Chapter 8

Formation and Excretion of Urine

Overview of Renal functions

1. Eliminates most of the waste metabolites.

2. Regulates ----- of *body fluid*
   total volume,
   acid-base balance (pH),
   electrolyte composition.

3. Produces hormones, including
   renin,
   EPO (erythropoietin)
   1,25-dihydroxy-cholecalciferol (and PGs)

3 steps of urine formation:

Filtration: *glomeruli* filter blood plasma, and *ultra*filtrate forms

*Re*absorption: *ultra*filtrate is processed in and by *renal tubules* & *collecting ducts (CD)*

Secretion: NH_3 , K^+ , H^+ are secreted by *renal tubules* & CDs

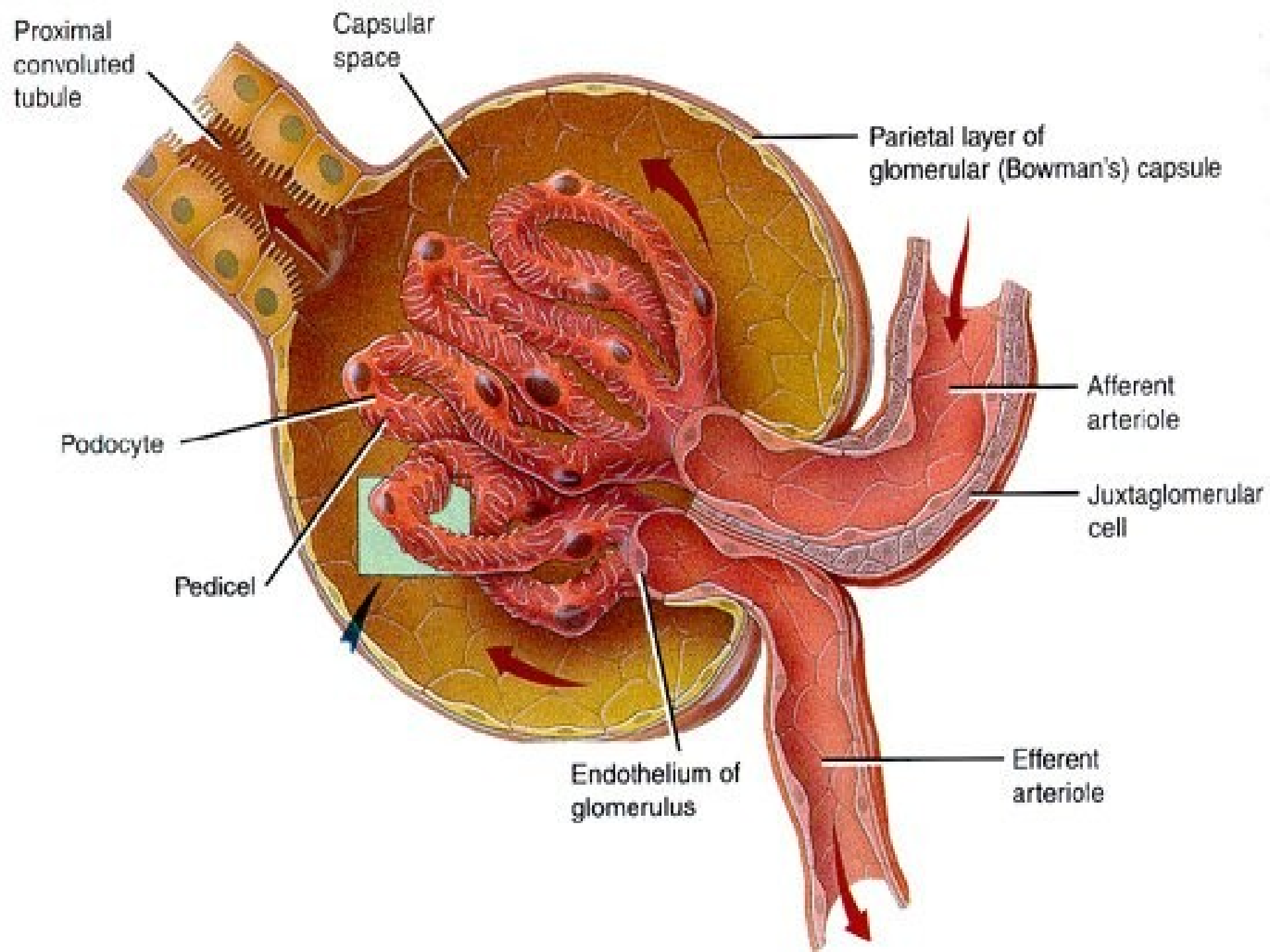
Section 1

Functional anatomy and blood flow of the kidney

1. The **Nephron**

1.10 the Nephron

- renal corpuscle
  - glomerulus
  - Bowman's capsule
- renal tubule
  - proximal tubule
    - P. *Convoluted* T.
    - P. straight T.
  - thin limb
    - TL, descending
    - TL, ascending
  - distal tubule
    - D. straight T.
    - D. *Convoluted* T.


