F2 莊惠倫
指導：張志宗 醫師

- Story beginning…
- Clinical presentation
- Differential diagnosis
- Bartter's syndrome
- Gitelman's syndrome
- Treatment
- What's else ?

Not so long ago…

1957 First case report:

2-month-old African-American boy

diarrhea, dehydration, failure to thrive,

persistent hypokalemia,

metabolic alkalosis,

hyperkaluria

1962 Bartter and colleagues:

Three African Americans:

5-year-old boy, 6-year-old girl, 25-year-old man

- Hypokalemia
- Hypochloremic metabolic alkalosis
- Increase urine excretion of K and PGs
- Renin, Aldosterone ↑ , but normotension
- Vascular resistance to Angiotensin II
- Hyperplasia of JG apparatus

- 1966 Gitelman et al

  hypomagnesemia & hypocalciuria
- 1988 28 cases review:

  in siblings or

  in children of consanguineous marriages

  ➔ autosomal recessive inheritance
- 1992 Gitelman

  A rose is a rose, or is it?

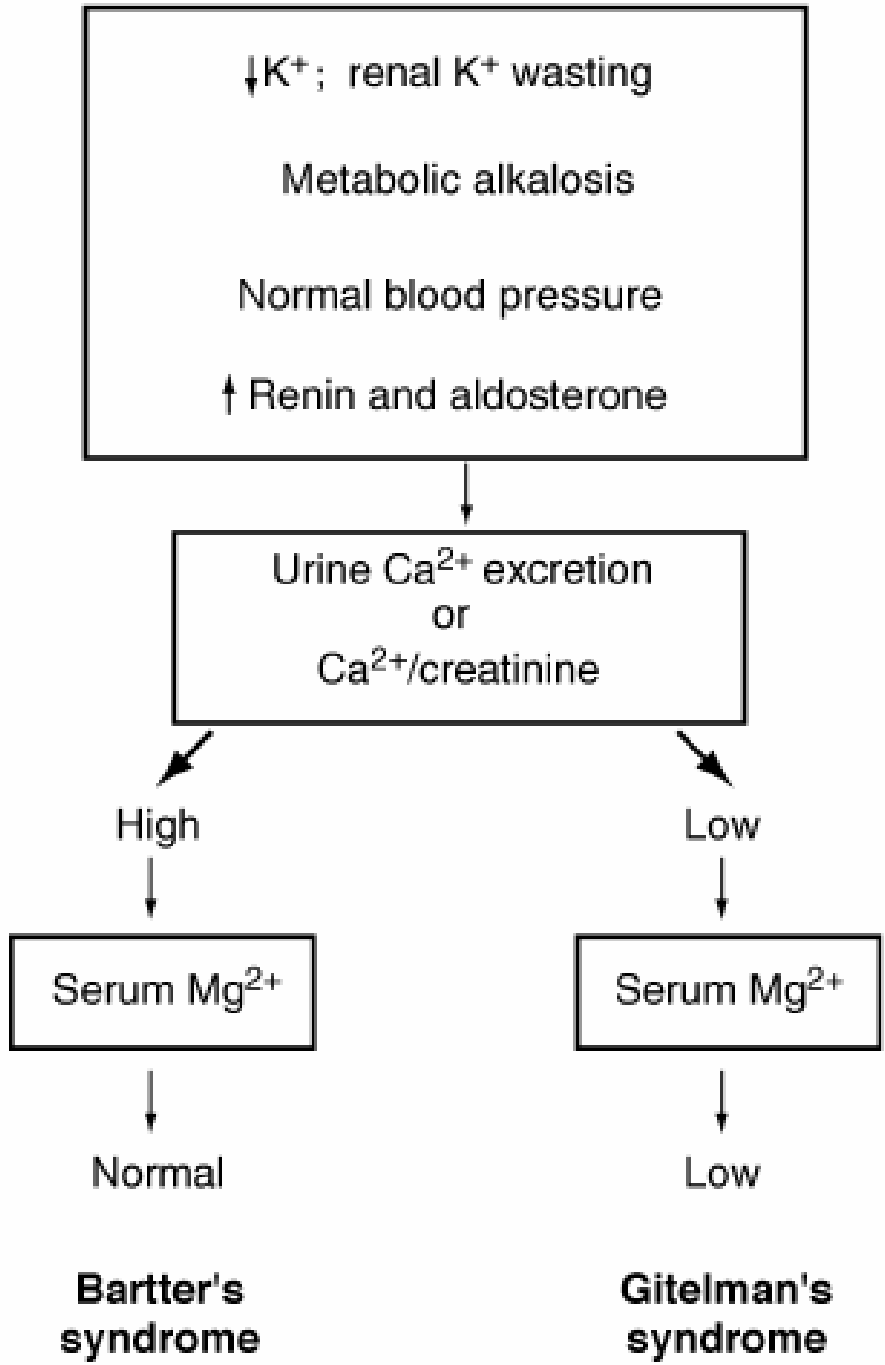
- Story beginning…
- Clinical presentation
  - What's the difference ?
- Differential diagnosis
- Bartter's syndrome
- Gitelman's syndrome
- Treatment
- What's else ?

Clinical presentation ~ Bartter

- Occurred in first few years of life
- Polydipsia, polyuria, nocturia
- Growth retardation - common
- Fatigue and generalized muscle weakness
- Hypokalemia and metabolic alkalosis
- Plasma renin activity, angiotensin II & aldosterone ↑ ↑
- Normotension
- Urinary excretion PG ↑

Clinical presentation ~ Gitelman

- A milder and later clinical presentation
- Diagnosed in school age children or adult
- Polyuria & polydipsia – not prominent
- Growth retardation – not prominent
- Fatigue and generalized muscle weakness
- Hypokalemia & metabolic alkalosis
- Plasma renin activity↑↑, aldosterone ↑/normal
- Normotension
- Urinary PG excretion normal
- Hypocalciuria and hypomagnesemia


↓K+; renal K+ wasting
Metabolic alkalosis
Normal blood pressure
↑ Renin and aldosterone
Urine Ca2+ excretion
or
Ca2+/creatinine
High
Low
Serum Mg2+
Serum Mg2+
Normal
Low
Bartter's syndrome
Gitelman's syndrome

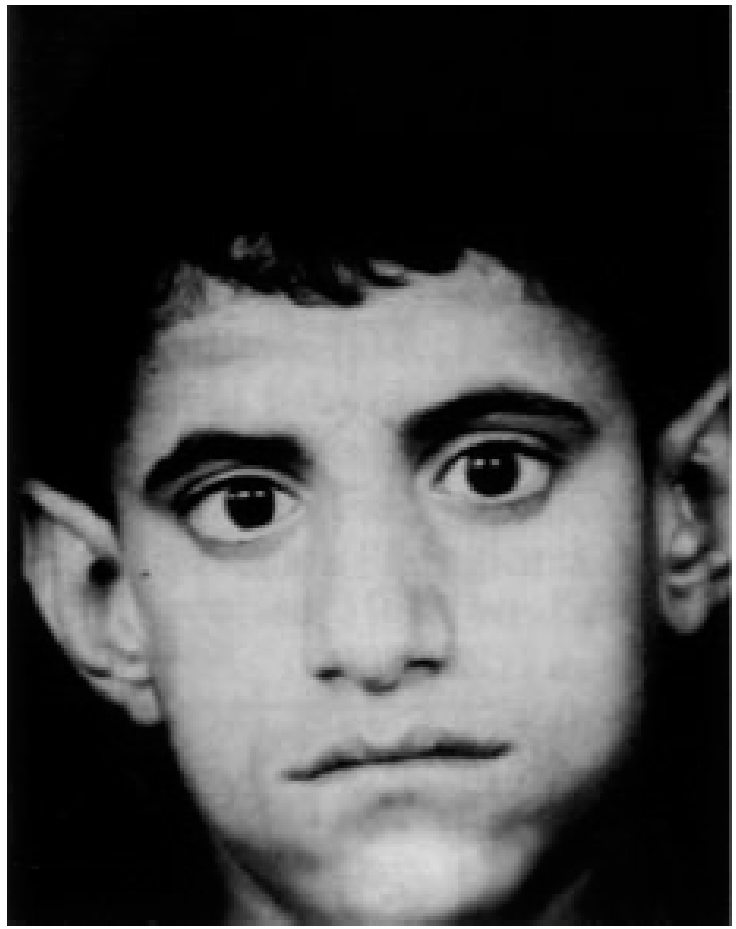
Bartter's syndrome	Gitelman's syndrome
Salt wasting	Salt wasting
Hypokalemia	Hypokalemia
Alkalosis	Alkalosis
High plasma renin activity and aldosterone	High plasma renin activity and aldosterone
✓ Childhood	Adulthood
✓ Hypercalciuria	Hypocalciuria
✓ Normomagnesemia	Hypomagnesemia

Recognize Bartter's syndrome ~ At a glance

- Prominent forehead
- Triangular face
- Drooping mouth
- Large eyes and pinnae

So, what do they look like ?


PRAY FOR MERCY



- Story beginning…
- Clinical presentation
- Differential diagnosis
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Differential diagnosis

- Renal
  - Renal artery stenosis, renin-secreting tumor…
  - Diuresis use/abuse
  - Tubular dysfunction…
- Adrenal
  - Conn's syndrome, nodular adrenal hyperplasia
    Liddle syndrome, mineralcorticoid excess…
- GI
  - Nasogastric aspiration
  - Diarrhea: congenital Cl diarrhea, colonic adenoma
    chronic laxative use…
  - Sweat: cystic fibrosis…

Difficulty in differentiation

- Very low incidence of the disease:
  1.2 cases / million

- Clinical heterogeneity

Pathogenesis

1) primary juxtaglomerular hyperplasia
2) primary insensitivity to angiotensin II
3) primary prostaglandin overproduction
4) primary defects in NaCl transport in various nephron segment
5) primary defect in K transport resulting excessive K excretion
6) primary defect in Cl transport in the TAL of henle's loop or the DCT

1) Primary juxtaglomerular hyperplasia

- Not unique feature
- A common characteristic of chronic hypovolemic states with hypokalemia
  - Chronic vomiting, chronic laxative abuse, familial Cl diarrhea…

~ Annu Rev Med., 1980

2) Primary insensitivity to angiotensin II

- Not unique feature
- Due to volume contraction,
  elevation of vasodilator: prostaglandins…

~ Eur J Clin Invest., 1993

- Volume expansion restore pressor sensitivity

~ Am J Med., 1977

- PG inhibitor reverse the pressor resistance

~ Am J Med., 1978

- Ag II antagonist cause hypotension *~ NEJM, 1976*

3) Primary prostaglandin overproduction

- Not specific feature
- In multiple disorder associated with hypovolemia and K depletion
- Mediated by hypokalemia, Ag II, ADH…

~ KI, 1986

- COX inhibitor are not sufficient to correct all the manifestations

~ Pediatr Nephrol, 1987

Pathogenesis

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4) primary defects in NaCl transport in various nephron segment
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- **Story beginning…**
- **Clinical presentation**
- **Differential diagnosis**
- **Bartter's syndrome**
  - Bartter's syndrome vs. Lasix
  - Genotypes and pump families
- **Gitelman's syndrome**
- **Treatment**
- **What's else ?**

Bartter's syndrome

- Free water clearance (C_{H2O}) ↓
  Cl clearance ↑

~ Am J Med., 1978

- Loop diuretics can produce the same physiologic derangement
  Na-K-2Cl cotransporter

~ Textbook of Clinical Nephrology, 1991

- Not response to Lasix,
  Normal response to Thiazide

~ Miner Electrolyte Metab, 1992

Bartter's syndrome	**Lasix**
Salt wasting	Salt wasting
Hypokalemia	Hypokalemia
Alkalosis	Alkalosis
Hypercalciuria	Hypercalciuria
High plasma renin activity and aldosterone	High plasma renin activity and aldosterone
	NKCC inhibition ?

Channels

- 1973 Rocha AS et al.

  NACC: Na-K-2Cl cotransporter

- 1993 Ho K et al.

  ROMK: apical K channel

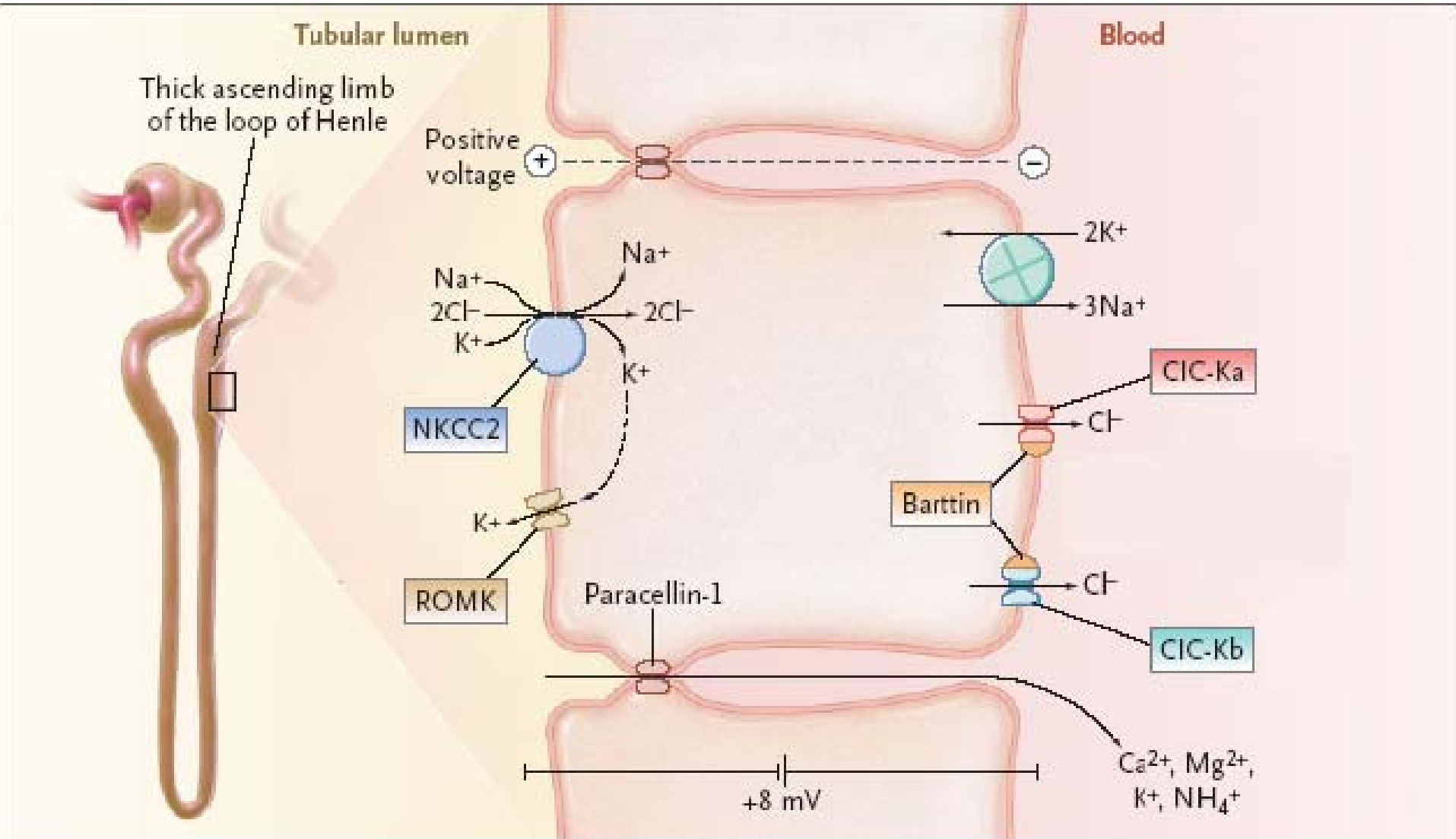
  Uchida S et al.

  ClC-Kb: basolateral Cl channel

- 1994 Hebert SC

  ROMK 1~5

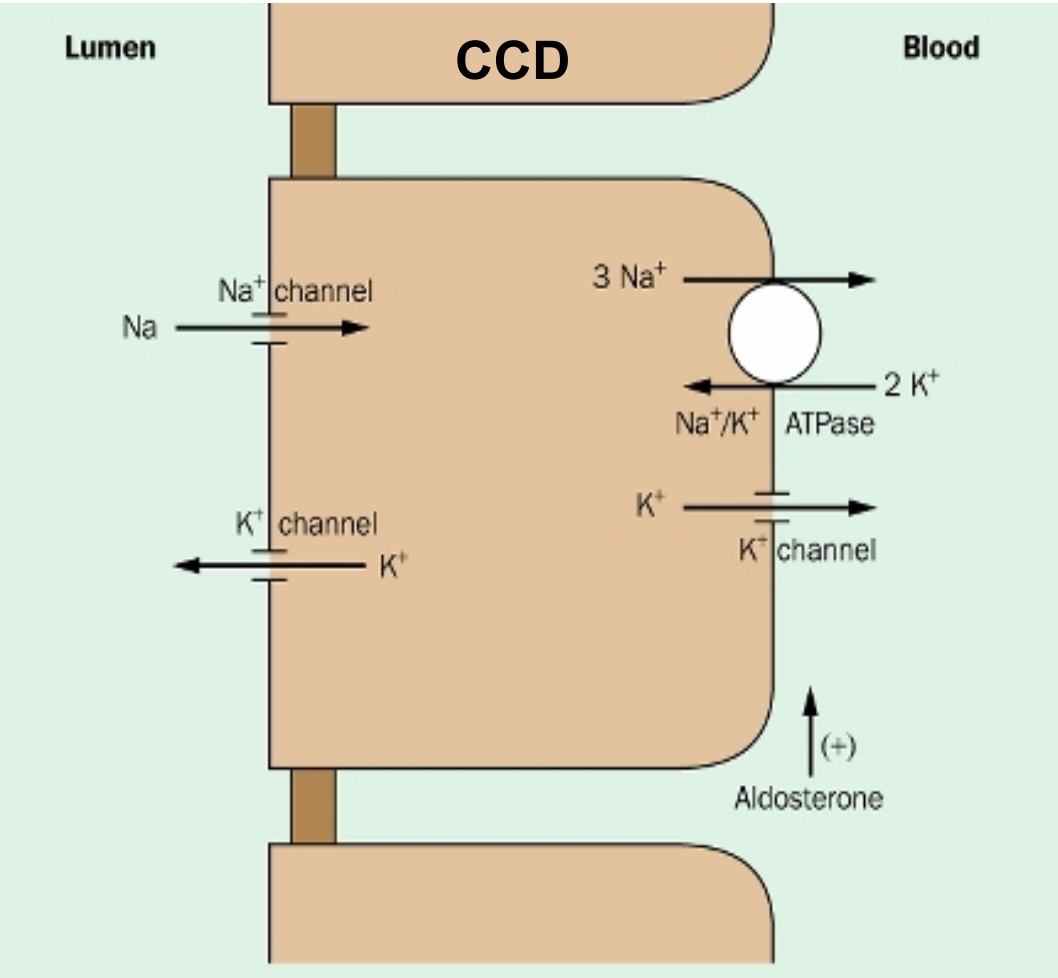
Basic effect of TAL



Polyuria

- Impaired reabsorption of NaCl in the TAL
- Salt delivery to distal nephron
- Salt wasting
- Polyuria and volume contraction

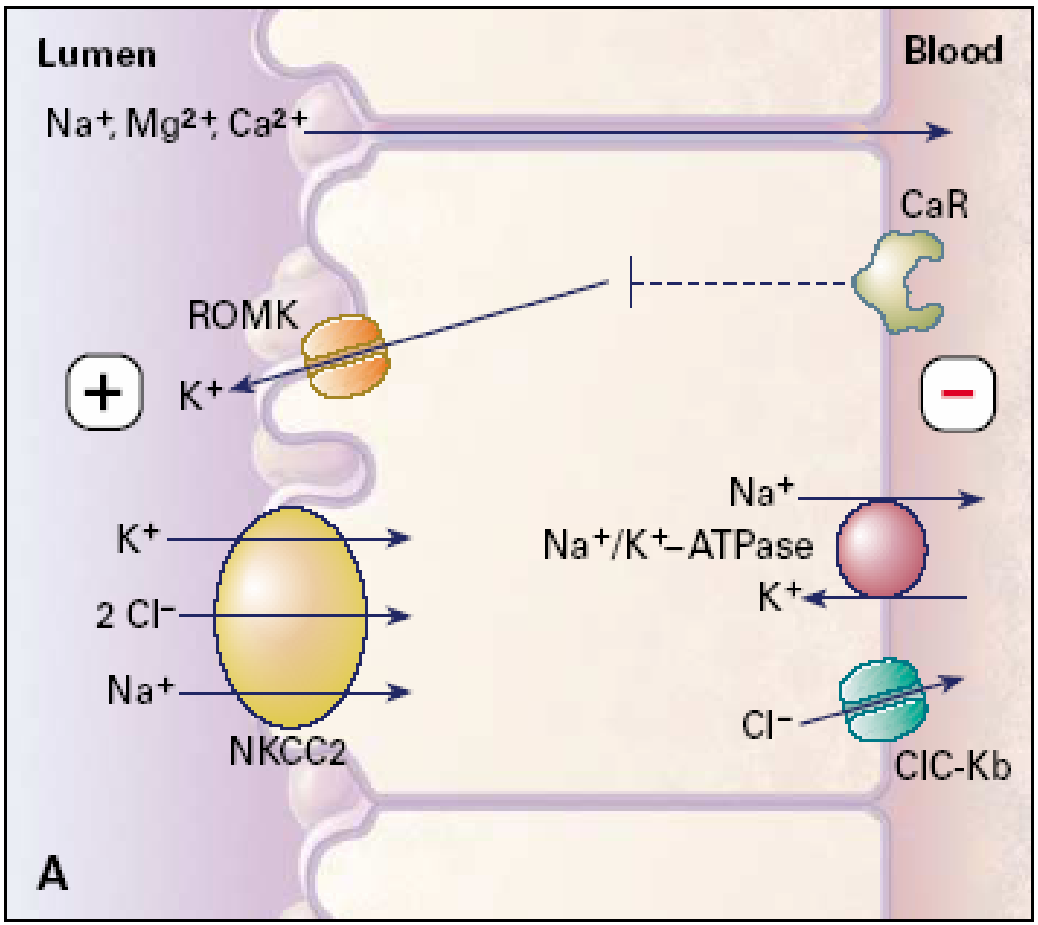
Hypokalemia



- Increase flow rate in the CCD
- Increase aldosterone-dependent ENaC activity
- Increase basolateral Na-K-ATPase
- Increase the luminal number of open Na & K channel

