeability; paracellin-mediated
- Na avid
- ↓ $V_M$
- ↓ K, H secretion: CCT
- low renin hypertension
- responsive to diuretics, Na restriction

# GORDON'S SYNDROME

## *A DCT DISEASE*



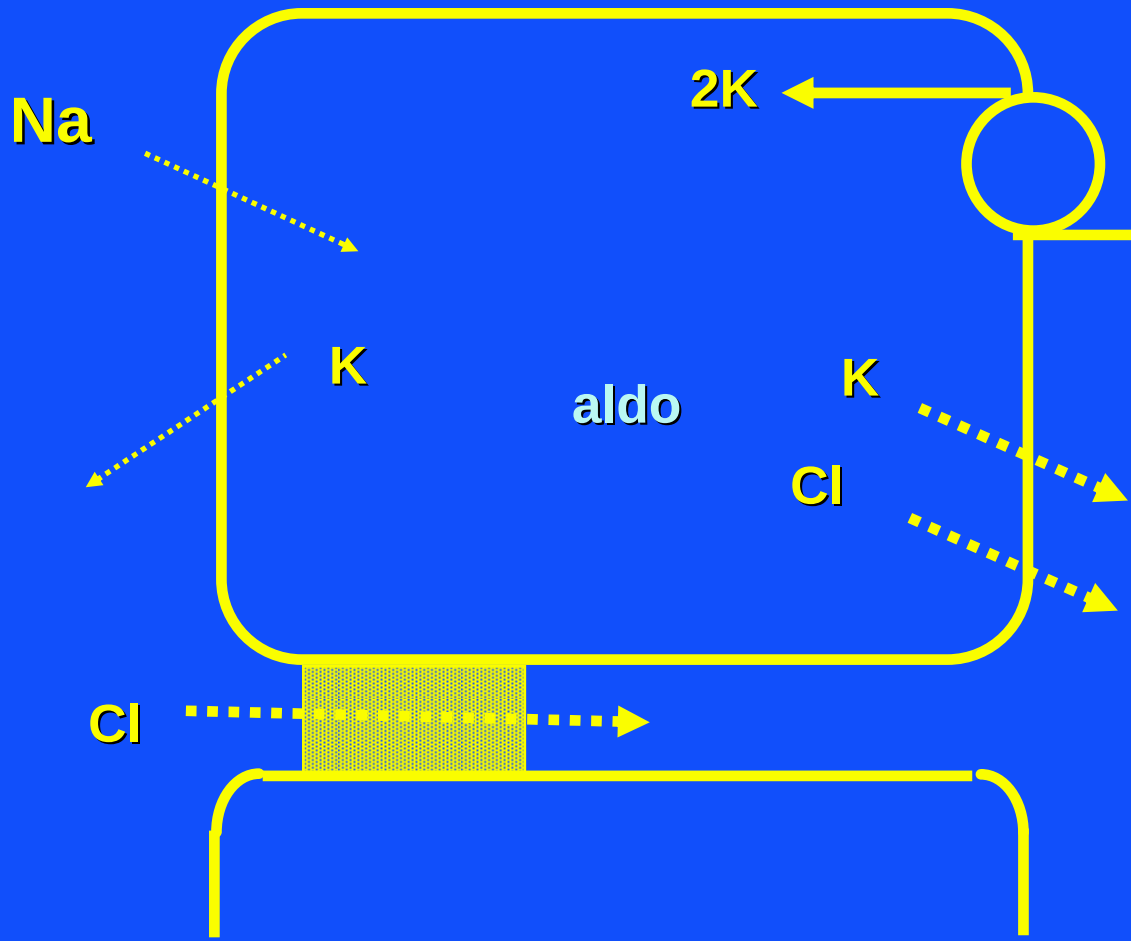

**WNK: with no lysine**
**WNK I: ↑ NCC activity**
**WNK IV: function unknown**

**Yang *et al.***
***JCI* 111:1039, 2003**

# PRINCIPAL CELL DISEASES

## *HYPORENINEMIC HYPOALDOSTERONISM*

## *(GENERALIZED DISTAL NEPHRON DISEASE)*




- Interstitial renal disease
- ↓ renin, aldosterone
- Na wasting
- ↓ $V_M$
- ↓ K, H secretion
- low renin hypertension
- furosemide benefits

# "INTERSTITIAL" RTA: MAJOR UNCERTAINTIES

## Pathophysiology

1) Failure to secrete aldosterone in response to hyperkalemia

2) Renal unresponsiveness to Florinef

3) Precise roles of : { ANP; renal prostacyclin production }

## Treatment

1) Balance between ↑ distal $Na^+$ delivery and b.p.