Proximal convoluted tubule
Capsular space
Parietal layer of glomerular (Bowman's) capsule
Afferent arteriole
Podocyte
Juxtaglomerular cell
Pedicel
Endothelium of glomerulus
Efferent arteriole

1.11

Cortical nephrons

v.s.

***Juxta*-medullary nephrons**

vesa recta

	cortical nephron	juxta-medullary nephron
location	outer, middle	inner cortex
number(%)	85~90	10~15
gl. volume	small	large
arteriole Φ :	af-. > efferent	af-. ~ efferent
ef. arteriole forms	capillaries	capillaries and U-shaped *vasa recta*
Henle loop	short	long, to inner medulla

1.12* Collecting ducts (CDs)

morphologically, are not of the nephrons;

in organogenesis, are the branched buds of urethra.

distal tubule →
connecting tubule →
cortical CD →
outer medullary CD →
inner medullary CD → pelvis

principal cells (Na^+-handling)

intercalated cells (HCO_3^--handling)

from wiki :

Principal cells [edit]

The principal cell mediates the collecting duct's influence on sodium and potassium balance via sodium channels and potassium channels located on the cell's apical membrane. Aldosterone determines expression of sodium channel transport ions[3][*verification needed*]. Aldosterone increases the number of Na^+/K^+-ATPase pumps[4] that help reabsorb sodium ions and secrete potassium ions.[5] and vasopressin determines the expression of aquaporin channels on the cell surface.[6] Together, Aldosterone and vasopressin let the principal cell control the quantity of water which is reabsorbed.

Intercalated cells [edit]

Intercalated cells come in α and β varieties and participate in acid-base homeostasis.

Type of cell	Secretes	Reabsorbs
α-intercalated cells	acid (via an apical H^+-ATPase and H^+/K^+ exchanger) in the form of hydrogen ions	bicarbonate (via band 3, a basolateral Cl^-/HCO_3^- exchanger)[7]
β-intercalated cells	bicarbonate (via pendrin a specialised apical Cl^-/HCO_3^-)	acid (via a basal H^+-ATPase)

For their contribution to acid-base homeostasis, the intercalated cells play important roles in the kidney's response to acidosis and alkalosis. Damage to the α-intercalated cell's ability to secrete acid can result in distal renal tubular acidosis (RTA type I, classical RTA).