~ Nephron, 2002

Hypercalciuria

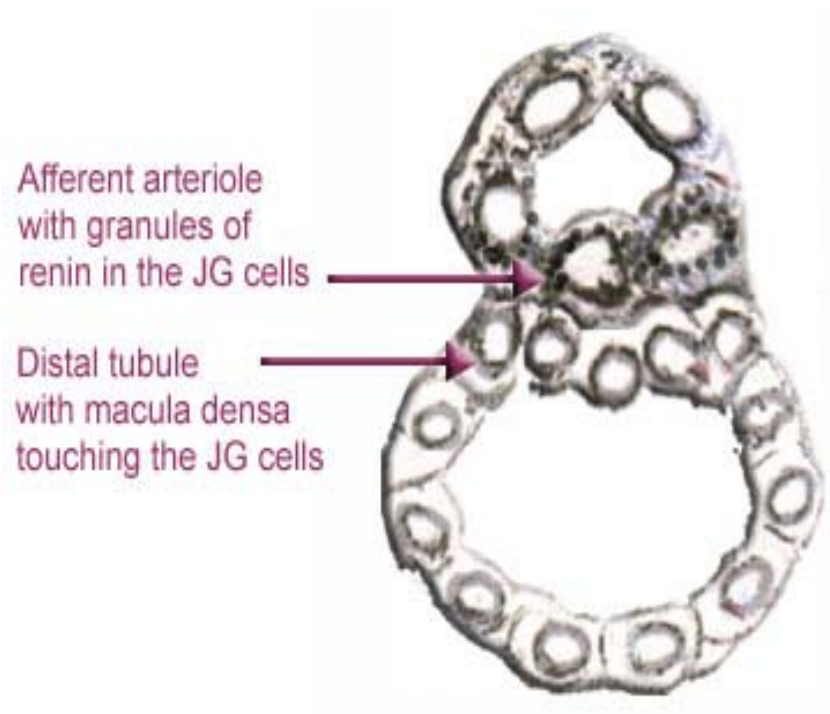


- Decrease lumen-positive transepithelial voltage
- Decrease paracellular reabsorption

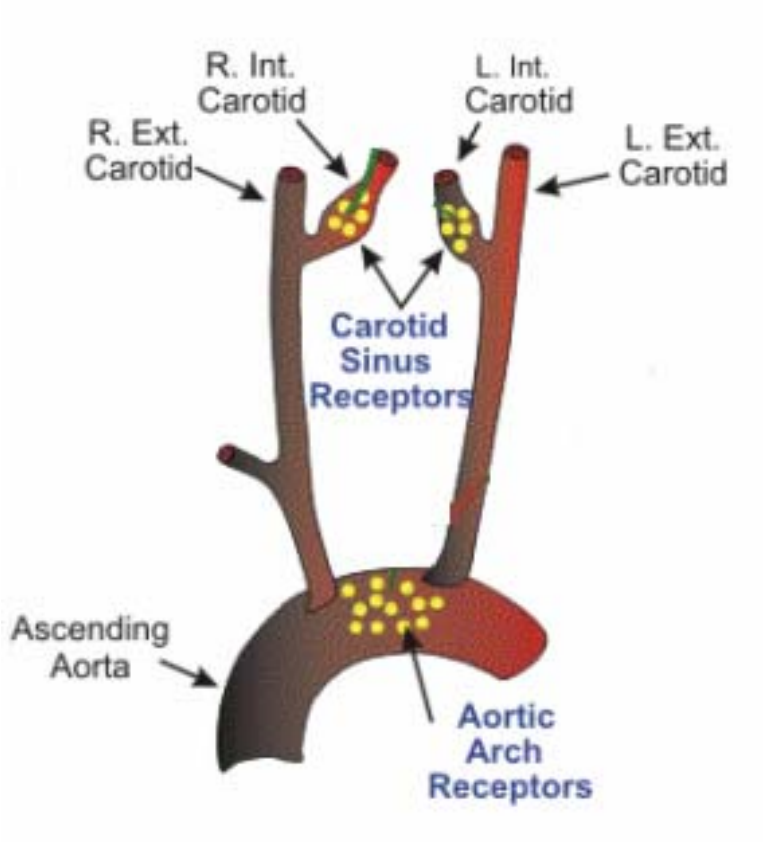
➔ Nephrocalcinosis

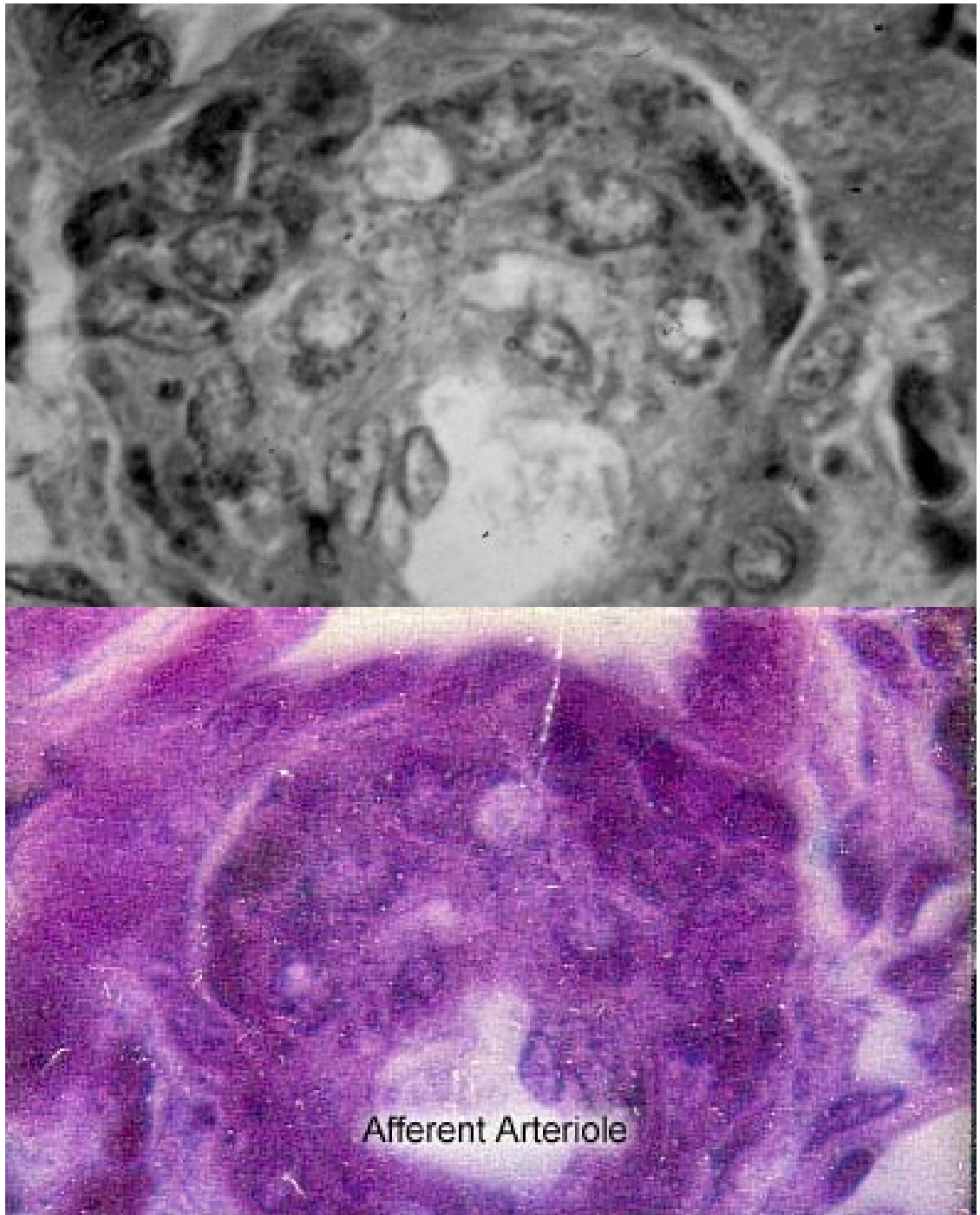
Hyperrenin & hyperaldosterone

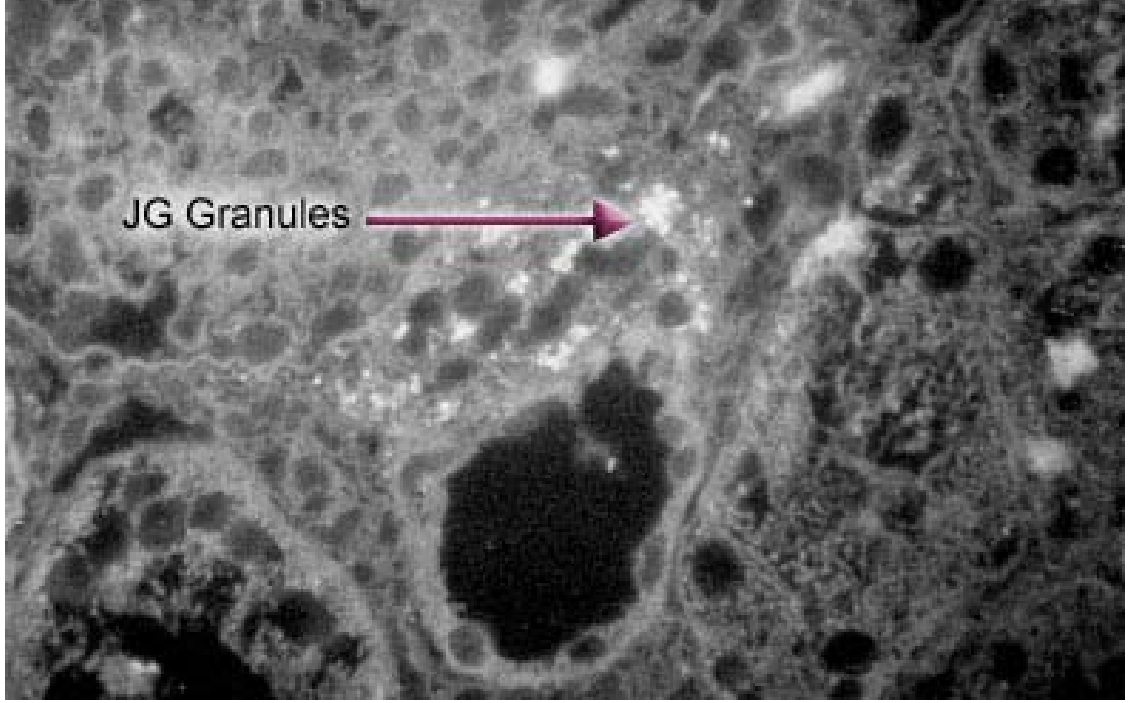
Macula densa

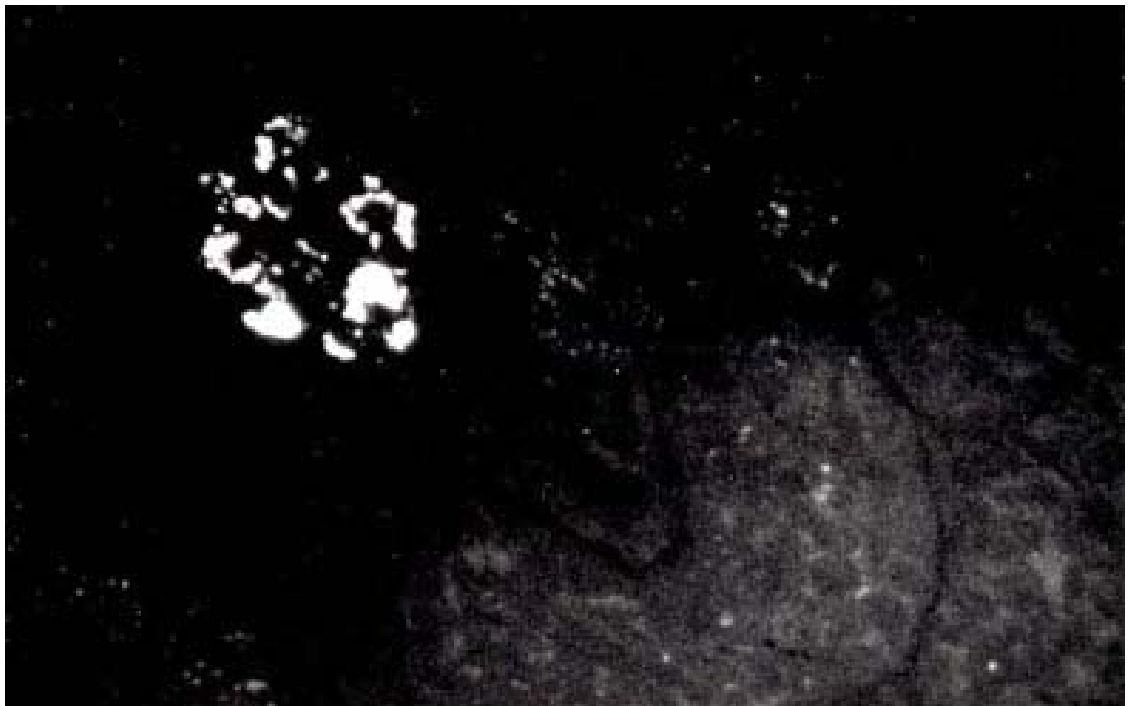


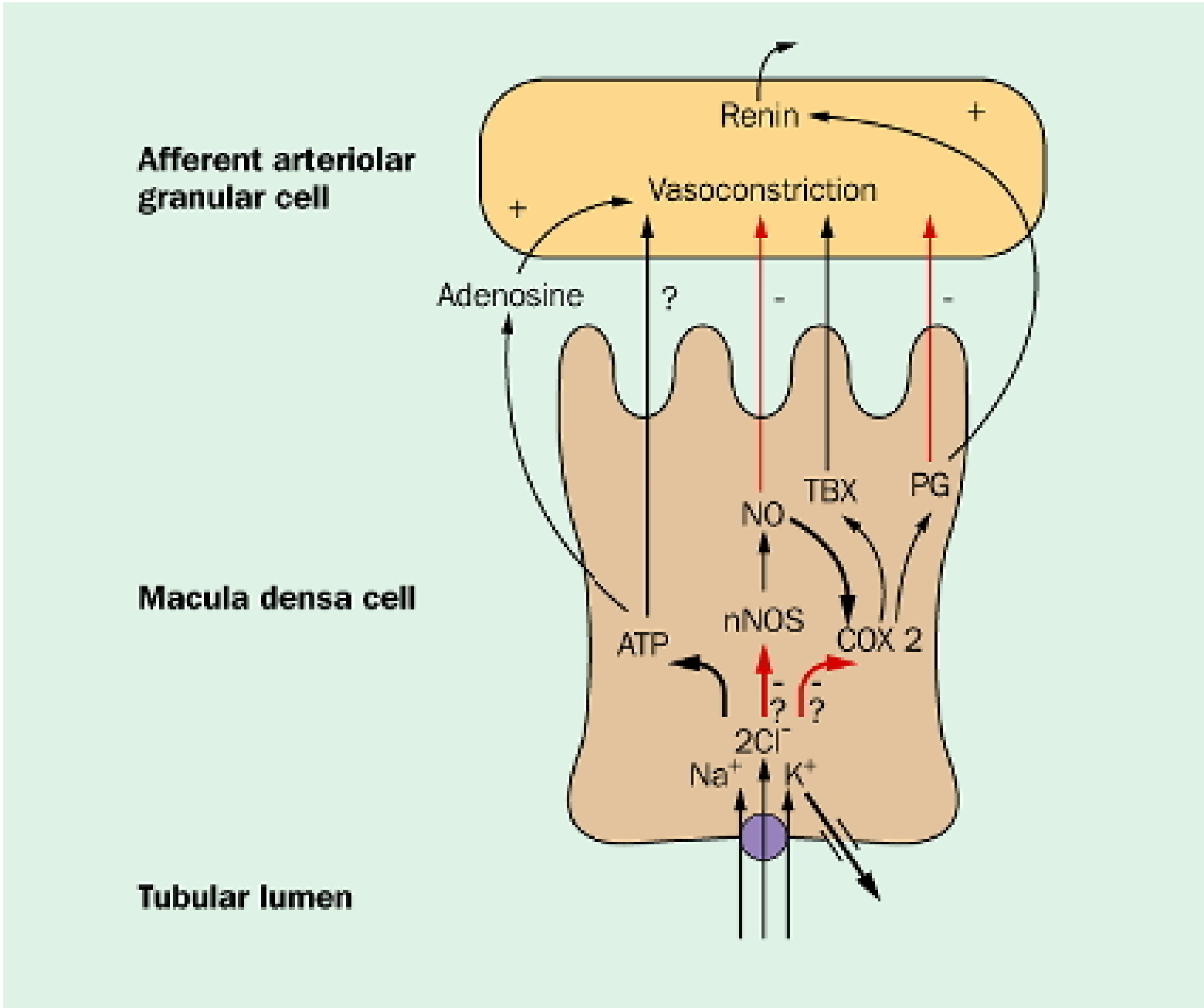
Baroreceptor

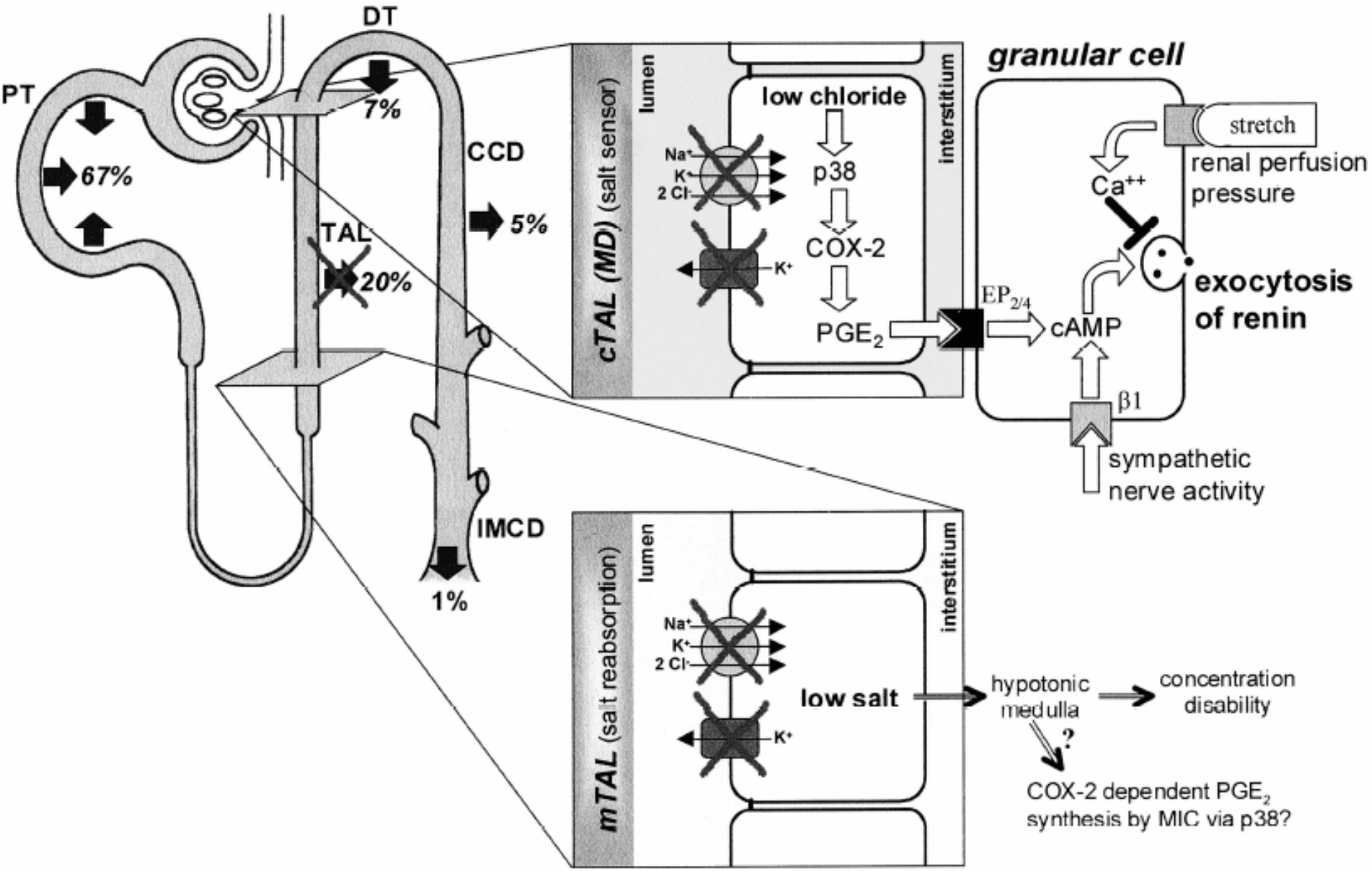



Afferent Arteriole

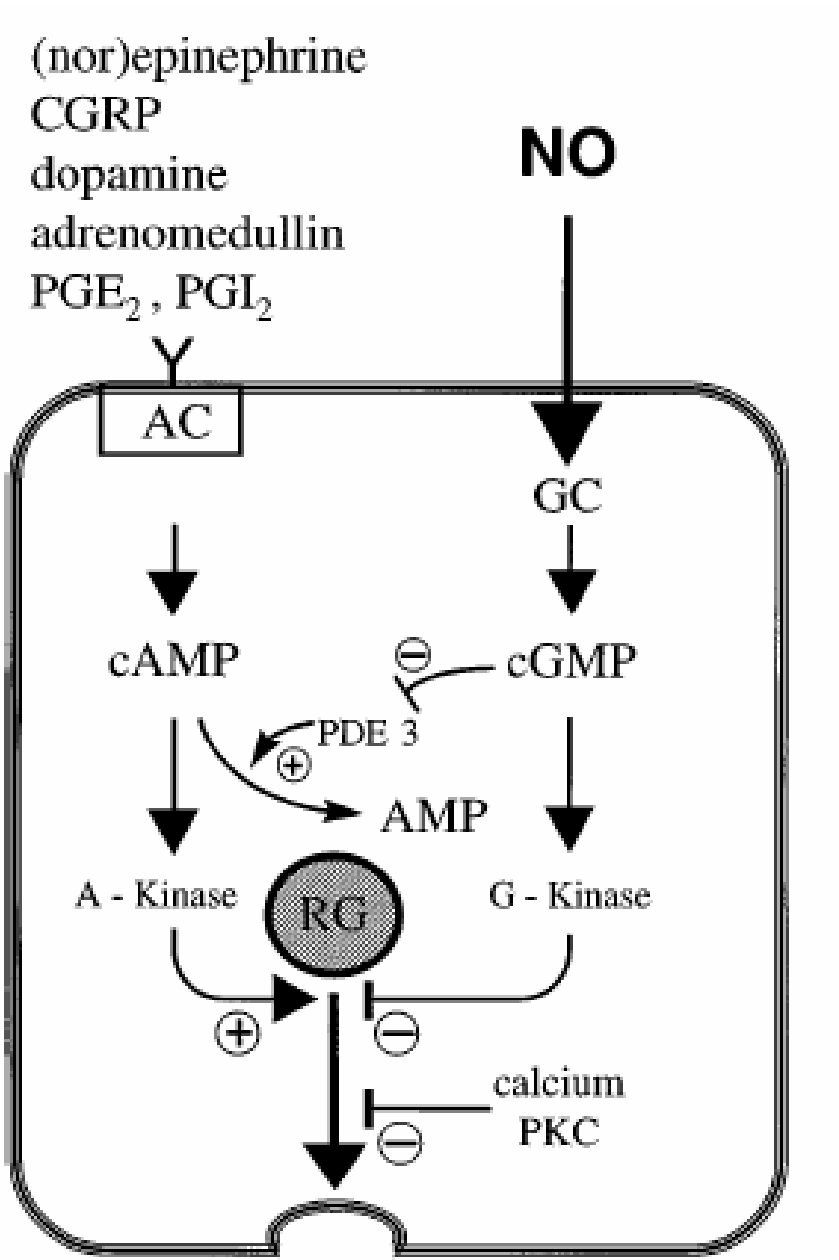

JG Granules




Afferent arteriolar granular cell
Macula densa cell
Tubular lumen
Renin
+
Vasoconstriction
+
Adenosine
?
-
-
NO
TBX
PG
nNOS
ATP
COX 2
-
?
-
?
2Cl⁻
Na⁺
K⁺


DT
PT
7%
67%
CCD
5%
TAL
20%
IMCD
1%
cTAL (MD) (salt sensor)
lumen
interstitium
low chloride
Na+
K+
2 Cl-
p38
COX-2
K+
PGE2
granular cell
stretch
renal perfusion pressure
Ca++
exocytosis of renin
EP2/4
cAMP
β1
sympathetic nerve activity
mTAL (salt reabsorption)
lumen
interstitium
Na+
K+
2 Cl-
low salt
K+
hypotonic medulla
concentration disability
?
COX-2 dependent PGE2 synthesis by MIC via p38?