# HYPERKALEMIC RTA

- **Clinical spectrum:**
  - **generalized disease: interstitial nephritis**
  - **$Na^+$ channel blockade: amiloride**
  - **anti-aldosterone drugs**

- **Treatment:**
  - **↑ $Na^+$ delivery to CCD**
    - ***$Na^+$, Lasix, daily weights***

- **Key unsolved issue:**
  - **Failure of hyperkalemia to ↑ aldo secretion**

# THE RTA SYNDROMES

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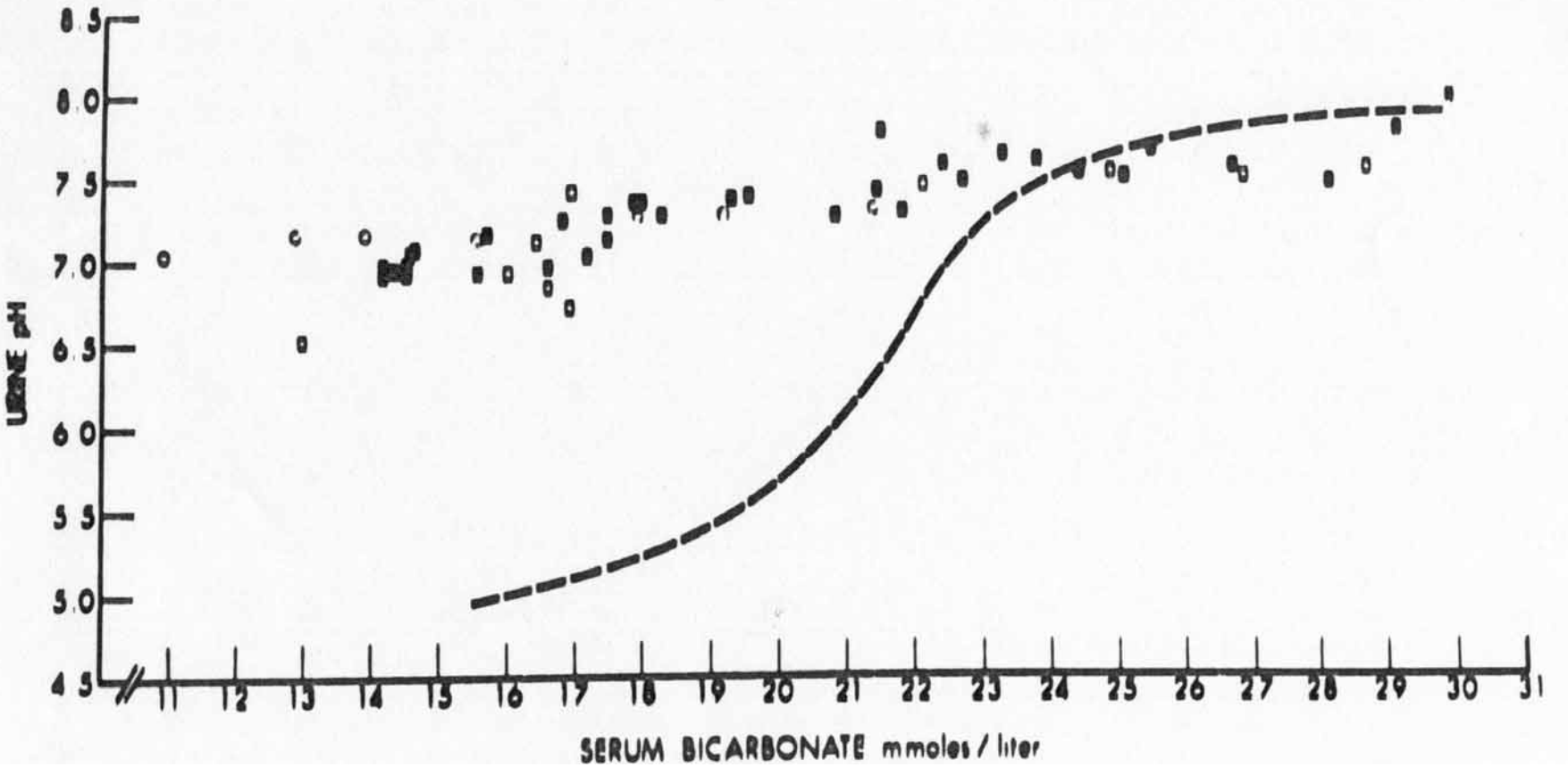
# BICARBONATE TITRATION CURVE IN GRADIENT-LIMITED RTA