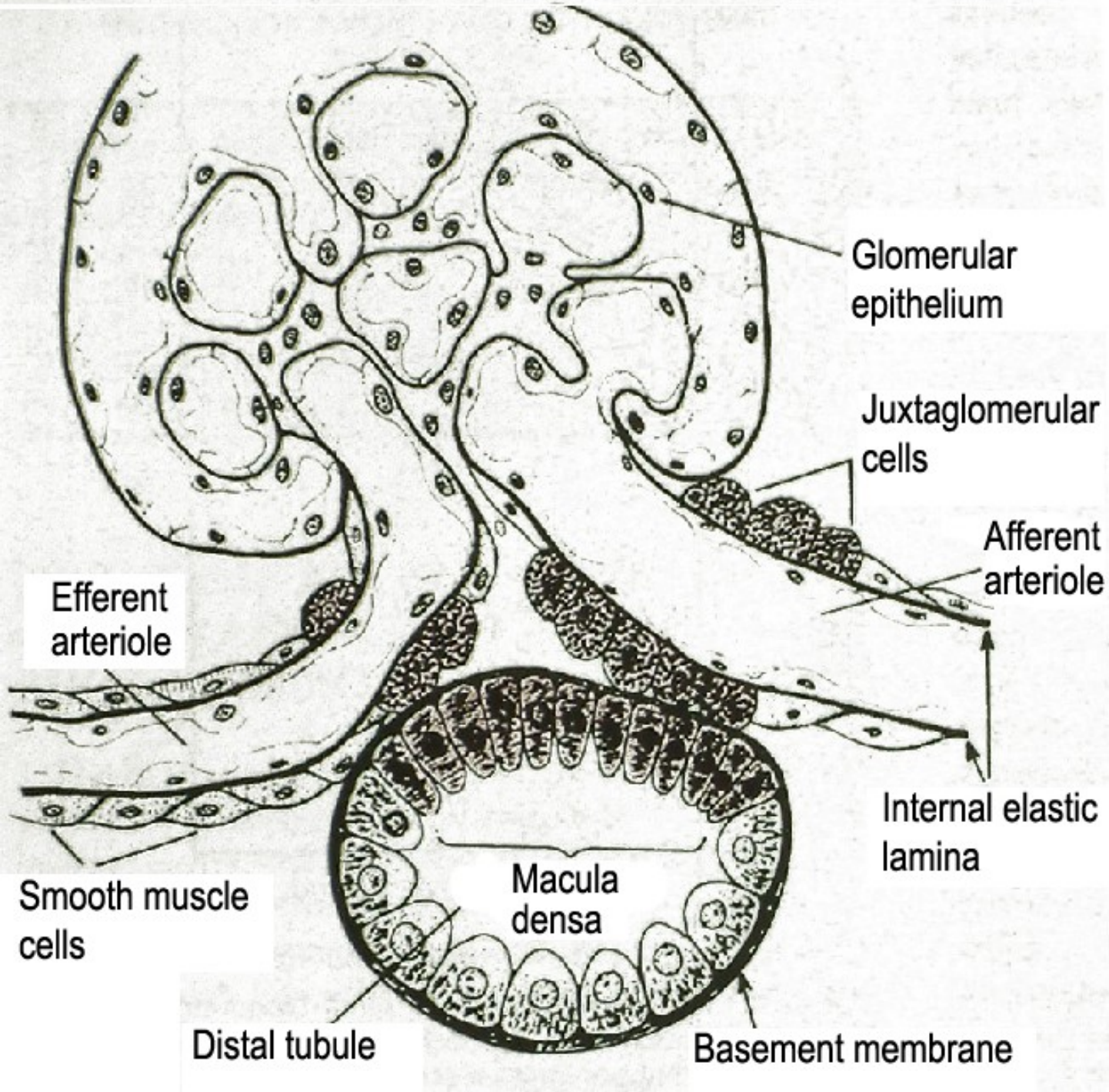


Figure 26-14

Structure of the juxta-glomerular apparatus, demonstrating its possible feedback role in the control of nephron function.

1.30 Innervation of the kidney

thoracic 12 ~ lumbar 2 ;