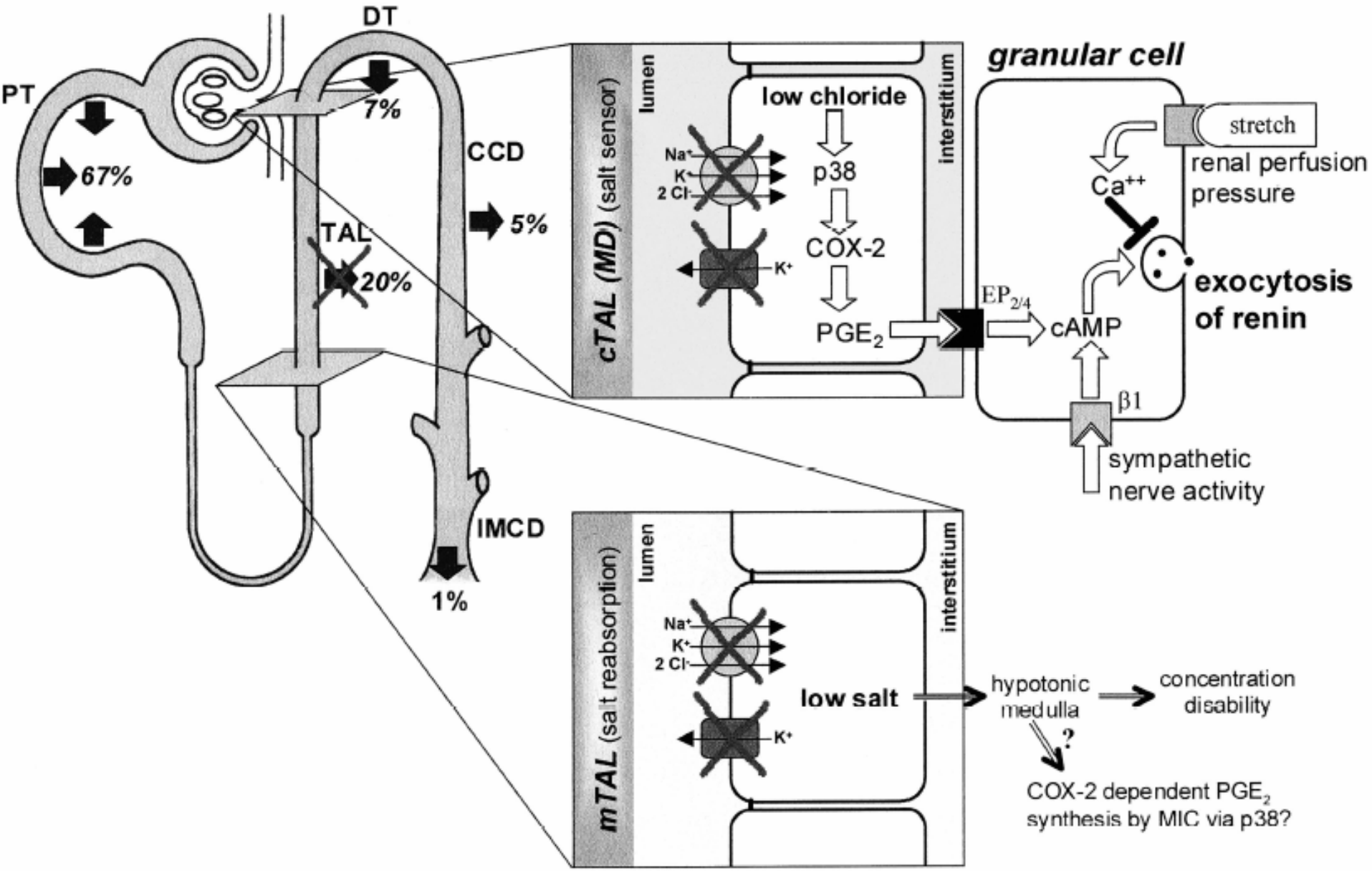
~KI, 2002


(nor)epinephrine
CGRP
dopamine
adrenomedullin
PGE_2 , PGI_2
NO
AC
GC
cAMP
cGMP
PDE 3
AMP
A - Kinase
RG
G - Kinase
calcium
PKC

Hyperprostaglandinemia

- Cyclooxygenase 1 (COX-1)
  - In principle cell
  - Modulate salt & water absorption
- Cyclooxygenase 2 (COX-2)
  - In macula densa cell
  - Involve glomerular-tubular feedback

~ Curr Opin Nephrol Hypertens, 2003


DT
PT
7%
67%
CCD
5%
TAL
20%
IMCD
1%
cTAL (MD) (salt sensor)
lumen
interstitium
low chloride
Na+
K+
2 Cl-
p38
COX-2
K+
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granular cell
stretch
renal perfusion pressure
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exocytosis of renin
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sympathetic nerve activity
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Na+
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low salt
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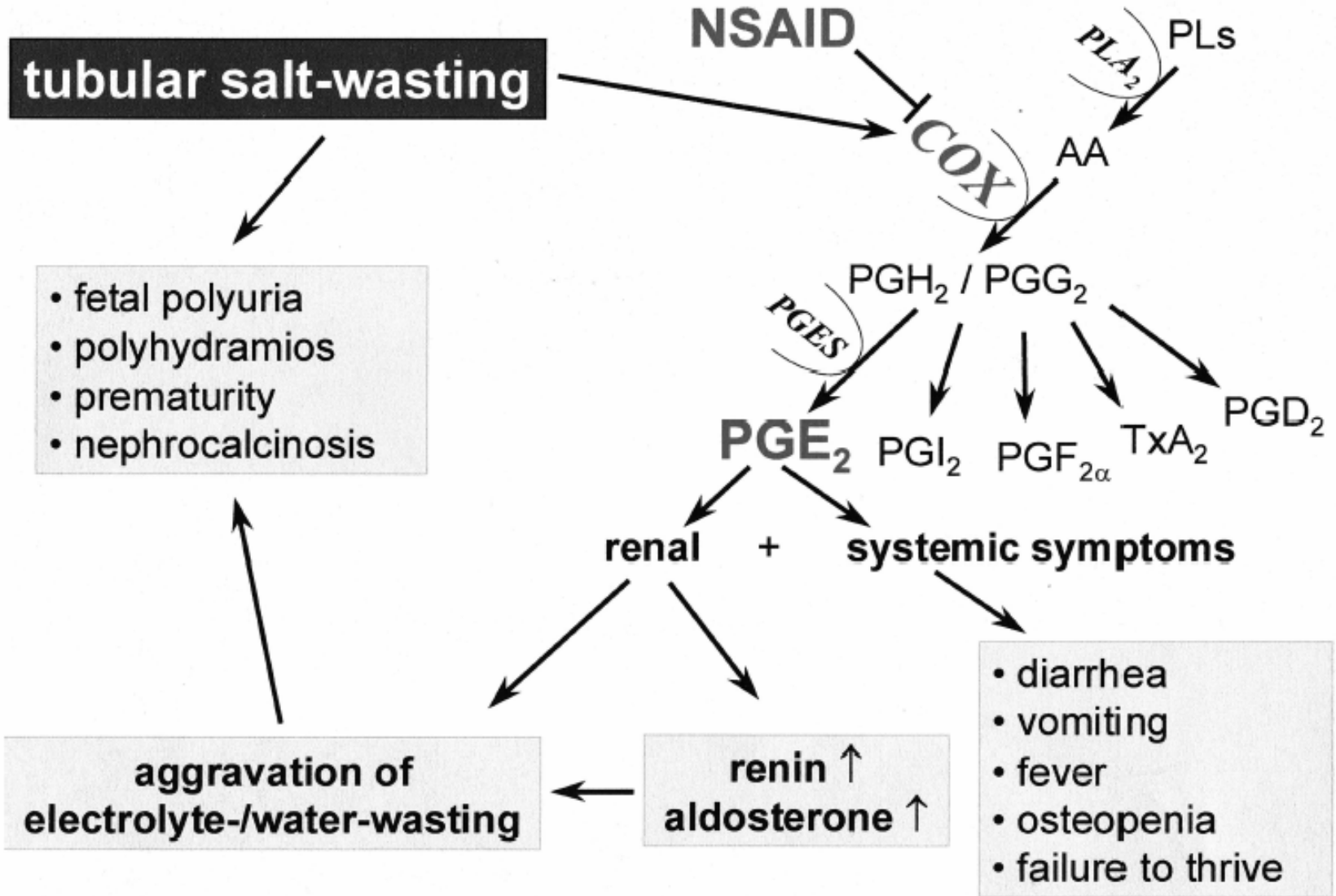
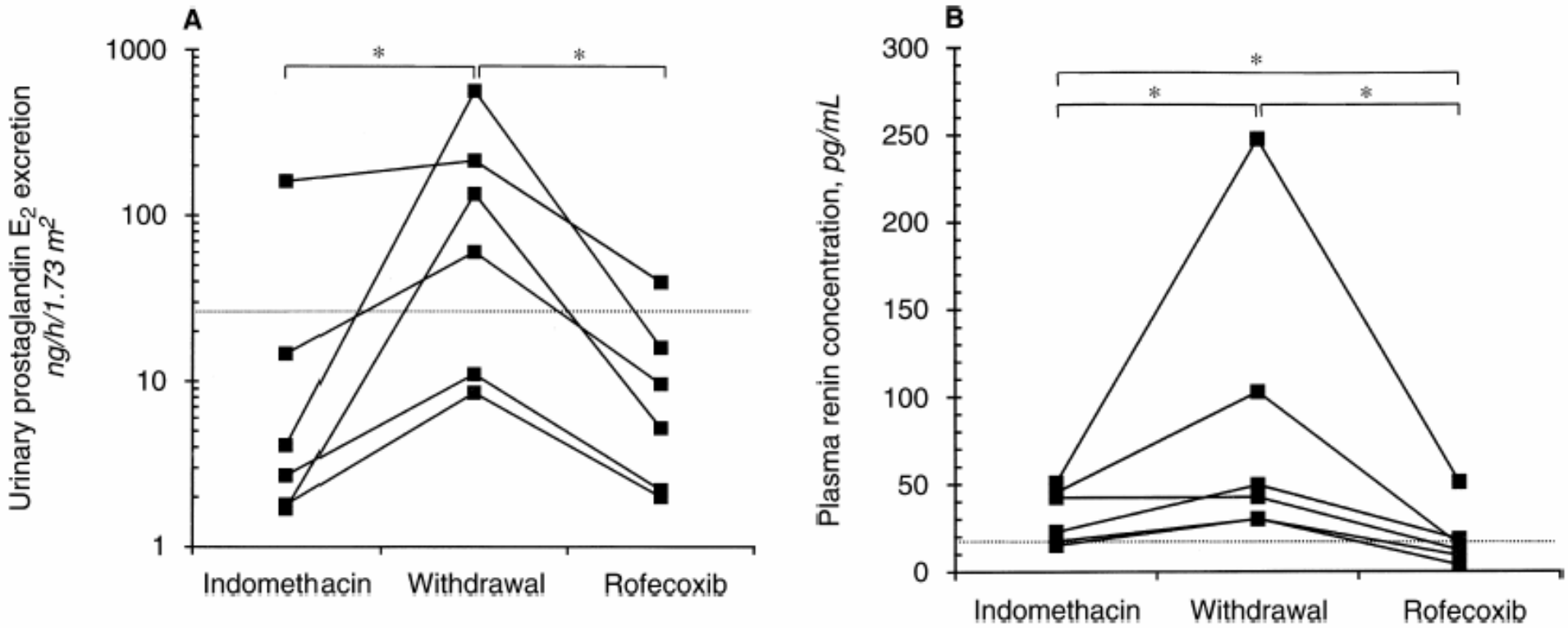
concentration disability
?
COX-2 dependent PGE2 synthesis by MIC via p38?

~KI, 2002


tubular salt-wasting
NSAID
PLs
PLA_2
COX
AA
PGH_2 / PGG_2
PGES
PGE_2
PGI_2
$PGF_{2\alpha}$
TxA_2
PGD_2
• fetal polyuria
• polyhydramios
• prematurity
• nephrocalcinosis
renal + systemic symptoms
• diarrhea
• vomiting
• fever
• osteopenia
• failure to thrive
renin ↑
aldosterone ↑
aggravation of
electrolyte-/water-wasting

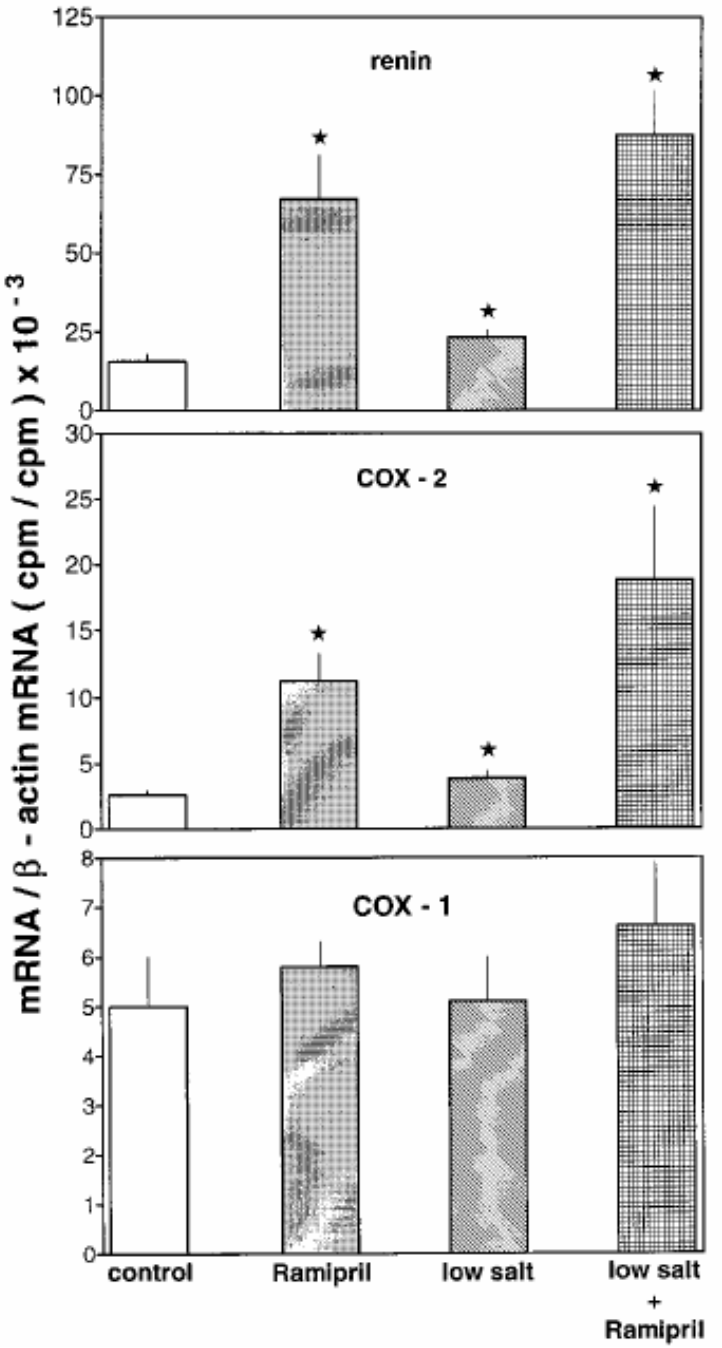
~KI, 2002

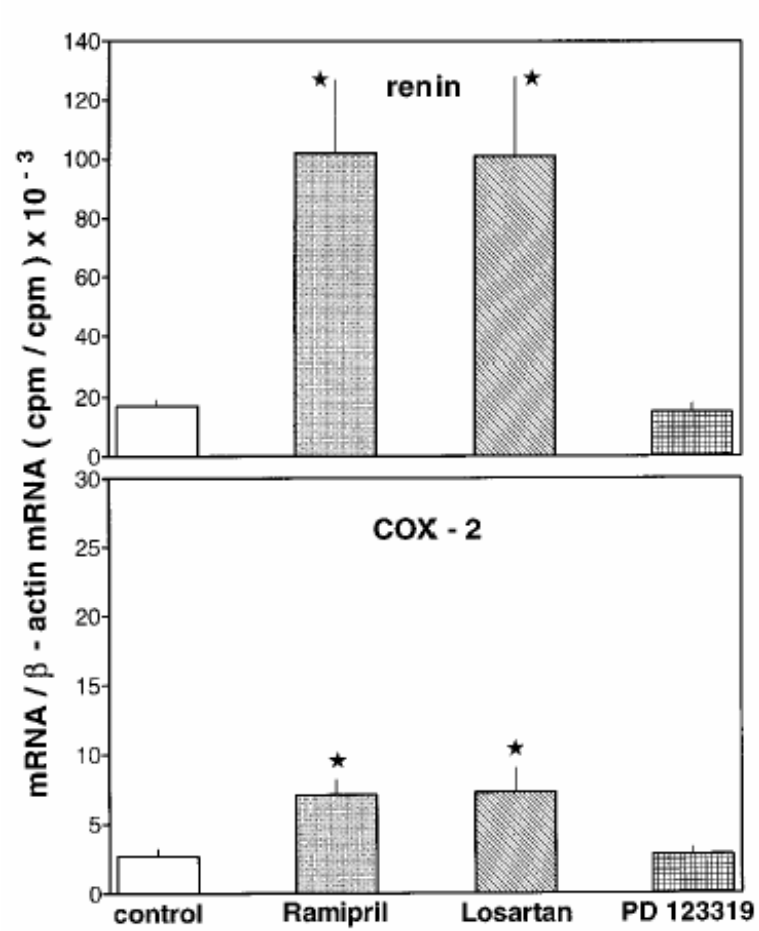

A
1000
100
10
1
Urinary prostaglandin E_2 excretion
ng/h/1.73 m²
*
*
Indomethacin
Withdrawal
Rofecoxib
B
300
250
200
150
100
50
0
Plasma renin concentration, pg/mL
*
*
*
Indomethacin
Withdrawal
Rofecoxib