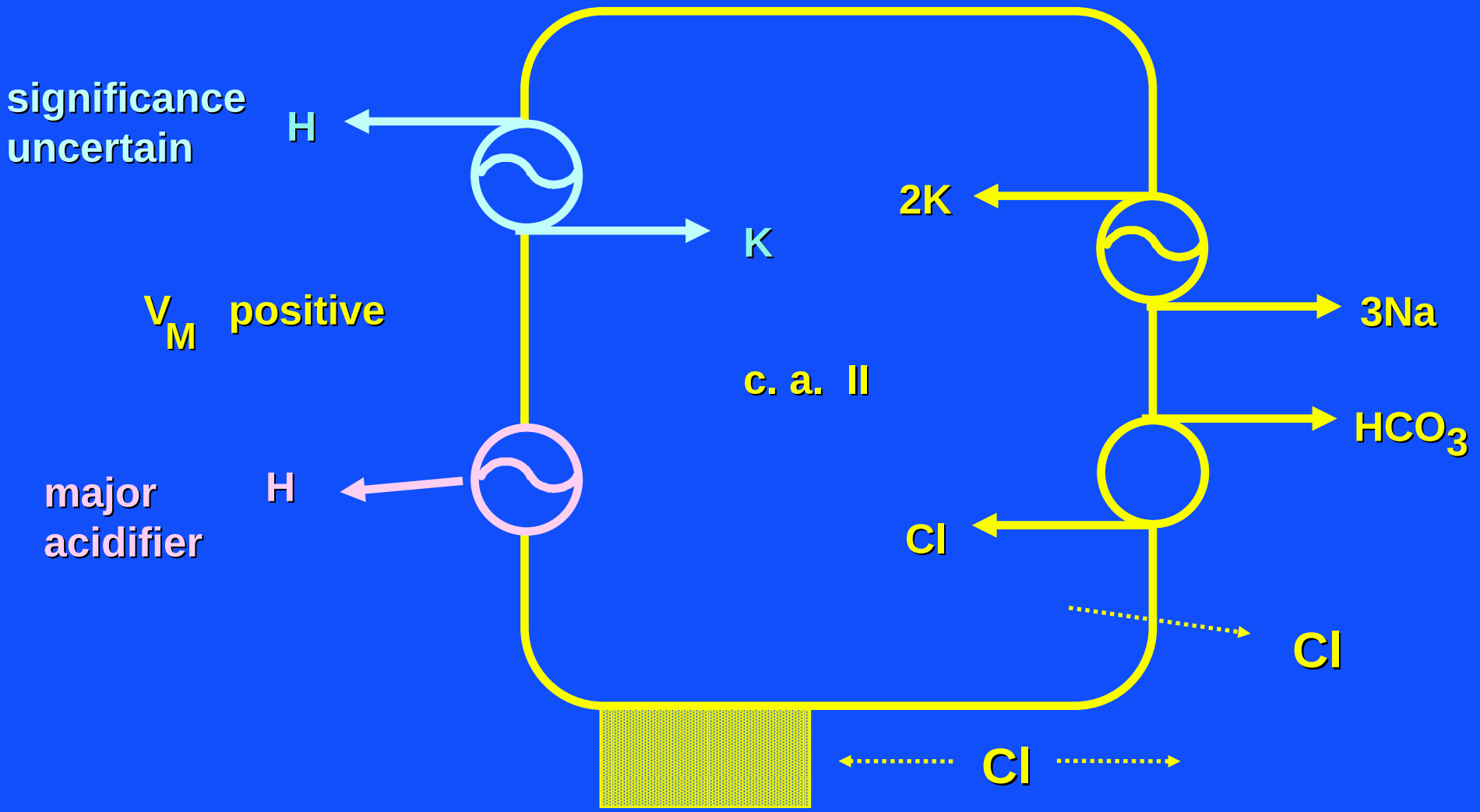
# GRADIENT-LIMITED DISTAL RTA

## *HYPOKALEMIC RTA*

- INAPPROPRIATELY ALKALINE URINE
- $HCO_3$ - RESPONSIVE ACIDOSIS
- K WASTING
- HYPERCALCIURIA AND NEPHROCALCINOSIS

# THE OMCD

## *TYPE A INTERCALATED CELL*

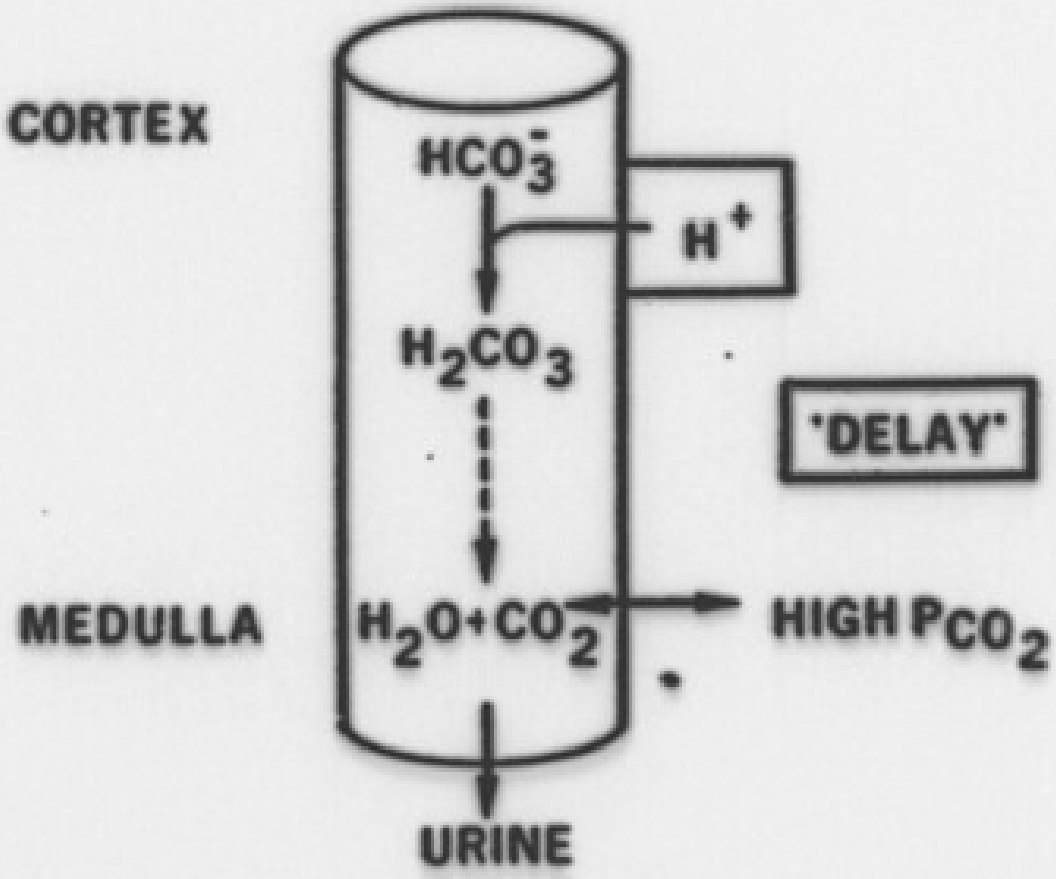


# THE (U-B) $pCO_2$ TEST

1. Alkaline diuresis with normally absent distal lumen c.a.
2. If distal $H^+$ secretion adequate:

$H_2CO_3$ formation
delayed $H_2CO_3$ dehydration
↑ (U-B) $pCO_2$

# THE U-B $P_{CO_2}$ DIFFERENCE

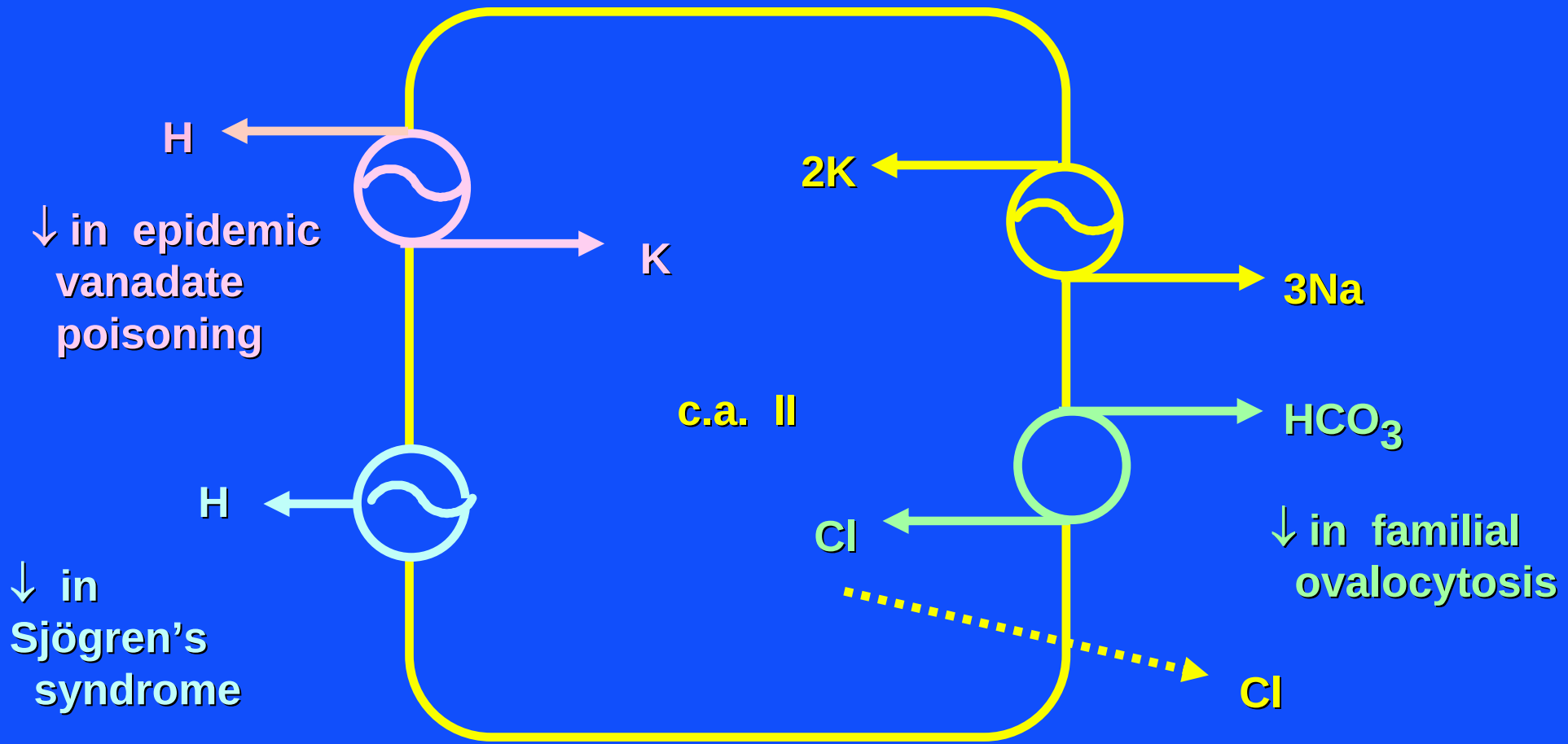


# HYPOKALEMIC DISTAL RTA: AN INTERCALATED CELL DISORDER

**Amphotericin B:** molecular "leak" model
probable $HCO_3$ leak