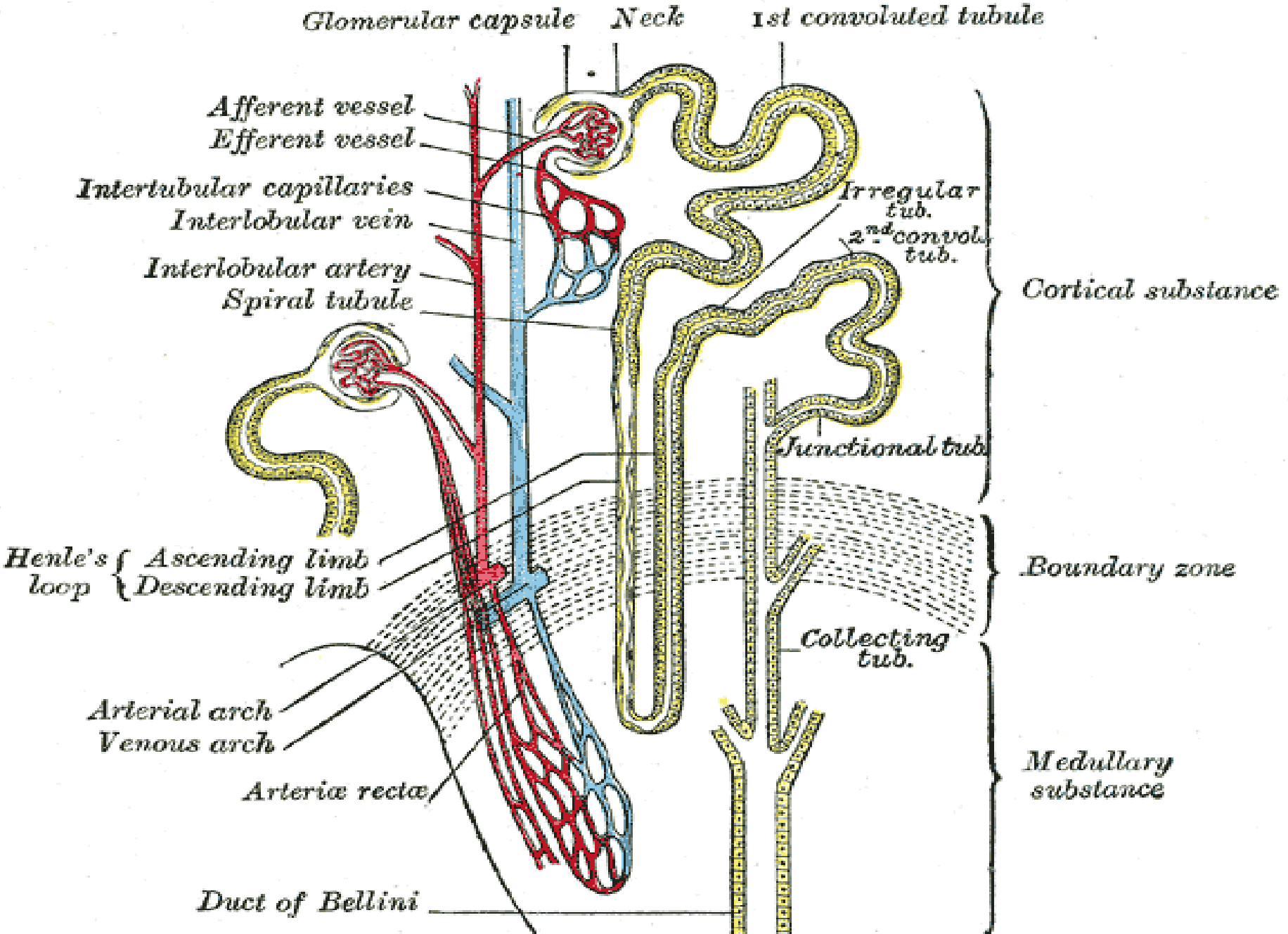
only sympathetic :

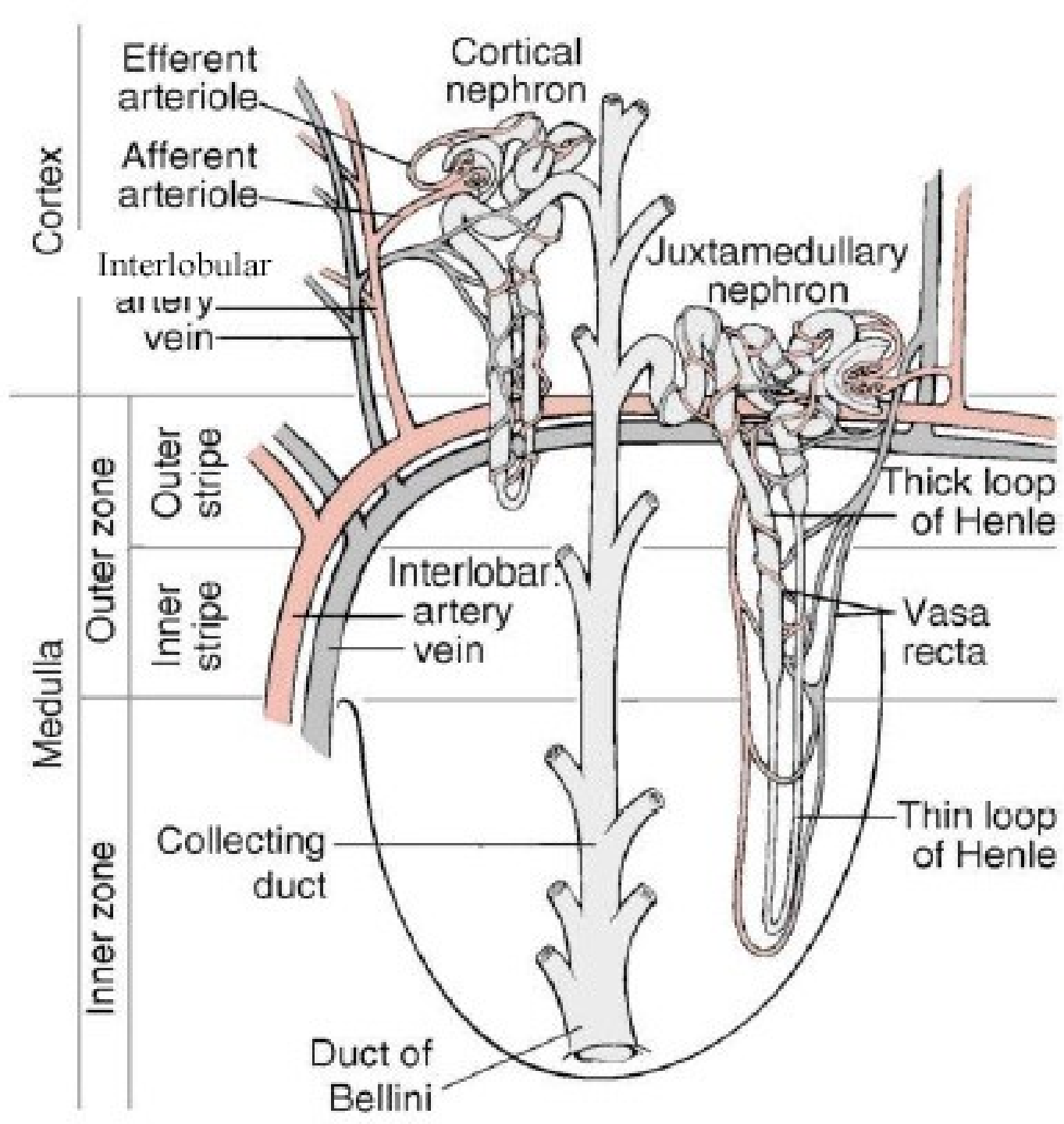
- *nor*epinephrine (NE)
  - → renal blood flow ↓
  - → GFR ↓
  - → reabsorption *changes*
  - → renin release ↑
- dopamine (DA) : renal blood flow ↑