~KI, 2002

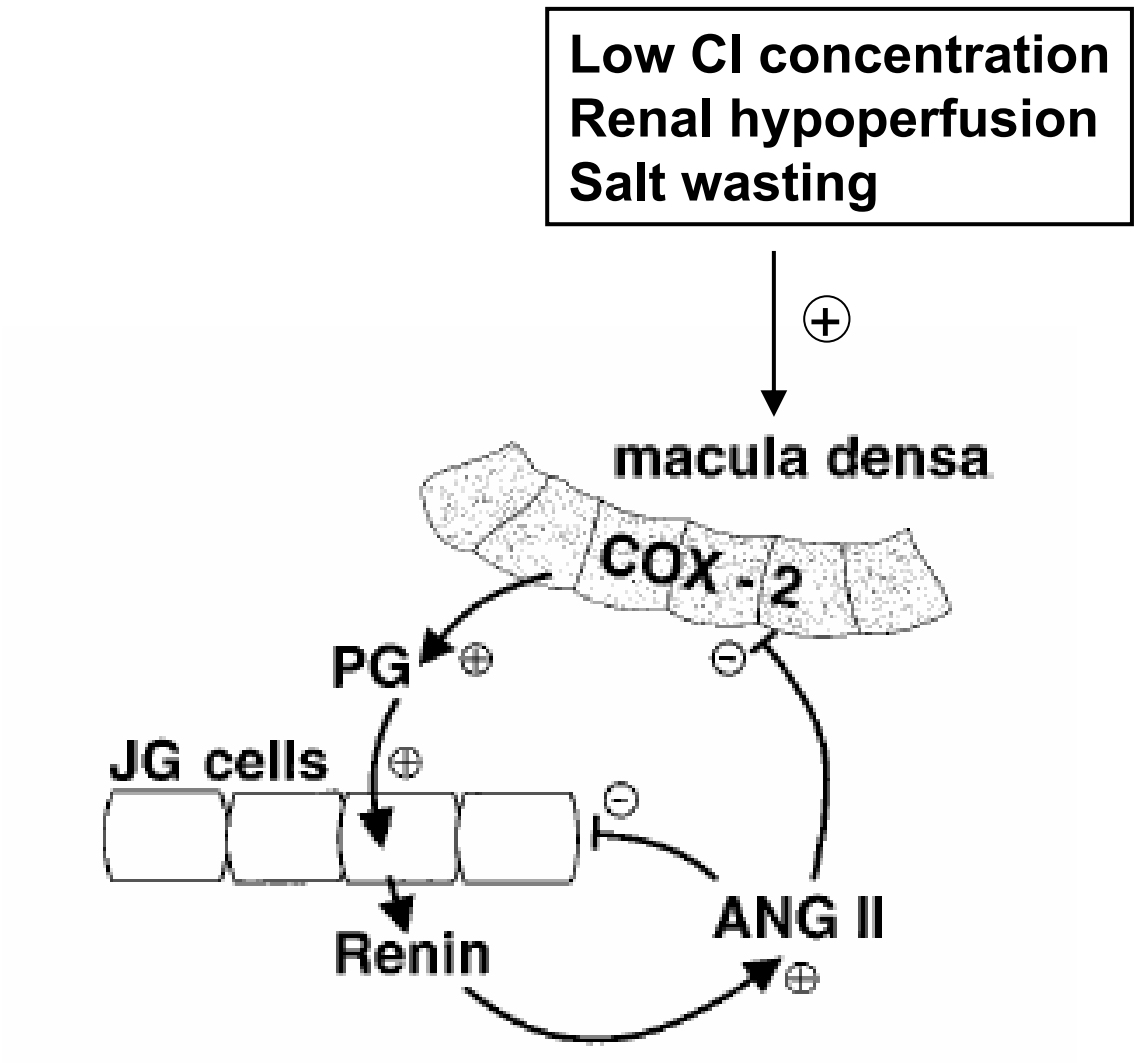
	Indomethacin	Withdrawal	Rofecoxib	Normal range
Serum potassium *mmol/L*	3.4 (3.1–4.3)	3.4 (2.9–3.7)	3.6 (3.3–4.3)	3.6–4.8
Serum pH	7.39[a] (7.37–7.40)	7.42 (7.40–7.44)	7.39[a] (7.36–7.42)	7.35–7.45
Serum chloride *mmol/L*	104 (101–107)	101 (99–104)	104 (102–106)	97–106
Aldosterone *ng/dL*	18.5[a] (4.0–51.2)	41.6 (15.8–144.0)	8.5[a] (5.6–28.1)	2.9–16.2
Diuresis *mL/kg*h*	2.0[a] (1.2–6.2)	3.1 (1.5–8.3)	1.9[a] (1.1–5.9)	1.0 ± 0.2[b]
FE potassium %	16.0 (5.5-51.0)	25.7 (14.0–38.2)	16.6[a] (9.8–26.8)	<15
Chloride excretion *mmol/kg/day*	2.1 (1.5–8.1)	4.0 (1.5–7.1)	3.0 (1.2–7.9)	2.3 ± 0.3[b]
Sodium excretion *mmol/kg/day*	1.8 (1.5–7.7)	3.7 (1.5–6.0)	2.7 (1.1–6.7)	1.9 ± 0.3[b]
Calcium excretion *mg/kg/day*	5.6[a] (2.4–22.2)	10.4 (3.7–28.6)	5.3[a] (2.3–20.3)	<4
Creatinine clearance *mL/min/1.73 m²*	87[a] (74–95)	106 (86–124)	82 (65–122)	80–160
Urinary osmolality *mOsmL/kg*	284 (163–377)	272 (132–377)	279 (200–417)	>300

~KI, 2002

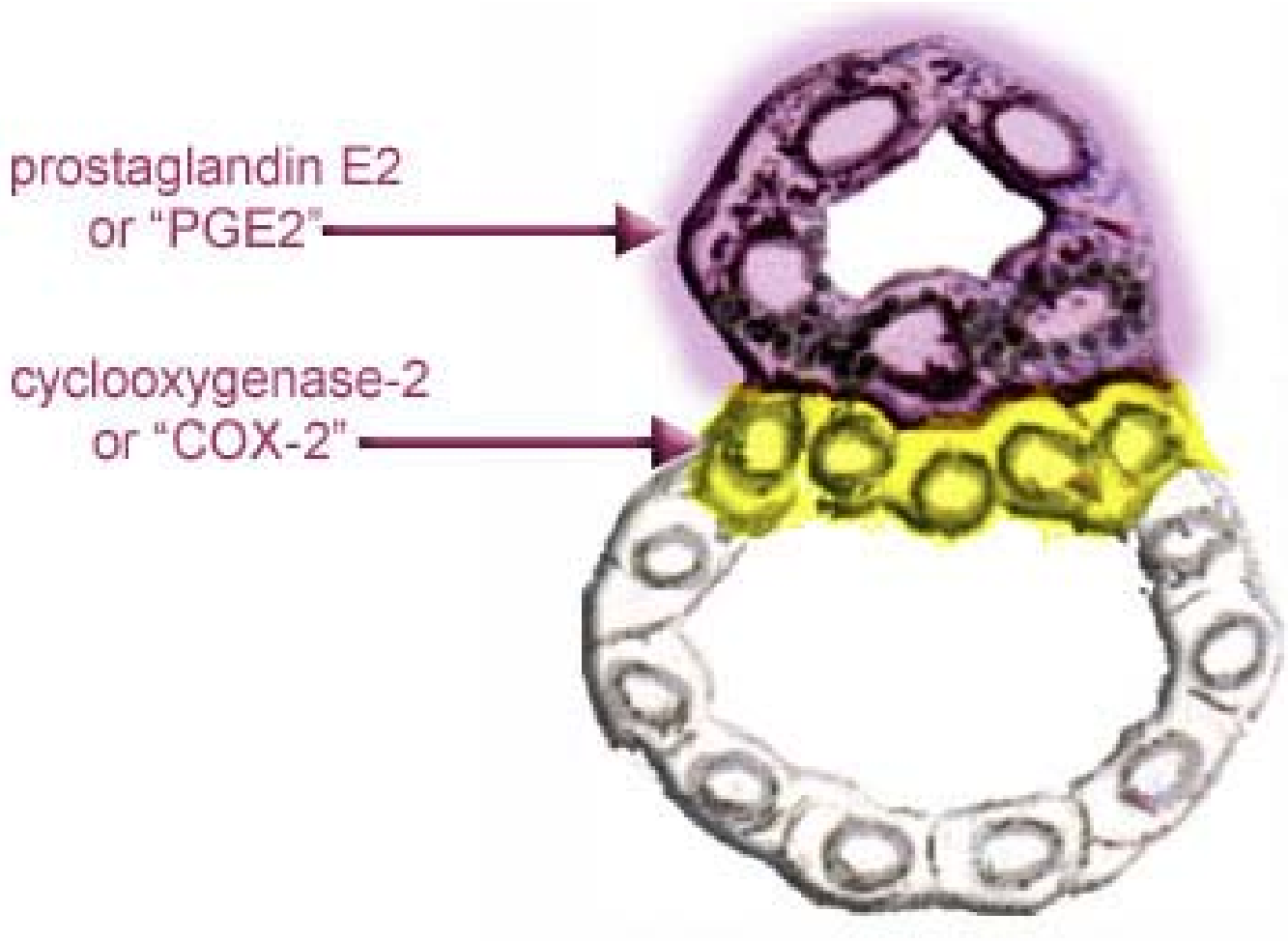


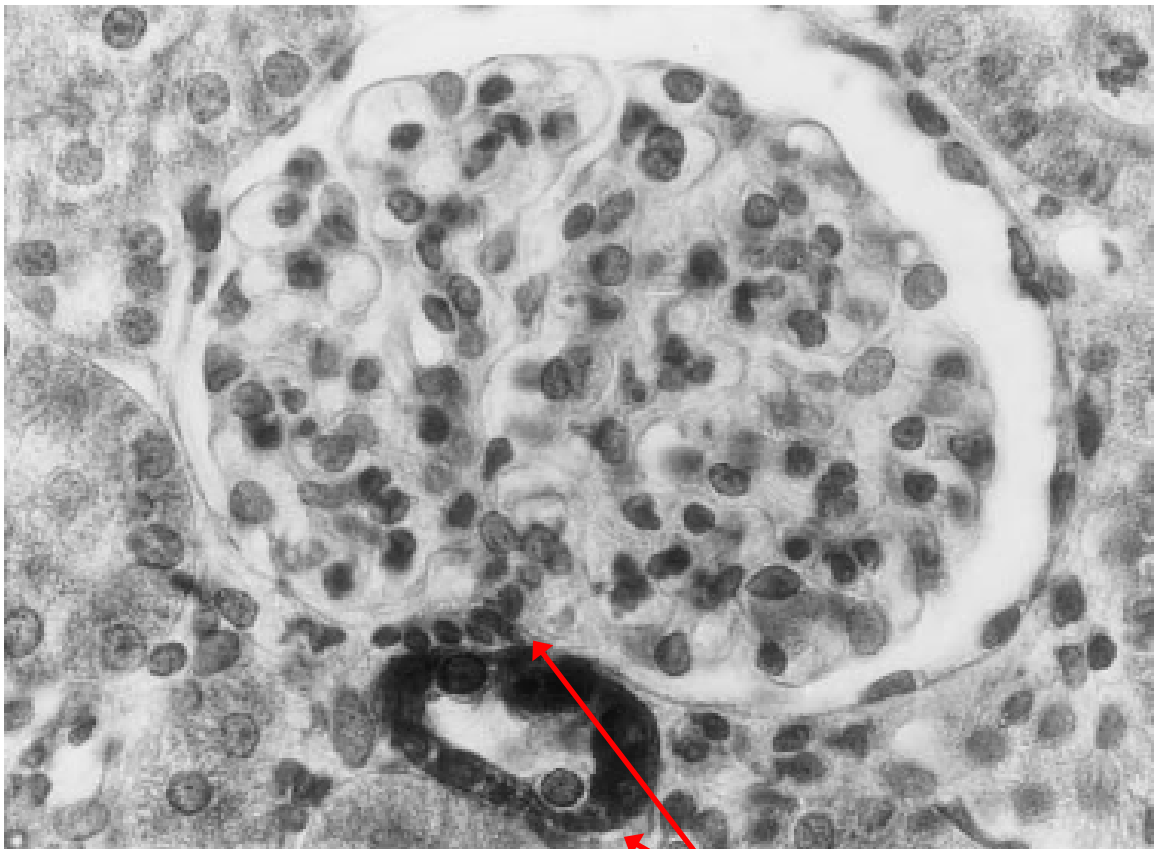


~ Hypertension, 1999

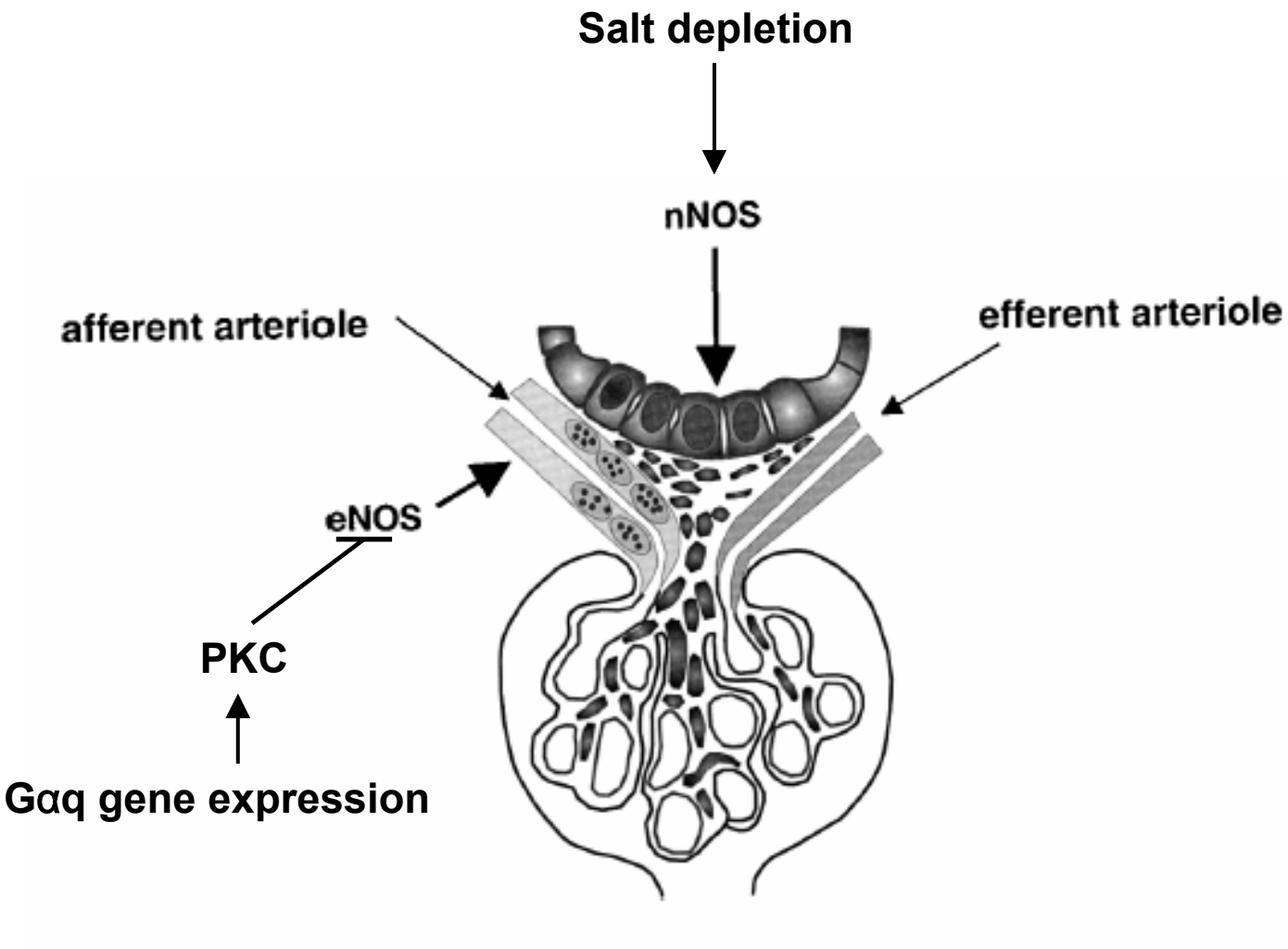


~ Hypertension, 1999

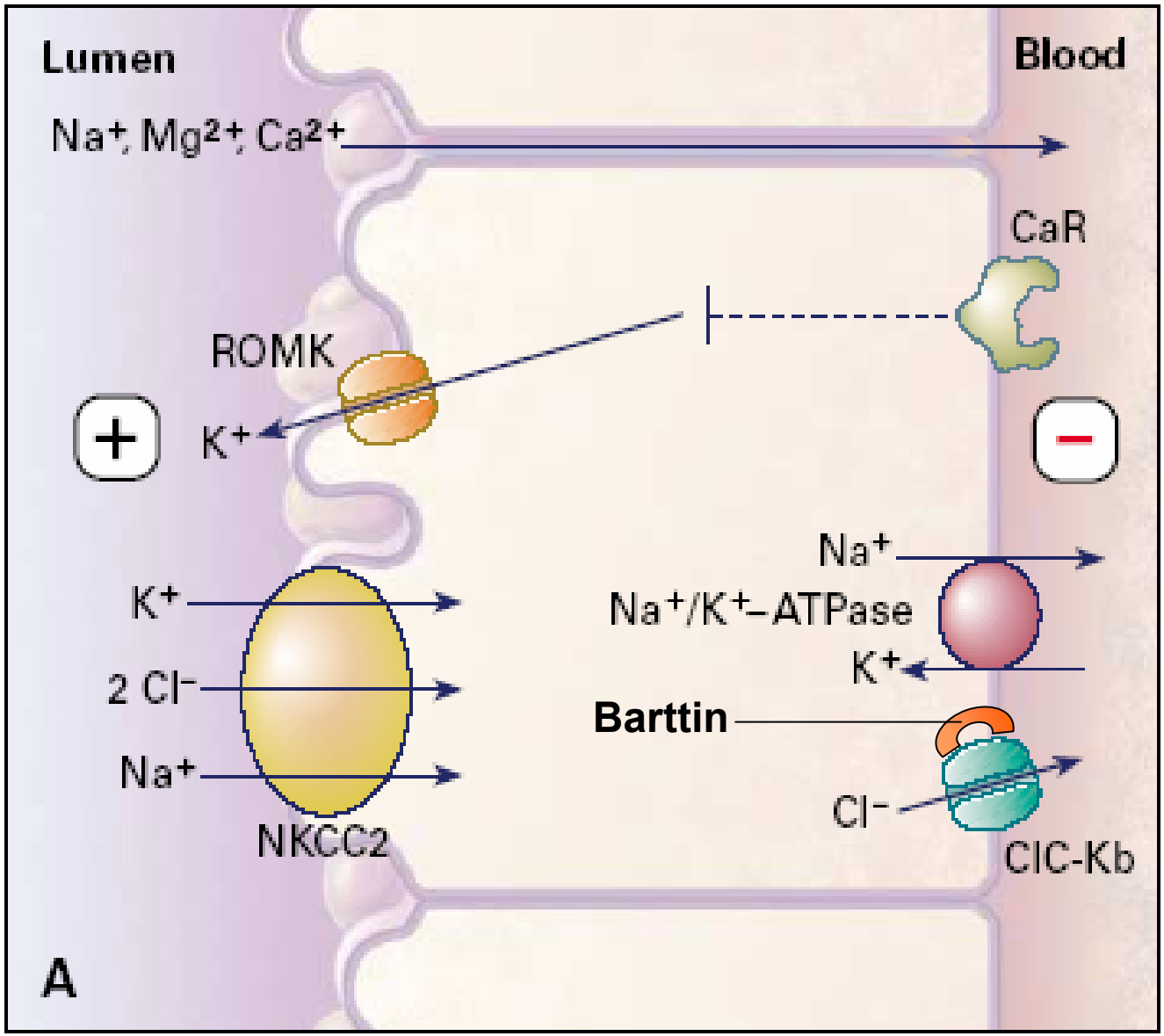

prostaglandin E2
or "PGE2"
cyclooxygenase-2
or "COX-2"