$\uparrow$ (U-B) $pCO_2$

**All others:** $\downarrow$ (U-B) $pCO_2$
pump deficit
$H^+$, $H_2CO_3$ leak

# GRADIENT-LIMITED RTA
## *AN INTERCALATED CELL DISEASE*



# BAND 3 MUTATIONS IN DISTAL RTA

- *AEI* (chromosome 17) codes for band 3 protein:
  911 amino acid $Cl^-/HCO_3^-$ exchanger

- Distal RTA: recessive band 3 mutations
  histidine for arginine - 589
  aspartate for glycine - 701
  val 850 deletion
  aspartate for alanine - 701

- 27 base deletion on *AEI* → deletion of a.a. 400-408
  *dominant mutation*
  *ovalocytocis (S.E. Asia)*
  *no RTA*

*Kidney Int.*
62:10, 2002

- Ovalocytosis + RTA: multiple mutations

# GRADIENT-LIMITED RTA
## *CLINICAL FEATURES*

- Impaired growth in children
- Inappropriately alkaline urine
- Hypokalemic muscle paralysis
- Hypercalciuria; nephrocalcinosis

# GRADIENT-LIMITED RTA
# *CLINICAL SPECTRUM*

- **Genetic:**
  - ***isolated***
  - ***sickle cell disease***
  - ***Ehler - Danlos***
- **Autoimmune disease**
- **Primary Hyperparathyroidism**
- **Drugs**
  - ***amphotericin B***
  - ***lithium***

# GRADIENT-LIMITED RTA
## *TREATMENT*

- **$NaHCO_3$ replacement:**
  - **adults: ~ 70 mEq/day**
  - **children: massive initial Rx**

- **$K^+$ supplementation**