COX-2 expression

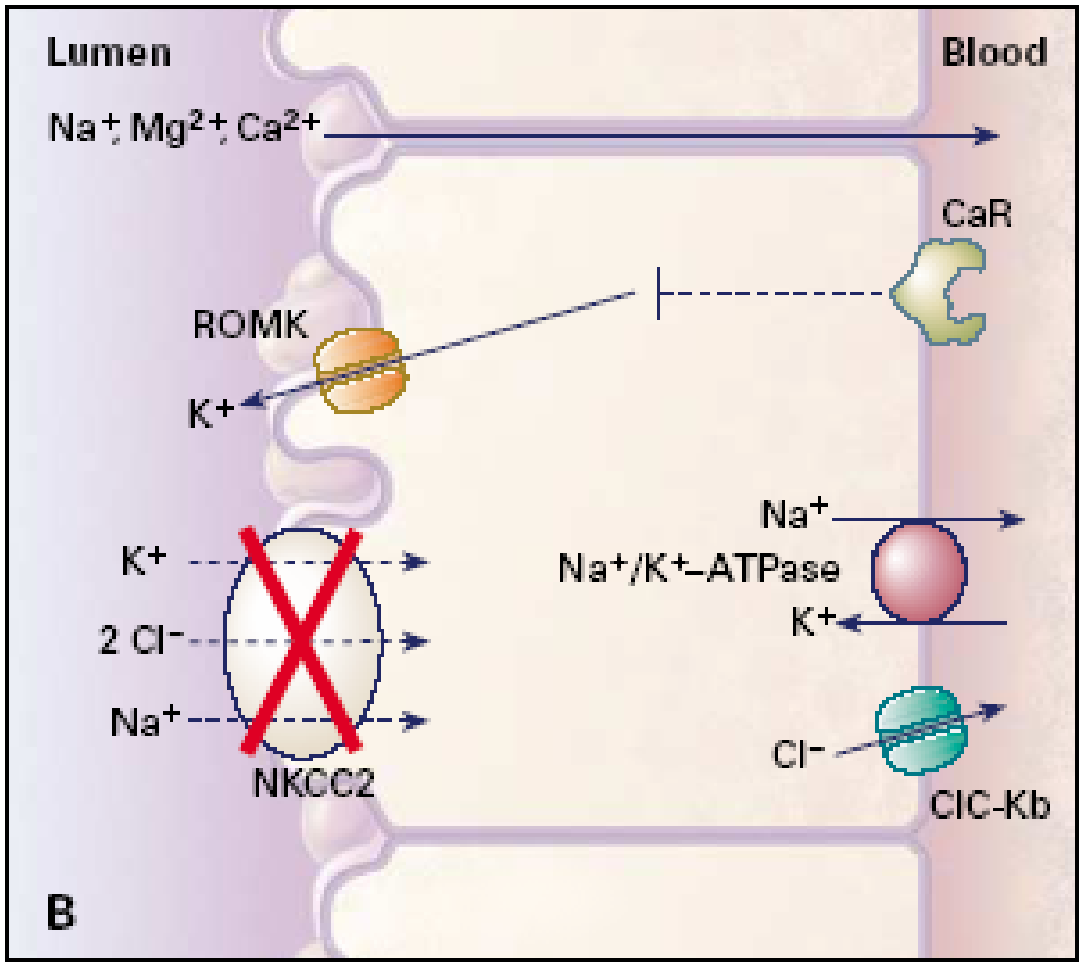
Vascular hyporesponse



Subtypes of Bartter's syndrome

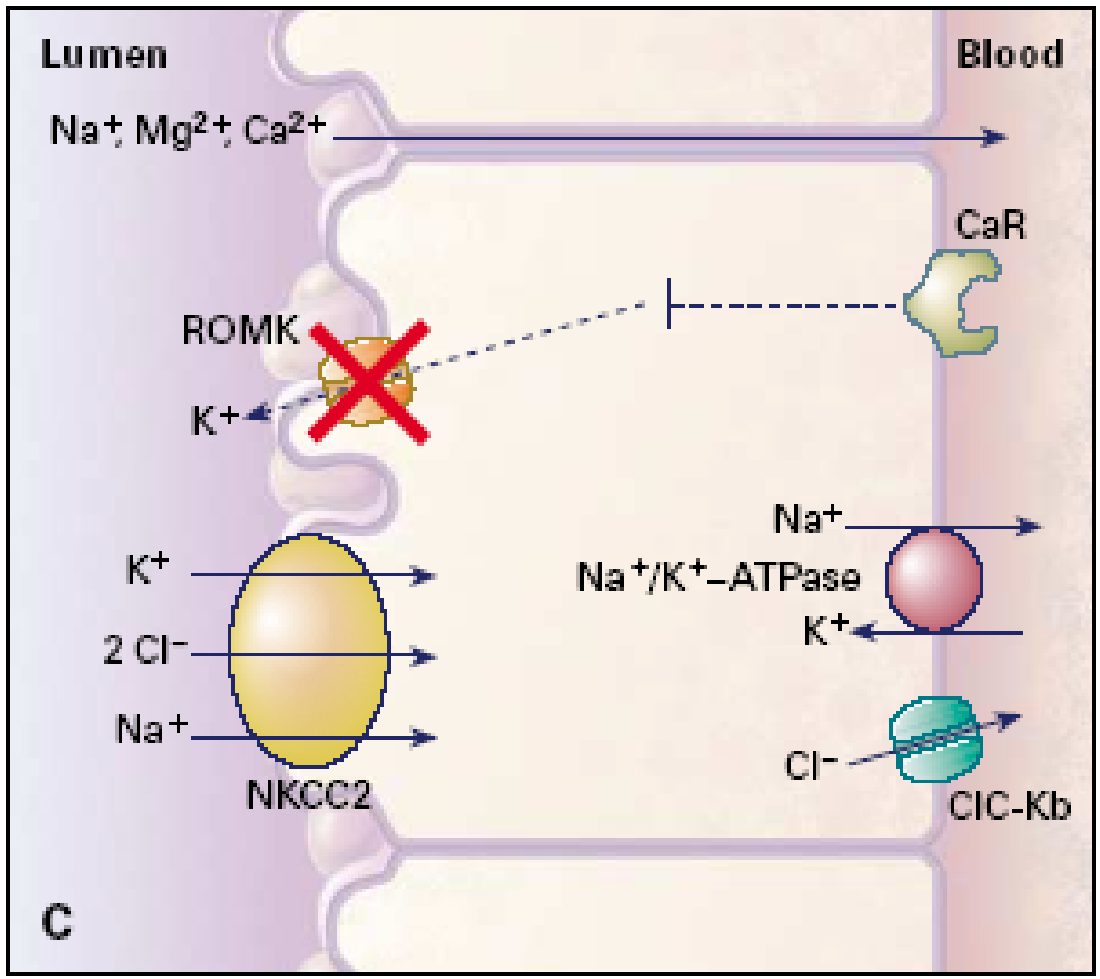


Bartter's syndrome ~ Type I



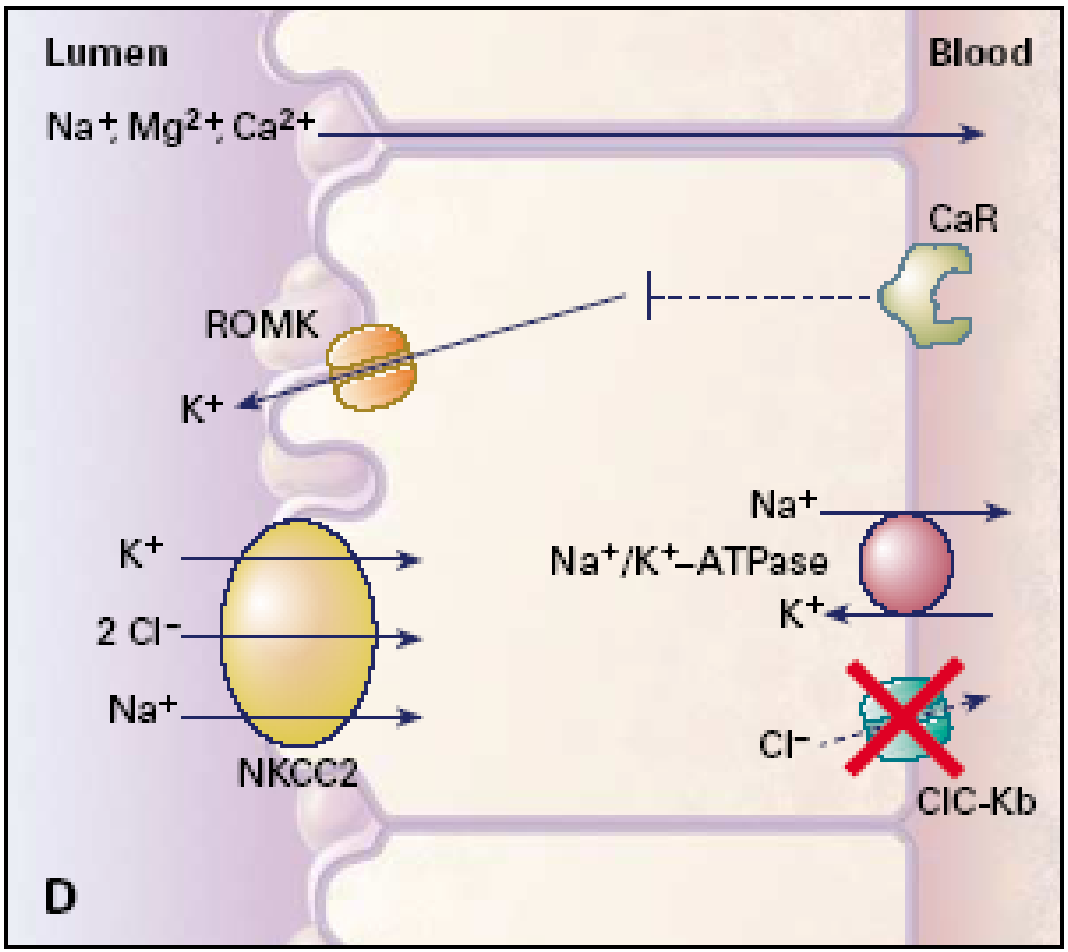
- NKCC2 mutation
- SCL12A1 gene in Chromosone 15q15-q21
- Bumetanide-sensitive cotransporter

Bartter's syndrome ~ Type II



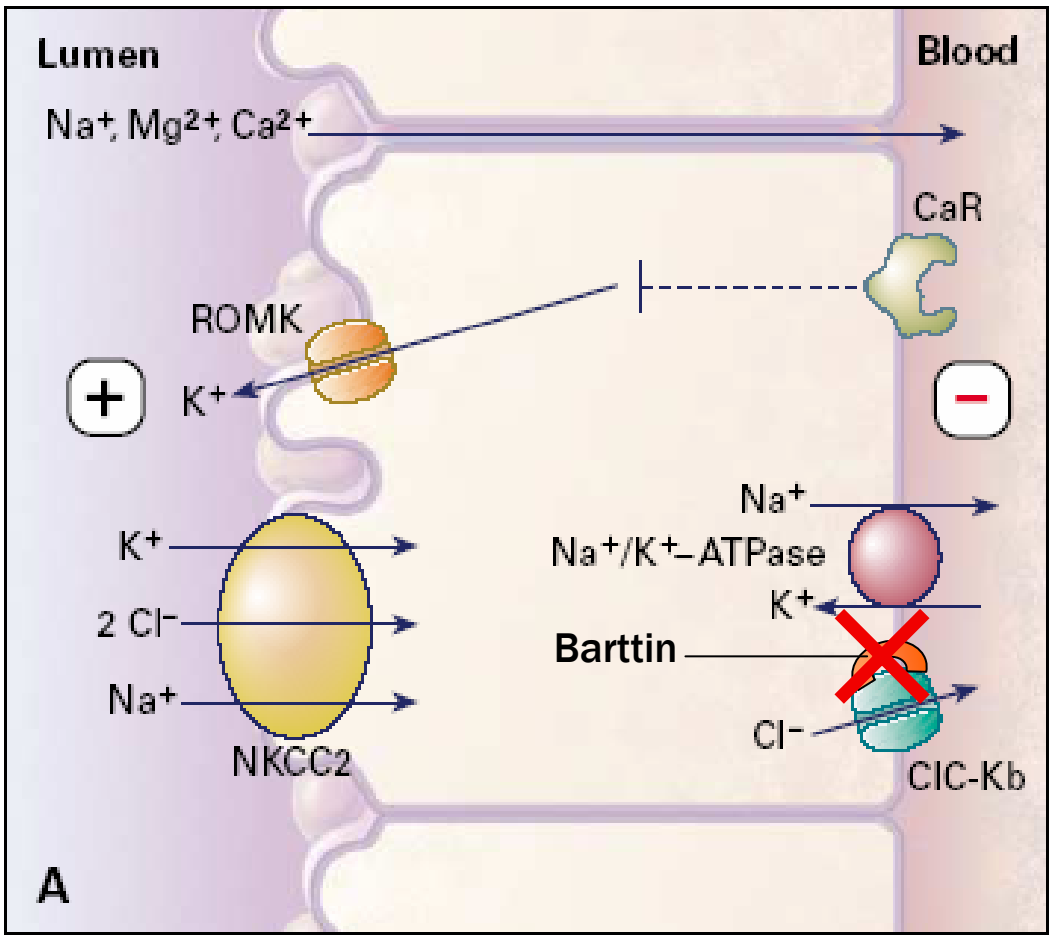
- ROMK mutation
- KCNJ1 gene in Chromosone 11q24-25
- Essential for NKCC2

Bartter's syndrome ~ Type III

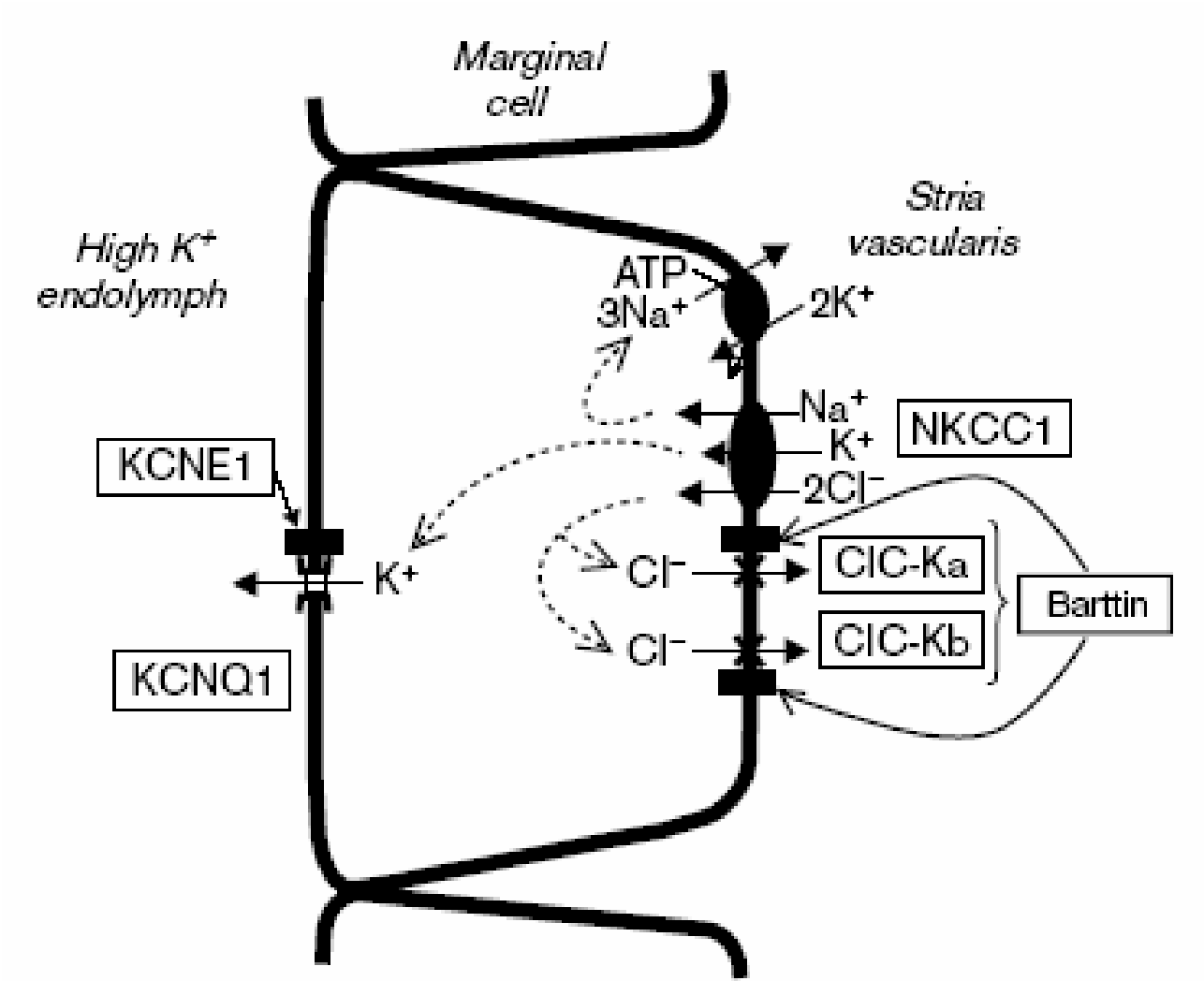


- ClC-Kb mutation
- CLCNKB gene in Chromosone 1p36
- No nephrocalcinosis

Barter's syndrome ~ Type IV

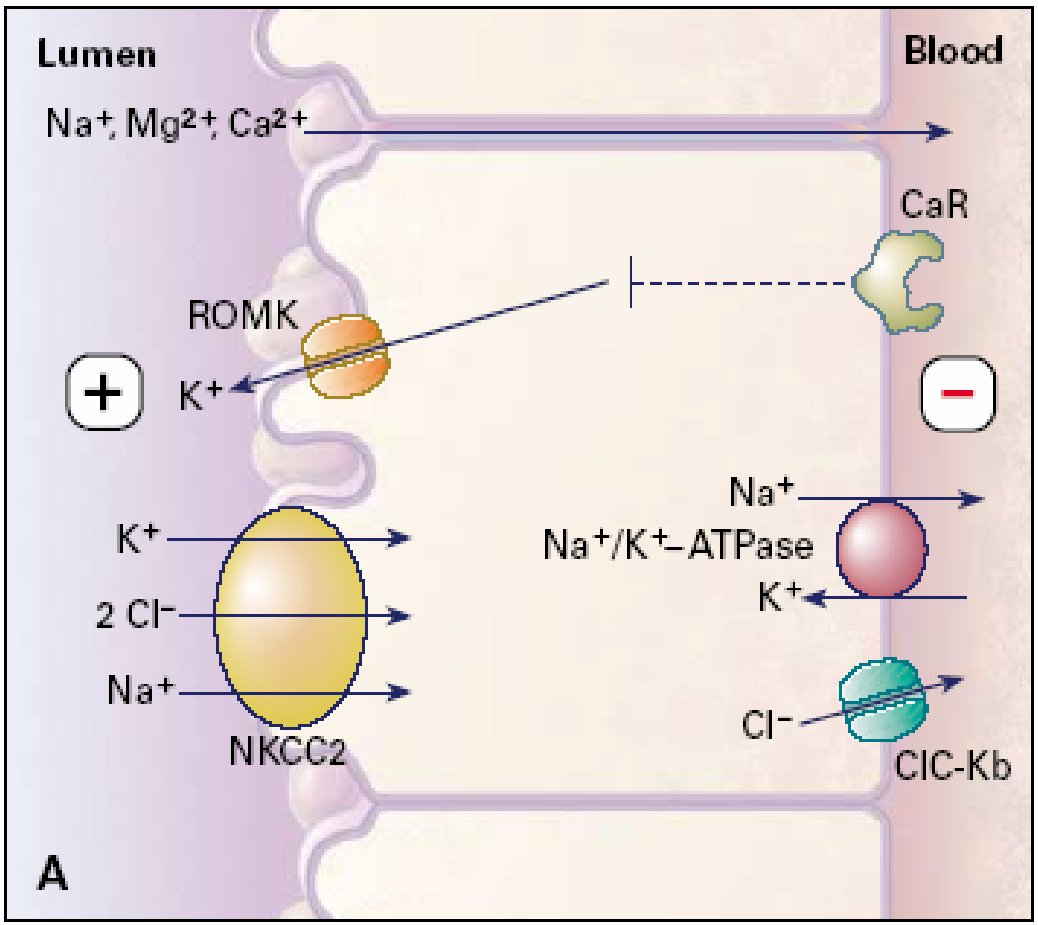


- Barttin mutation
- β-subunit for ClC-Kb & ClC-Ka
- BSND gene in Chromosone 1p31
- In thin ascending limb & marginal cells (stria vascularis of cochlea)
- Sensorineural deafness
- Extreme growth retardation

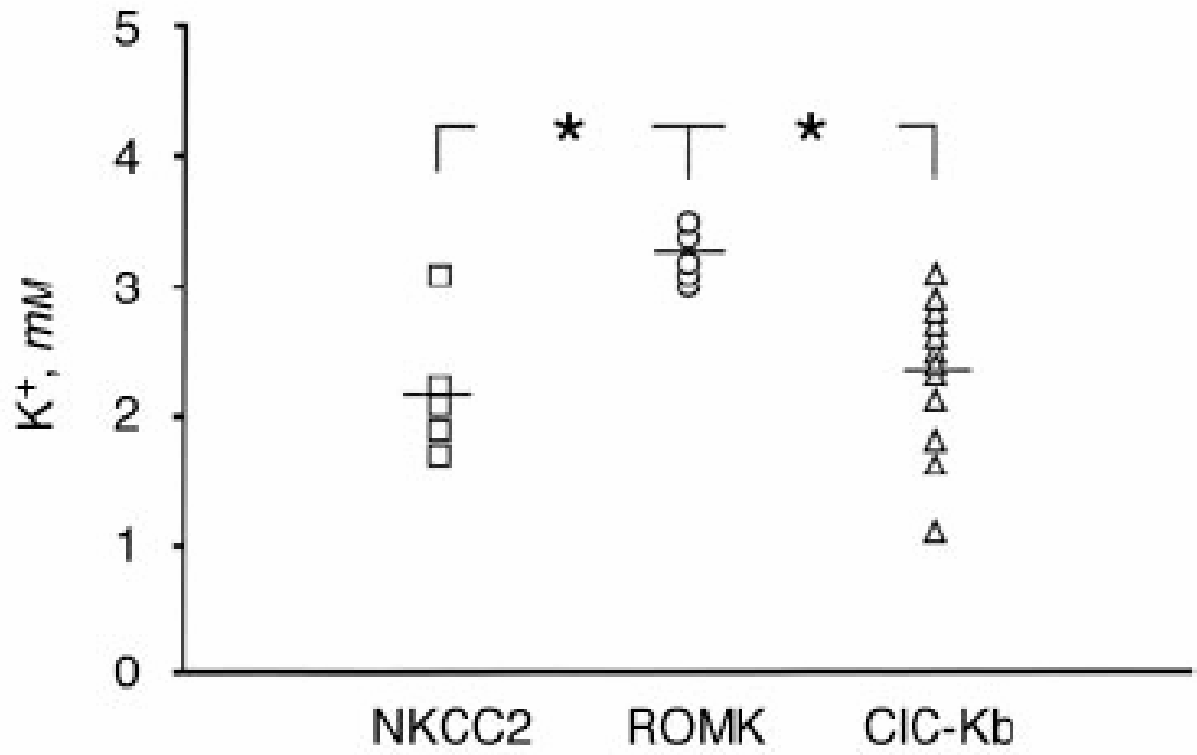


~ Curr Opin Nephrol Hypertens, 2003

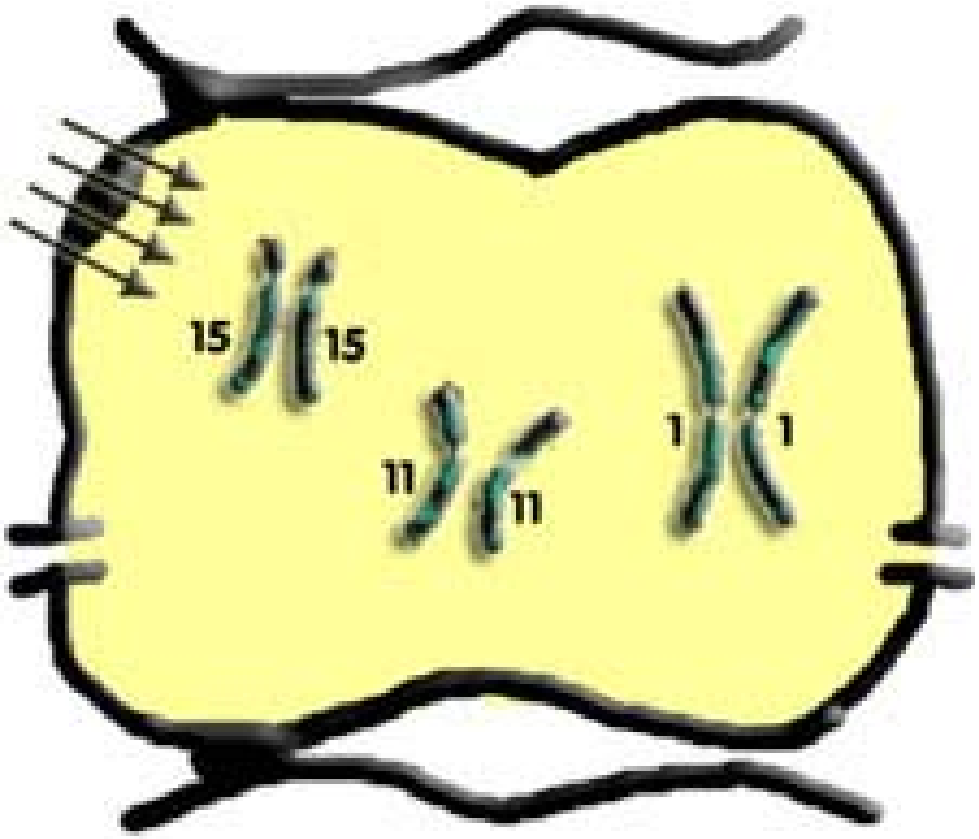
Bartter's syndrome ~ Type V



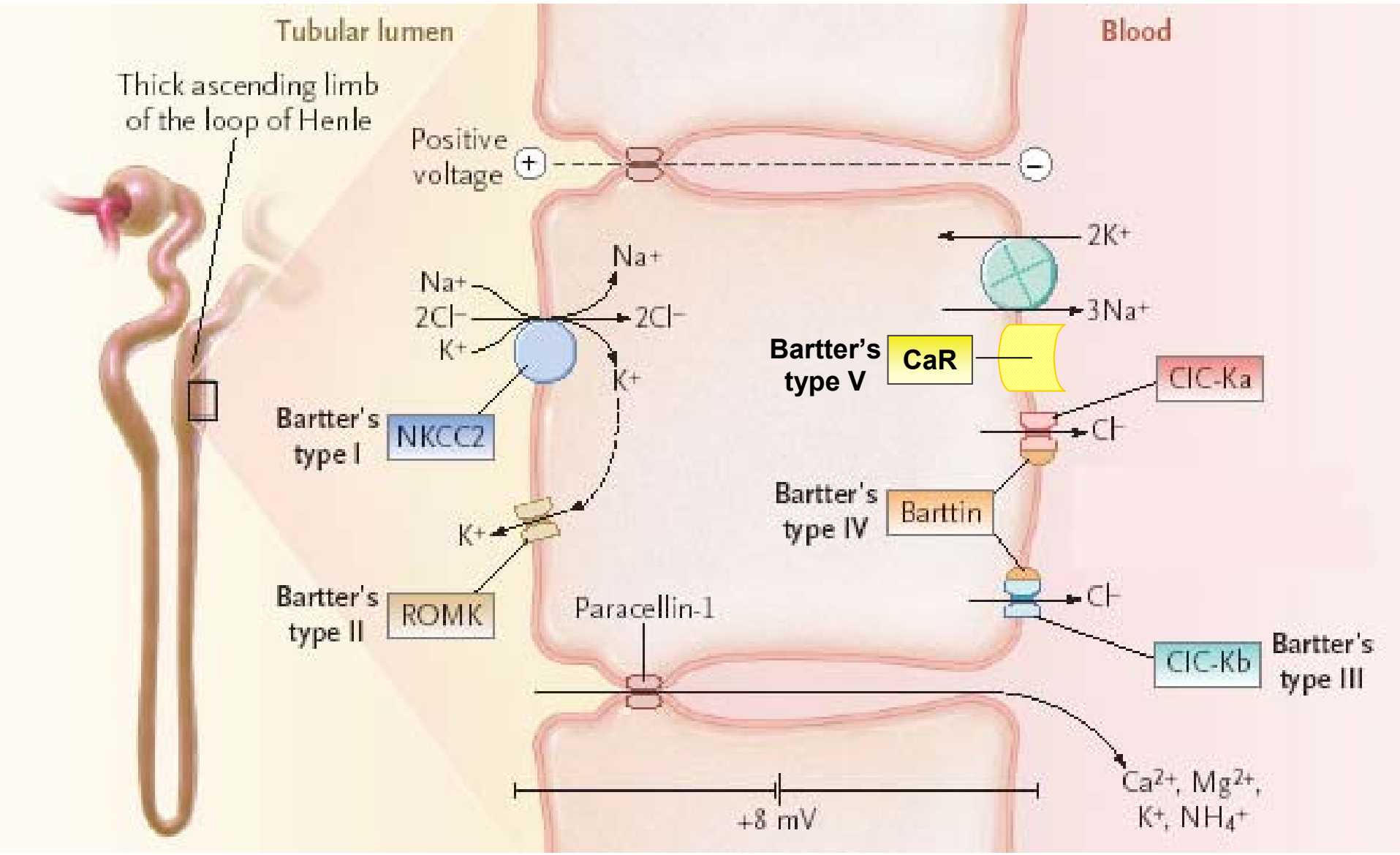
- Gain-of function mutation in CaSR
  (G-protein coupled)
- CASR gene
- Autosomal dominant



~ KI, 1998


15
15
11
11
1
1

Disorder	Inheritance	Clinical Features	Hypokalemic Metabolic Alkalosis	Calcium Excretion	Serum Mg	Gene	Protein
Bartter/Gitelman syndromes							
Bartter type I	AR	Antenatal presentation, salt-wasting, nephrocalcinosis	+	High	Normal	*NKCC2*	Bumetanide-sensitive Na-K-2Cl cotransporter
Bartter type II	AR		+	High	Normal	*KCNJ1*	ROMK potassium channel
Bartter type III	AR	"Classic" Bartter syndrome, less severe, occasionally overlaps with Gitelman or antenatal	+	High	Normal or low	*CLCNKB*	CLC-Kb basolateral chloride channel
Bartter type IV	AR	Antenatal Bartter syndrome with sensorineural deafness	+	High	Normal	*BSND*	Barttin, chloride channel subunit
Bartter type V	AD	Hypocalcemia	+	High	Low	*CASR*	Epithelial calcium-sensing receptor


Tubular lumen
Blood
Thick ascending limb of the loop of Henle
Positive voltage
+
−
Na+
Na+
2Cl−
2Cl−
K+
K+
Bartter's type I
NKCC2
K+
Bartter's type II
ROMK
Paracellin-1
+8 mV
2K+
3Na+
Bartter's type V
CaR
ClC-Ka
Cl−
Bartter's type IV
Barttin
Cl−
ClC-Kb
Bartter's type III
Ca2+, Mg2+, K+, NH4+

- **Story beginning…**
- **Clinical presentation**
- **Differential diagnosis**
- **Bartter's syndrome**
- **Gitelman's syndrome**
  - Gitelman's syndrome vs. Thiazide
  - Divalent cation in Gitelman's syndrome
- **Treatment**
- **What's else ?**

Gitelman's syndrome

- Thiazide can produce the same electrolyte imbalance

  Na-Cl cotransporter
- No response to Thiazide

  Normal response to Lasix

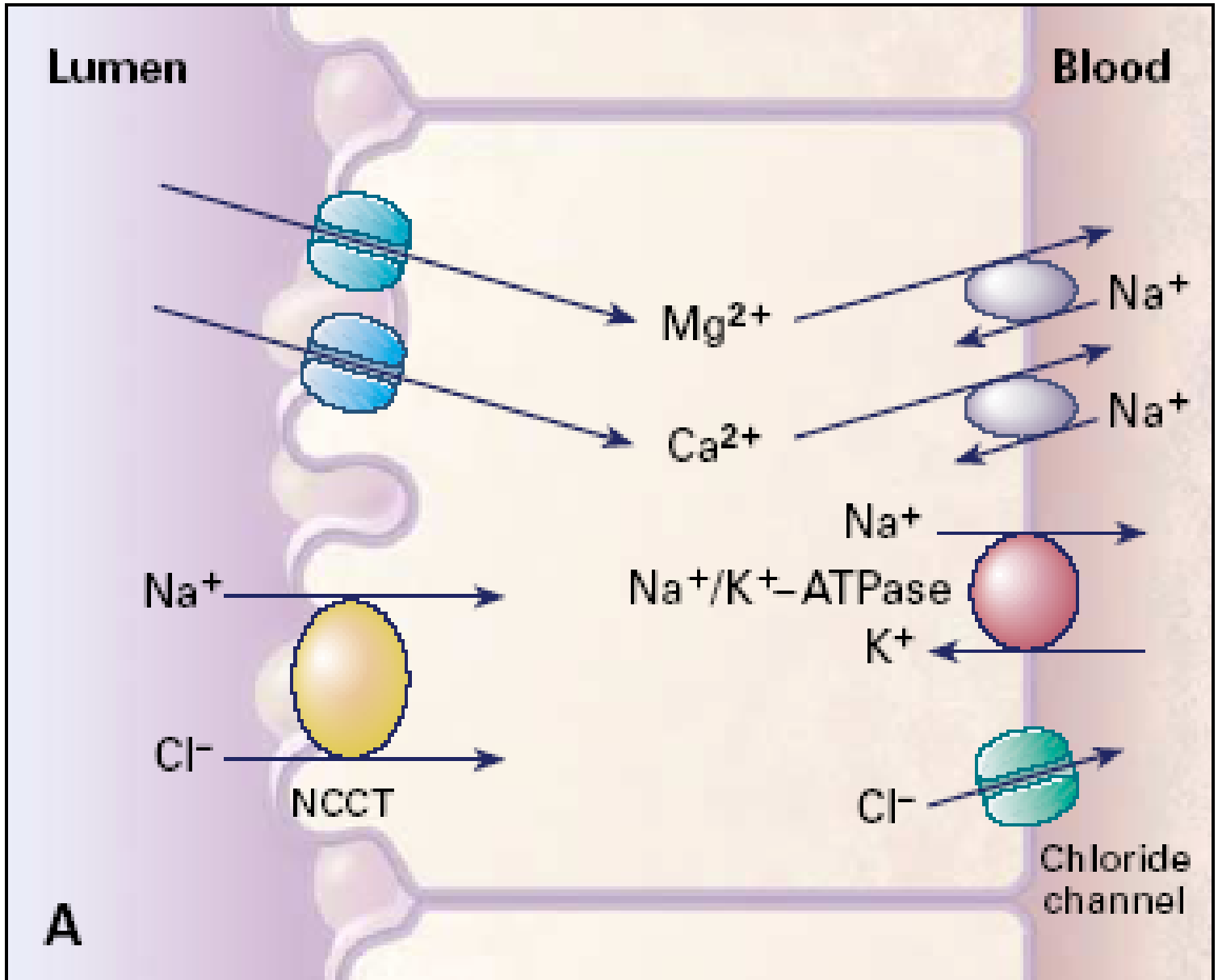
~ Miner Electrolyte Metab., 1992

- TSC (NCCT) : Na-Cl cotransporter

~ J Biol Chem., 1994

Gitelman's syndrome	**Thiazide**
Salt wasting	Salt wasting
Hypokalemia	Hypokalemia
Alkalosis	Alkalosis
Hypocalciuria	Hypocalciuria
High plasma renin activity and aldosterone	High plasma renin activity and aldosterone
	Na/Cl inhibition ?

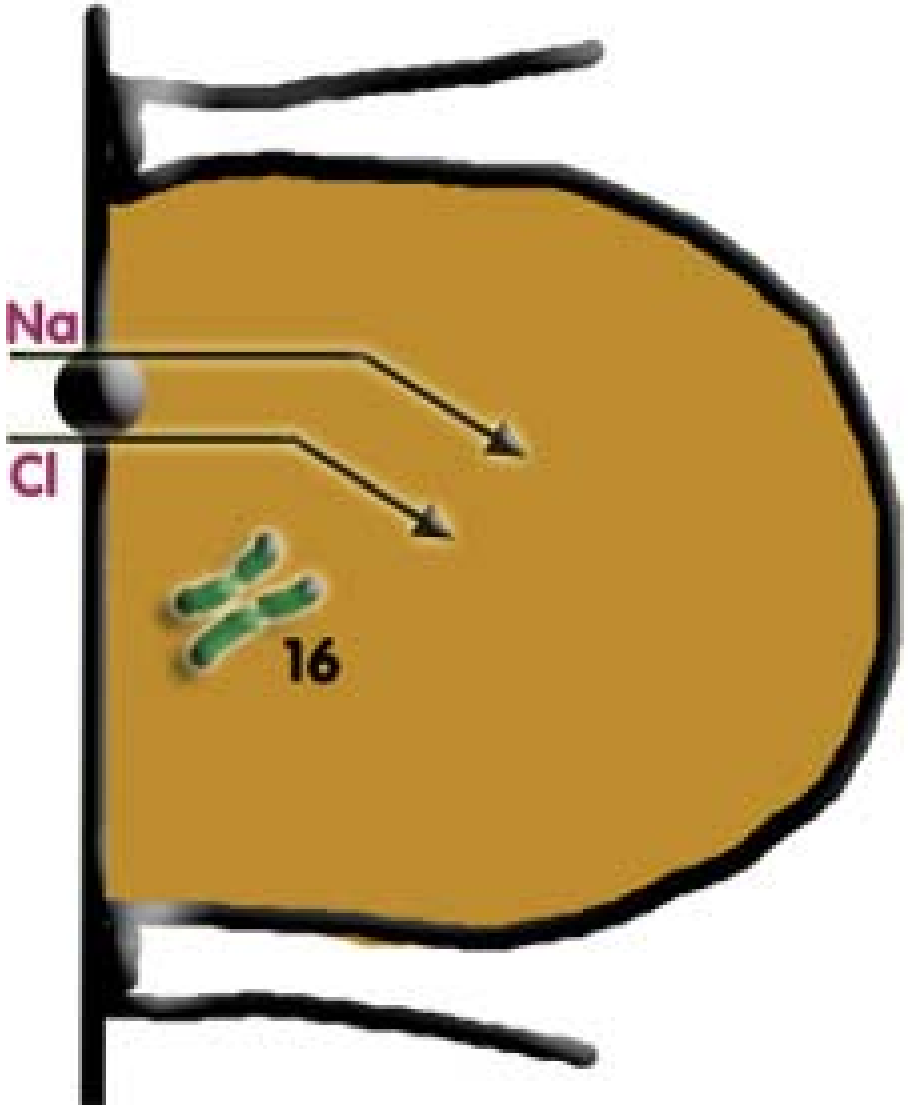
Basic effect of DCT



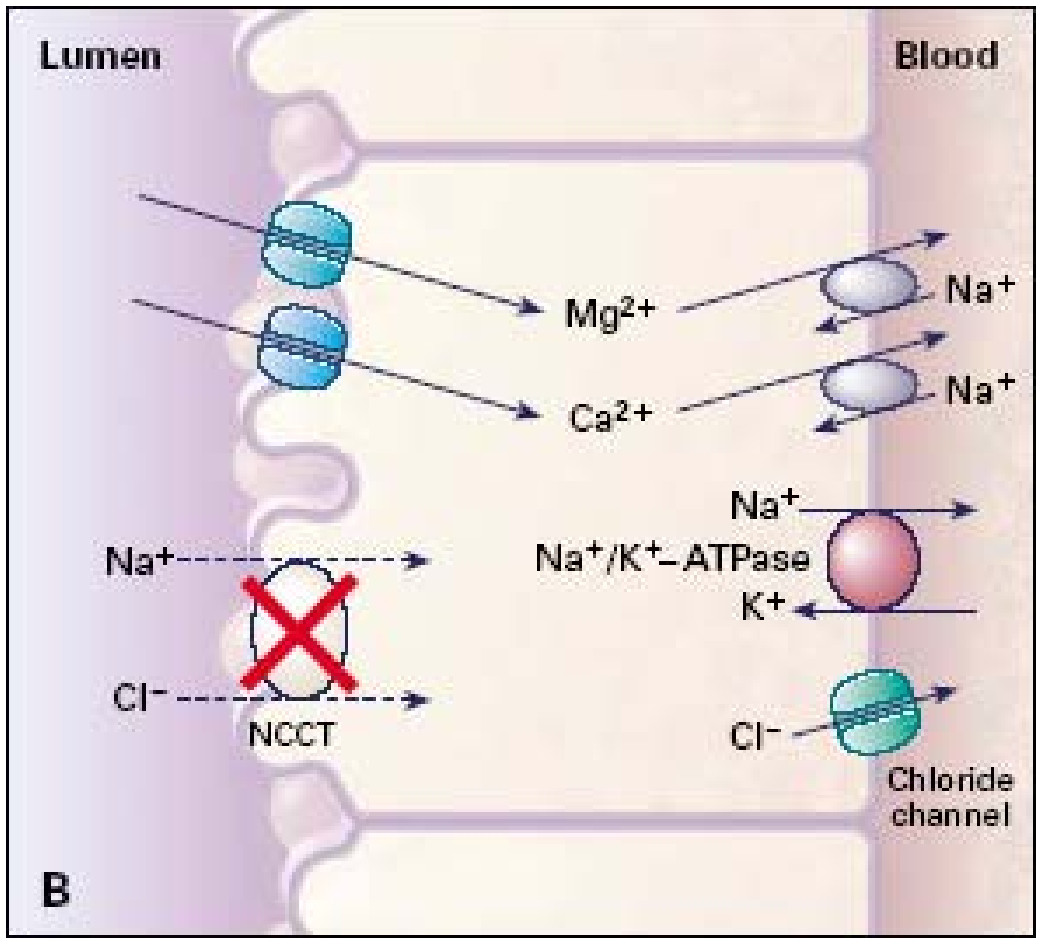
Gitelman's syndrome

- Genetically homogeneous
- Polyuria and polydipsia: less
- Hypokalemia
- Hyperrenin & hyperaldosterone: less
- Prostaglandin: normal
- Hypocalciuria, hyomagnesemia
- Chondrocalcinosis

There is no "getting out" channel affected here.



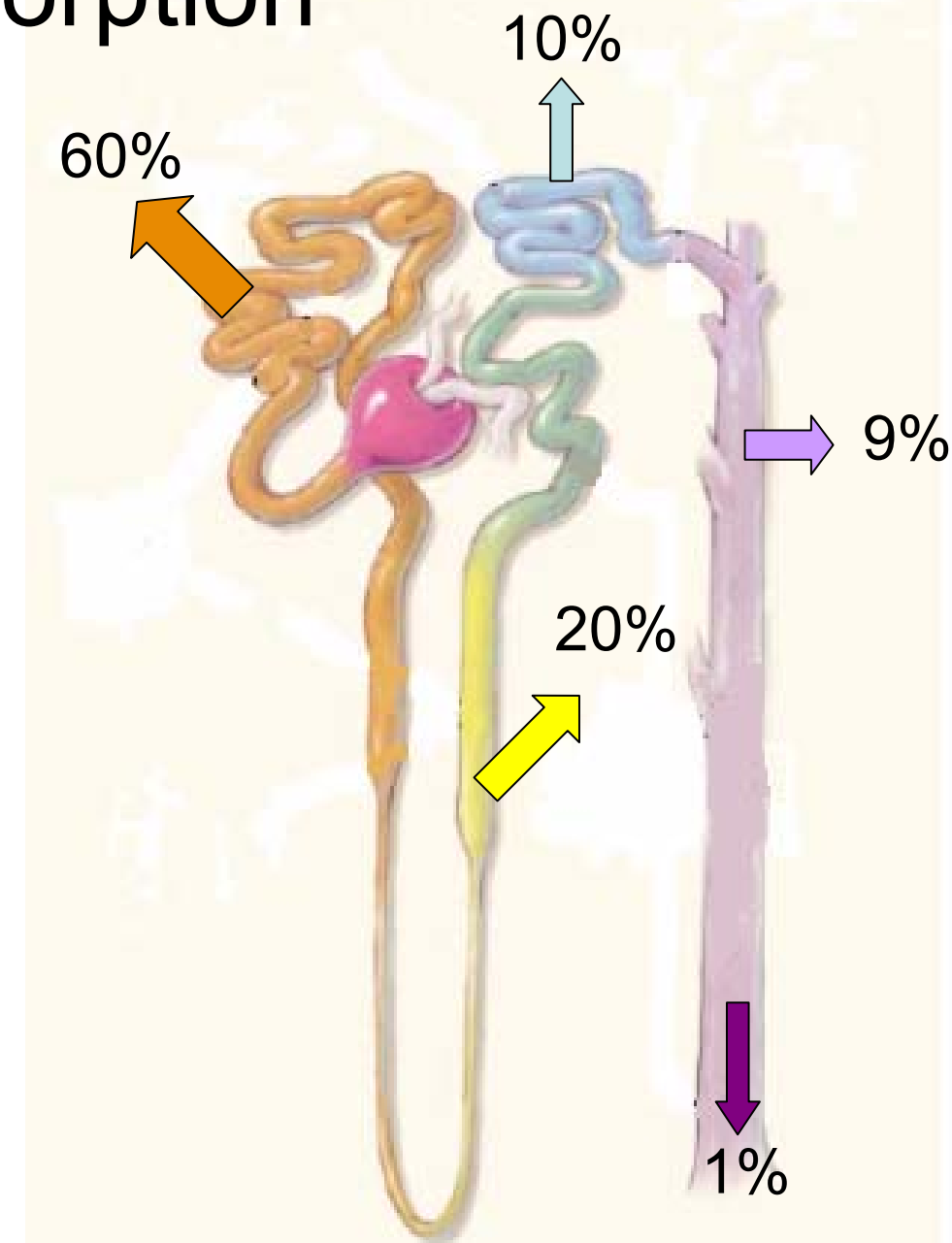
Gitelman's syndrome



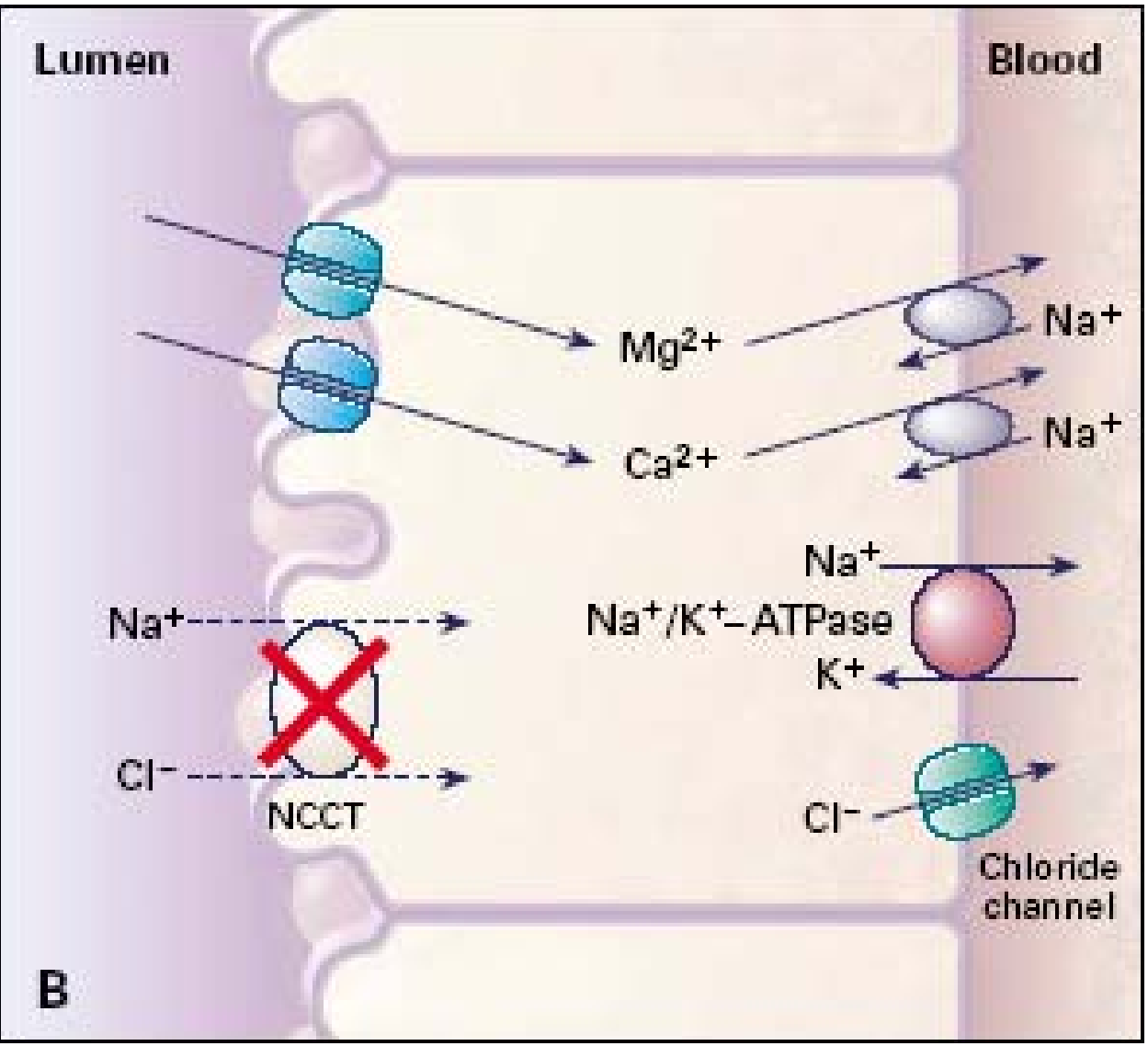
- NCCT mutation
- SCL12A3 gene in Chromosone 16q13
- Thiazide-sensitive cotransporter

- Hypocalciuria
- Hypomagnesemia

Ca reabsorption



Hypocalciuria



① Basolateral Na-Ca exchange ↑

→ Ca inflow via apical Ca channel ↑

~ KI, 1998

② Hyperpolarization

→ voltage-dependent Ca channel ↑

~ Biochem Biophys Res Commun, 1999

③ Upregulation of distal nephron

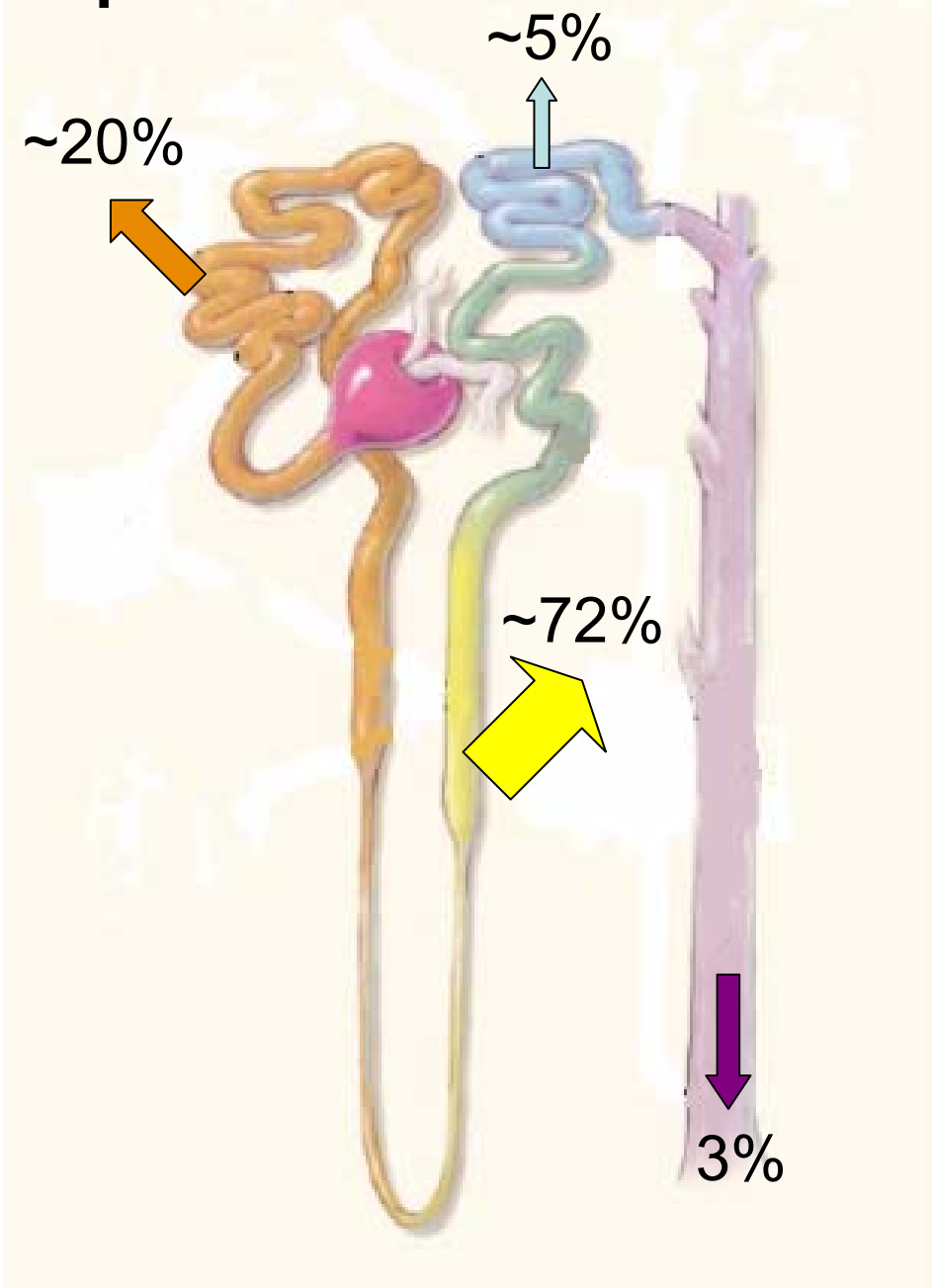
~ Nephron, 2002

④ Volume contraction

→ proximal Ca reabsorption ↑

~ KI, 2003

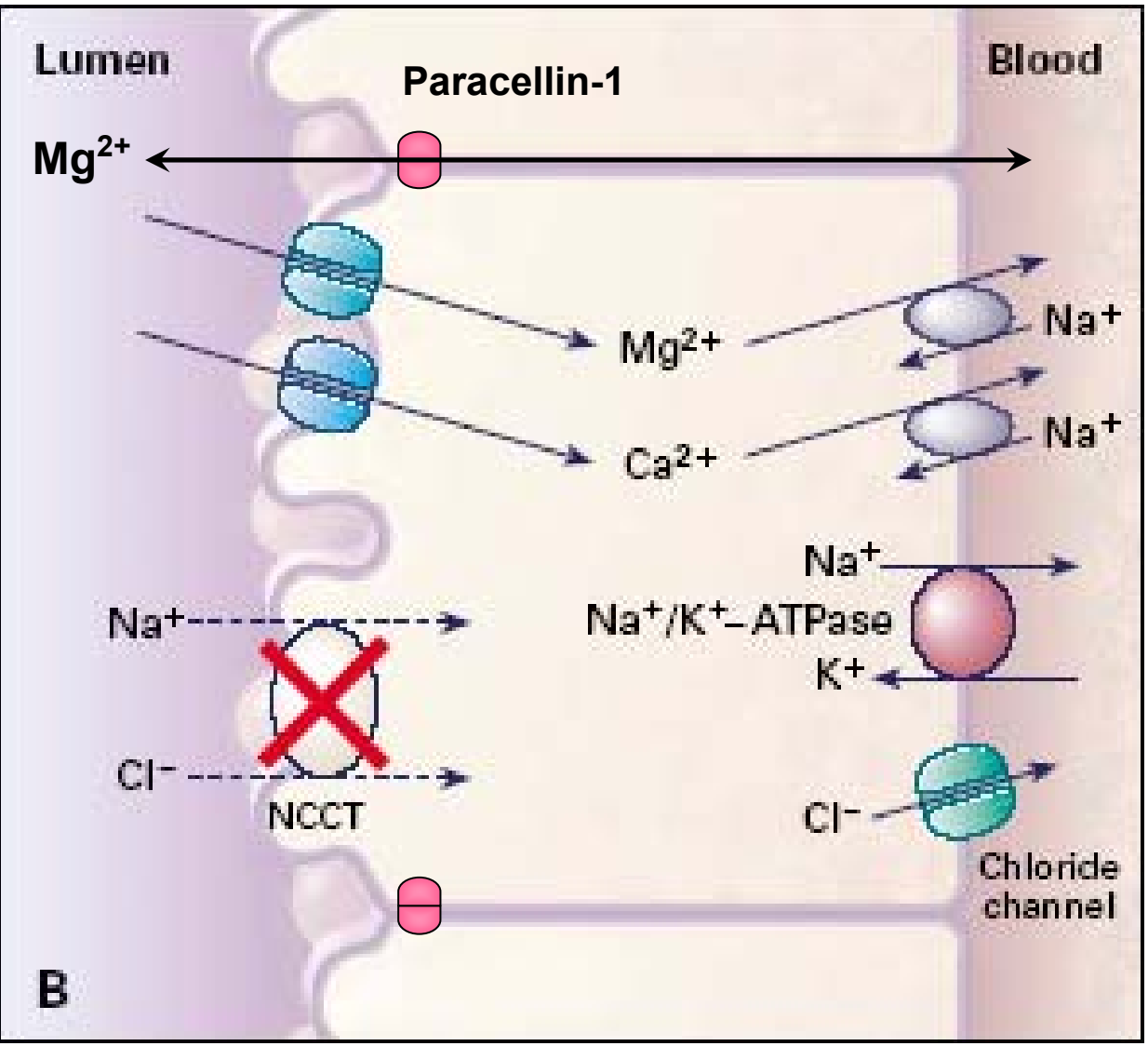
Mg reabsorption



Factors related to Mg reabsorption

- Promotive factor
  - ⊖ Volume depletion
  - ⊖ Metabolic alkalosis
  - – Vasopressin
  - – Parathyroid hormone
  - ⊖ Aldosterone
- Inhibitory factor
  - ⊖ K depletion
  - – Increase Mg
  - – Increase Ca

Hypomagnesemia



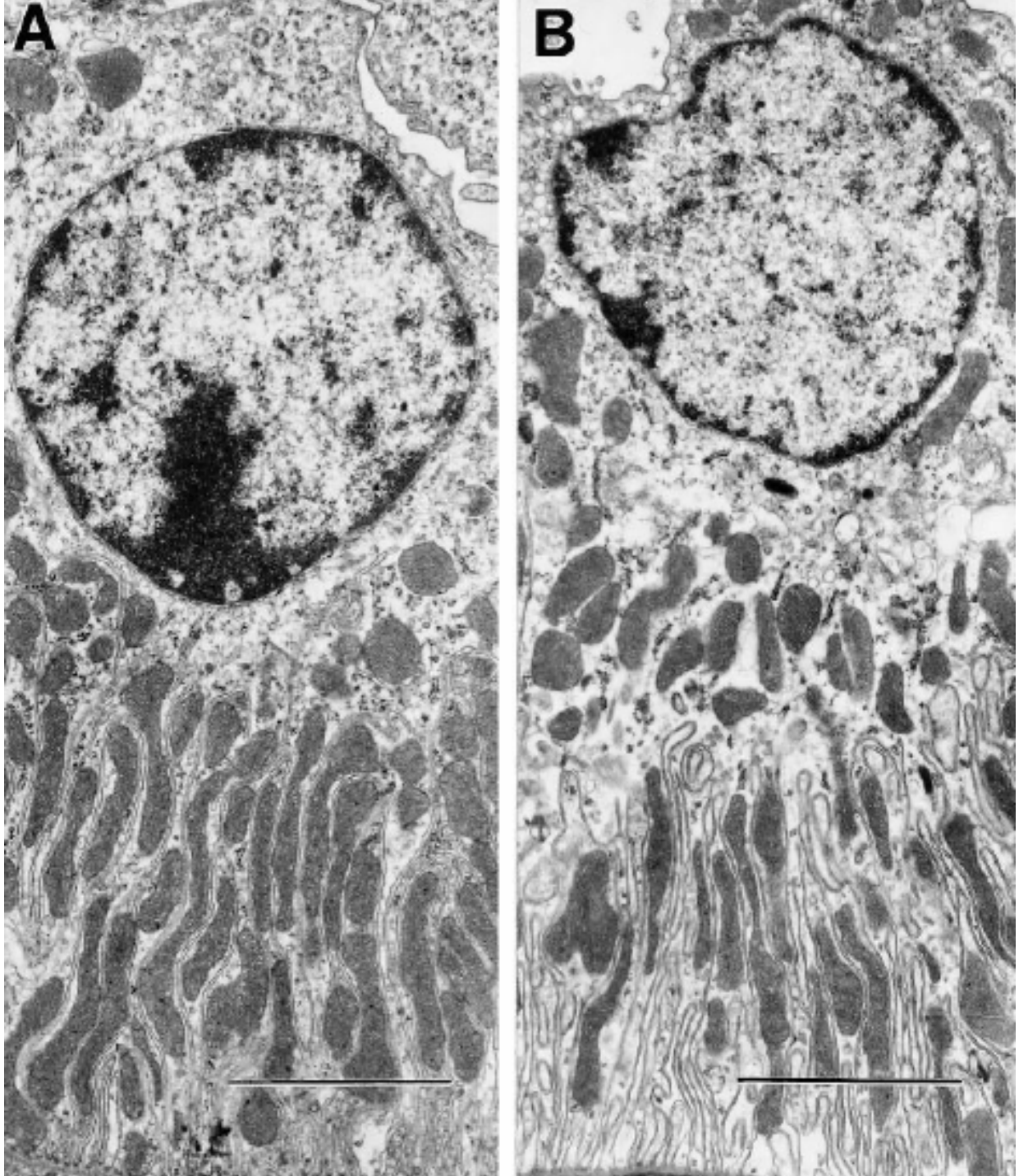
① Similar as Ca ?

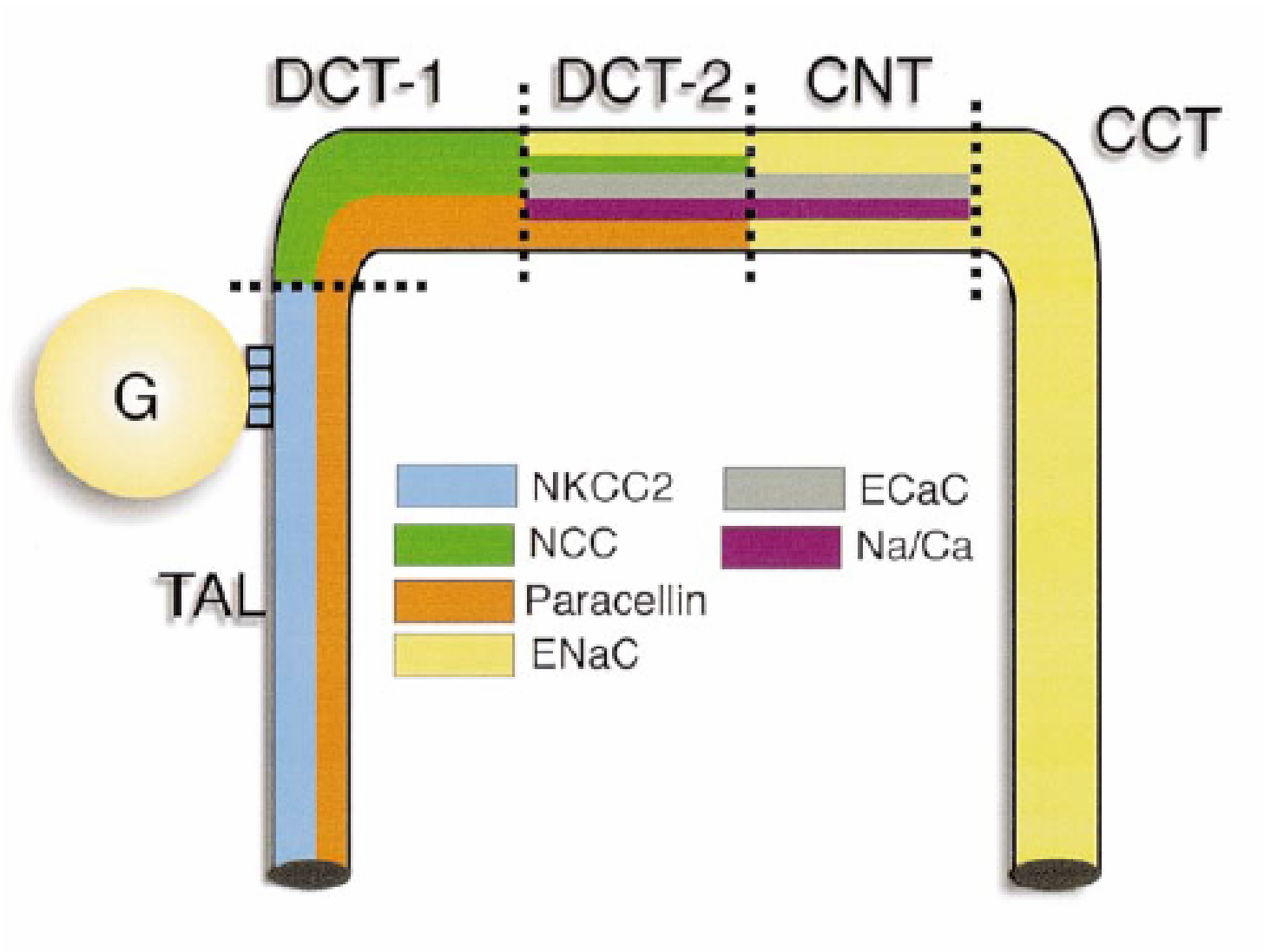
② Hypokalemia ?
Why Bartter's not ?

③ ENaC
→ Mg secretion ↑ ?

④ NCCT knockout mice
→ histological changes of DCT cells

~ J Biol Chem, 1998


A
B



~ Am J Physiol Renal Physiol, 2000

- Story beginning…
- Clinical presentation
- Differential diagnosis
- Bartter's syndrome
- Gitelman's syndrome
- Treatment
- What's else ?

Treatment

- Hypokalemia
  - Oral KCl: 10meq/Kg in children
    500meq/day in adult

    ~ AJM, 1998
  - K-sparing diuretics
    - Aldactone & Amiloride

➔ Increase growth rate in children

- Hyperprostaglandin
  - Indomethacin: 1.5~2.5 mg/Kg/day in divided dose

  ➔ Attenuate polyuria, salt wasting, hypokalemia, systemic symptoms of hyperprostaglandin

  ➔Not effective in preventing nephrocalcinosis
  - COX-2 inhibitor?
    - Diuresis and calcium excretion is reduced

    ~ NEJM, 2000
  - Contraindicated in neonate !!
    - Necrotizing enterocolitis, nephrotoxicity

    ~ Pediatr Nephrol, 1998
  - Useless in Gitelman's syndrome

- Hyperaldosterone
  - ACE inhibitor
    - Ameliorate the clinical symptoms
    - Improve hypokalemia and hyperaldosteronism
    - No benefit on NaCl reabsorption
  - Propanolol?
    - Decrease plasma renin activity and aldosterone
    - Did not alleviate hypokalemia
    - Lower BP result in paradoxical increase in renin & aldosterone

- Hypomagnesemia
  - Mg supplement
  - Chondrocalcinosis is the indication
  - Normalization of Mg is difficult

~AJKD, 1995

Intervention	Neonatal Batter's syndrome	Classic Bartter's syndrome	Gitelman's syndrome
Oral K supplement	Usually required	Usually required	Usually required
Oral Mg supplement	Not required	Not required	Usually required
NSAIDs	Used with caution in neonates	Indicated	Not indicated
ACE-inhibitor	Indicated	Indicated	Indicated
K sparing diuretics	Indicated	Indicated	Indicated
NaCl	Usually required IV perinatally	Recommend increased fluid intake	Recommend increased fluid intake
Audigram	Recommended	Not indicated	Not indicated
Growth hormone	May be beneficial	May be beneficial	May be beneficial
Beta-blocker	Not indicated	Not indicated	Not indicated

~ Am J Med Sci, 2001

- Story beginning…
- Clinical presentation
- Differential diagnosis
- Bartter's syndrome
- Gitelman's syndrome
- Treatment
- What's else ?

Q1. Why might the clinical phenotype change with time in a patient with a specific genetic disorder ?

1) 5 patients with Bartter's syndrome
   - Hypokalemia and ROMK mutation
   - Hyperkalemia and hyperaldosterone during neonate ~ pseudohypoaldosteronism

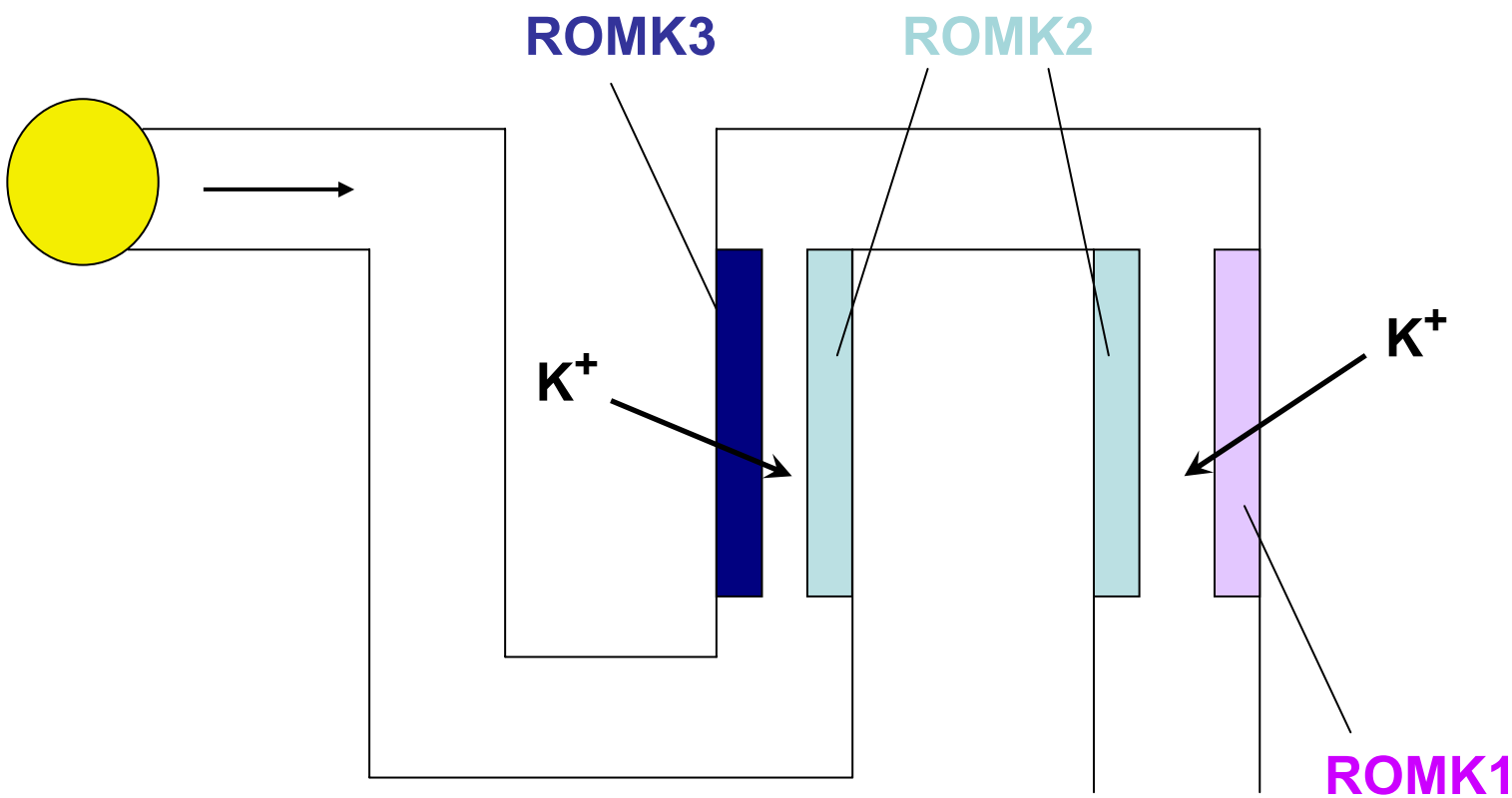
~ JASN, 1998

2) Patients with Bartter's syndrome first
   - Hypokalemia; high excretion of prostaglandin, response to Indomethacin
   - ClC-Kb mutation
   - Develop hypomagnesemia & hypocalciuria

   ➔ Gitelman's syndrome?

~ Pediatr Res, 2000

Hypothesis for (1)



Hypothesis for (2)

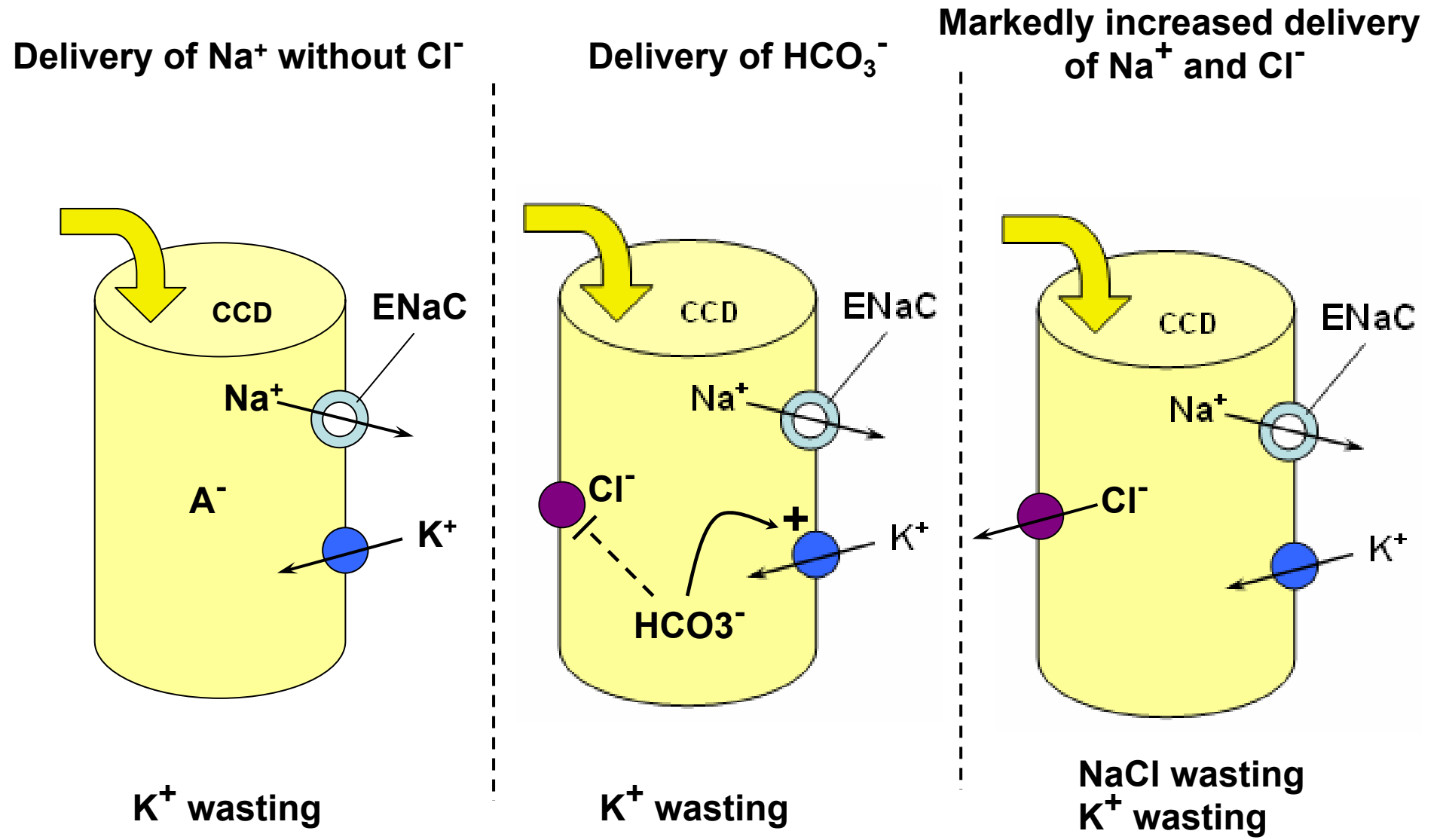
- Other Cl channel might be induced/activated in the loop of Henle
- Replace the function of ClC-Kb in TAL

Q2. What is the basis for the high rate of excretion of K^+ when Na^+ reabsorption is depressed in the LOH or DCT ?

- K^+ content in the CCD lumen
  = $[K^+]_{CCD} \times$ flow in the CCD

- High $[K^+]_{CCD}$ is the primary cause

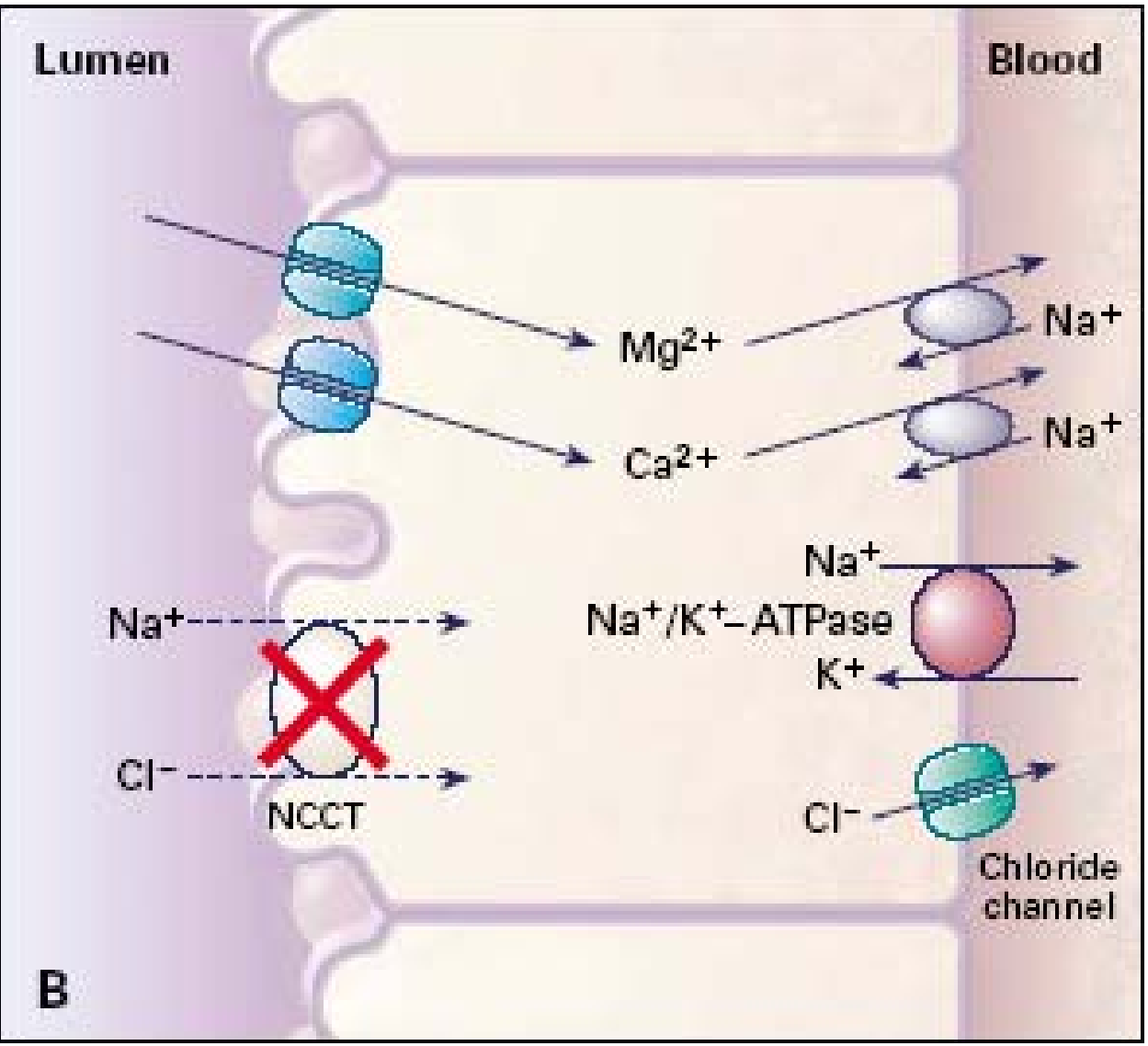
~ Am J Nephrol, 1998



~ *Nephron, 2002*

Q3. Why do hypocalciuria and hypomagnesemia develop in patient Gitelman's syndrome ?

Hypocalciuria



① Basolateral Na-Ca exchange ↑
→Ca inflow via apical Ca channel ↑

~ KI, 1998

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→voltage-dependent Ca channel ↑

~ Biochem Biophys Res Commun, 1999

③ Upregulation of distal nephron

~ Nephron, 2002

④ Volume contraction
→ proximal Ca reabsorption ↑

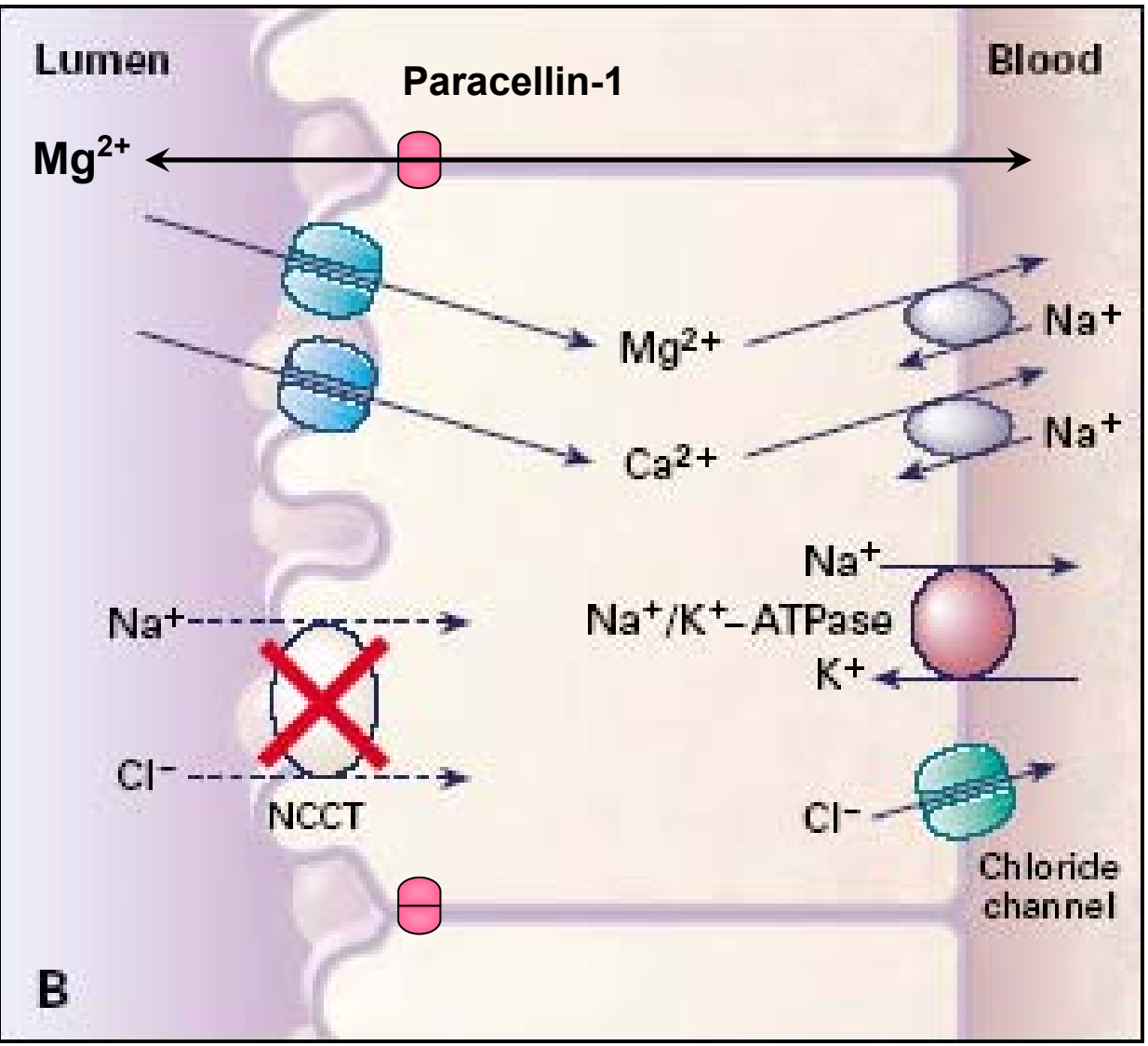
~ KI, 2003

- 2 patients had a negative mutation in the gene encoding γ -subunit of Na-K-ATPase

  – Had hypocalciuria?

~ Nature genetics, 2000

Hypomagnesemia

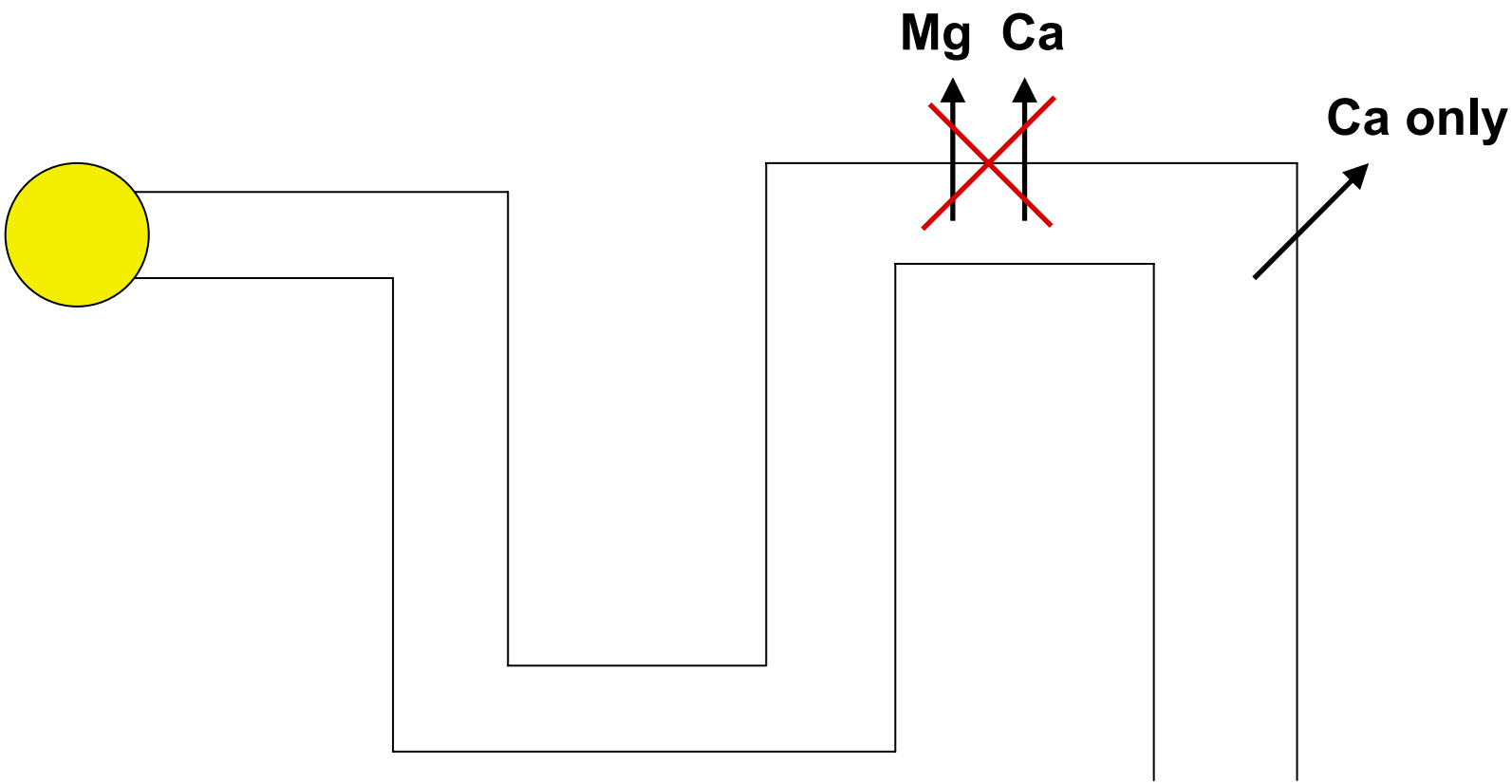


① Similar as Ca ?

② Hypokalemia ?
Why Bartter's not ?

③ ENaC
→ Mg secretion ↑ ?

Hypothesis by Halperin



Q4. Why are higher dose of ENaC blockers required in patients with Bartter's or Gitelman's syndrome ?

- Amiloride fail to curtail kaliuresis
- Flow in the CCD =
  number of osmoles in the CCD / P_{osm}
- The concentration of drug is diluted !!

Q5. Why dose hypokalemia persisted despite therapy with KCl in patients with Bartter's and Gitelman's syndrome ?

- K supplement: 500 meq/day

  K-sparing diuretics
- When more severe hypokalemia occurs

  ➔ ROMK in CCD down-regulation

  ➔ K secretion ↓

  ➔ $[K^+]_{plasma}$ ↑

  ➔ K supplement

  ➔ ROMK conductance ↑

Differential diagnosis of hypokalemia

B. metabolic alkalosis
   i. gastric alkalosis—low urine chloride
   ii. diuretics or other drugs, infection…
   iii. genetic
      a. Bartter syndrome (thick ascending limb transport)
         1. inactive NaK2Cl cotransporter (NaKCC2)
         2. inactive basolateral chloride channel (CLCNKb)
         3. inactive barttin (β-subunit for CLCNKb)
         4. inactive renal outer medullary potassium channel (ROMK)
         5. activated calcium sensing receptor
      b. Gitelman syndrome (distal convoluted tubule transport)
         1. inactive NaCl cotransporter

Disorder	Inheritance	Clinical Features	Hypokalemic Metabolic Alkalosis	Calcium Excretion	Serum Mg	Gene	Protein
Bartter/Gitelman syndromes							
Bartter type I	AR	Antenatal presentation, salt-wasting, nephrocalcinosis	+	High	Normal	*NKCC2*	Bumetanide-sensitive Na-K-2Cl cotransporter
Bartter type II	AR		+	High	Normal	*KCNJ1*	ROMK potassium channel
Bartter type III	AR	"Classic" Bartter syndrome, less severe, occasionally overlaps with Gitelman or antenatal	+	High	Normal or low	*CLCNKB*	CLC-Kb basolateral chloride channel
Bartter type IV	AR	Antenatal Bartter syndrome with sensorineural deafness	+	High	Normal	*BSND*	Barttin, chloride channel subunit
Bartter type V	AD	Hypocalcemia	+	High	Low	*CASR*	Epithelial calcium-sensing receptor
Gitelman	AR	Presentation in young adults, hypomagnesemia, hypocalciuria	+	Low	Low	*NCCT*	Thiazide-sensitive NaCl cotransporter

Conclusion

- Hypokalemia, metabolic alkalosis, hyperrenin & hyperaldosterone ➔ B & G syndrome
- Bartter's syndrome is a rare disease.
  - NKCC, ROMK, ClC-Kb, Barttin, CaSR
- Gitelman's syndrome may be seen in adult.
  - NCCT
  - The mechanisms of hypomagnesemia and hypocalciuria are important but not well known
- K, Mg supplement, K-sparing diuretics, COX-2 inhibitor & ACEI are current mainstay therapy

Thank You