renal afferent nerves; Reno-renal reflex

1.40 Blood supply of the kidney

2 capillaries in series !!!


Glomerular capsule
Neck
1st convoluted tubule
Afferent vessel
Efferent vessel
Intertubular capillaries
Interlobular vein
Interlobular artery
Spiral tubule
Irregular tub.
2nd convol. tub.
Cortical substance
Junctional tub.
Henle's loop
Ascending limb
Descending limb
Boundary zone
Collecting tub.
Arterial arch
Venous arch
Medullary substance
Arteriæ rectæ
Duct of Bellini



Relations between blood vessels and tubular structures and

differences between cortical and juxtamedullary nephrons.

2. Renal blood flow & Regulation

2.10 Characteristics of Renal Blood Flow

* Renal Blood Flow (RBF) is high

1200 ml/min in adult, *i.e.* 1/5~1/4 of CO

energy expenditure : 10% of BMR

* medullary flow is very low

compared with cortical flow :

5% in outer, 1% in inner medulla

2.20 regulation

autoregulation *

nervous and humoral regulations

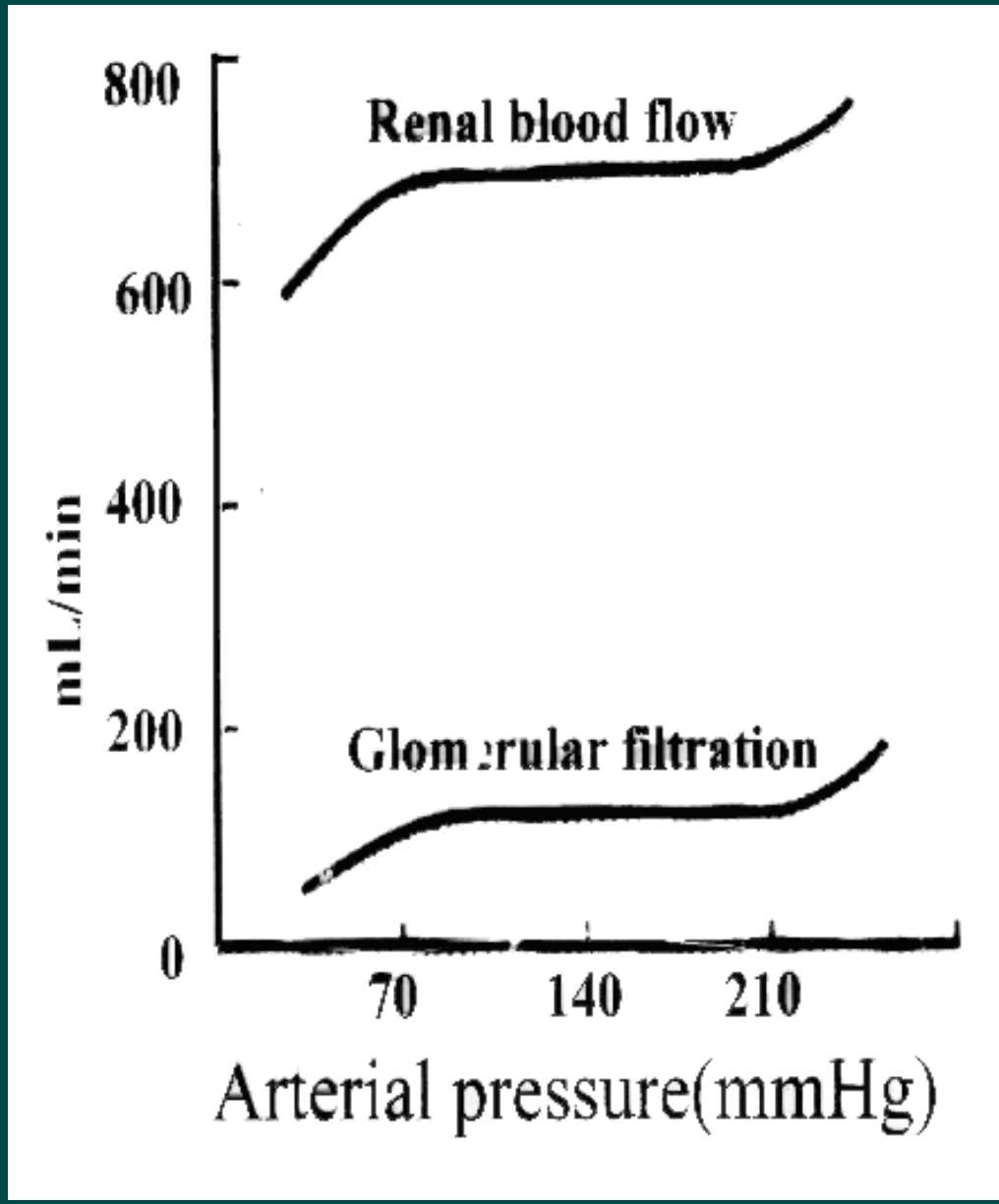
Autoregulation

perfusion pressure :
80 ~ 160 mmHg

renal vascular resistance *changes*, thus,

blood flow :
constant !!!

independent of innervation



Mechanisms:

a. Myogenic mechanism

the property of smooth muscle cells in afferent a.

papaverine (罂粟碱)

chloral hydroate (水合氯醛)

cyanide (CN^-, 氰化物)

b. Tubuloglomerular feedback

Macula densa,

when detects NaCl overload,

signals to afferent a. to contract

mesangial cells

local renin-angiotensin system, NO, PGs (20-HETE)

Nervous and *humoral* regulation

Renal sympathetic nerves: NE --

at rest, maintain a tonus;

upon stimulation, tonus ↑

-- smooth muscles : **α -receptor**

-- DA as a transmitter: *against* NE

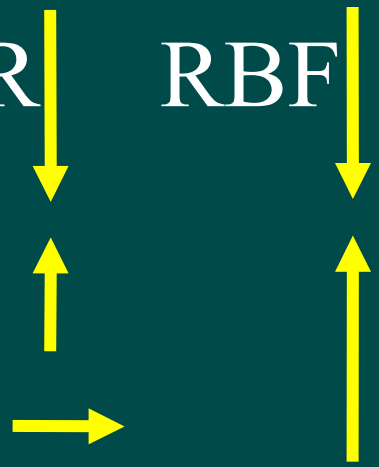
Humoral factors:

Ang-II (systemic and local)

endothelin, ADH

NO , bradykinin, ANP :

PGI_2 , PGE_2 (indomethacin)



Section 2

Glomerular Filtration

3 steps of urine formation:

Filtration: *glomeruli* filters blood plasma, and *ultra*-filtrate forms

Reabsorption: *ultra*filtrate is processed in and by *renal tubules* and *collecting ducts*

Secretion: NH_3 , K^+ , H^+ are secreted by *renal tubules* and *collecting ducts*

*ultra*filtration fluid, or *primary urine*,
or *ultra*-filtrate

GFR, glomerular filtration rate

effective filtration pressure, EFP

filtration fraction, FF

filtration coefficient, K_f

1.10 filtration barrier (memb.) *p299*

-- Capillary endothelial cells

fenestration: 70~90 nm,

blood cells…||

-- Basement membrane:

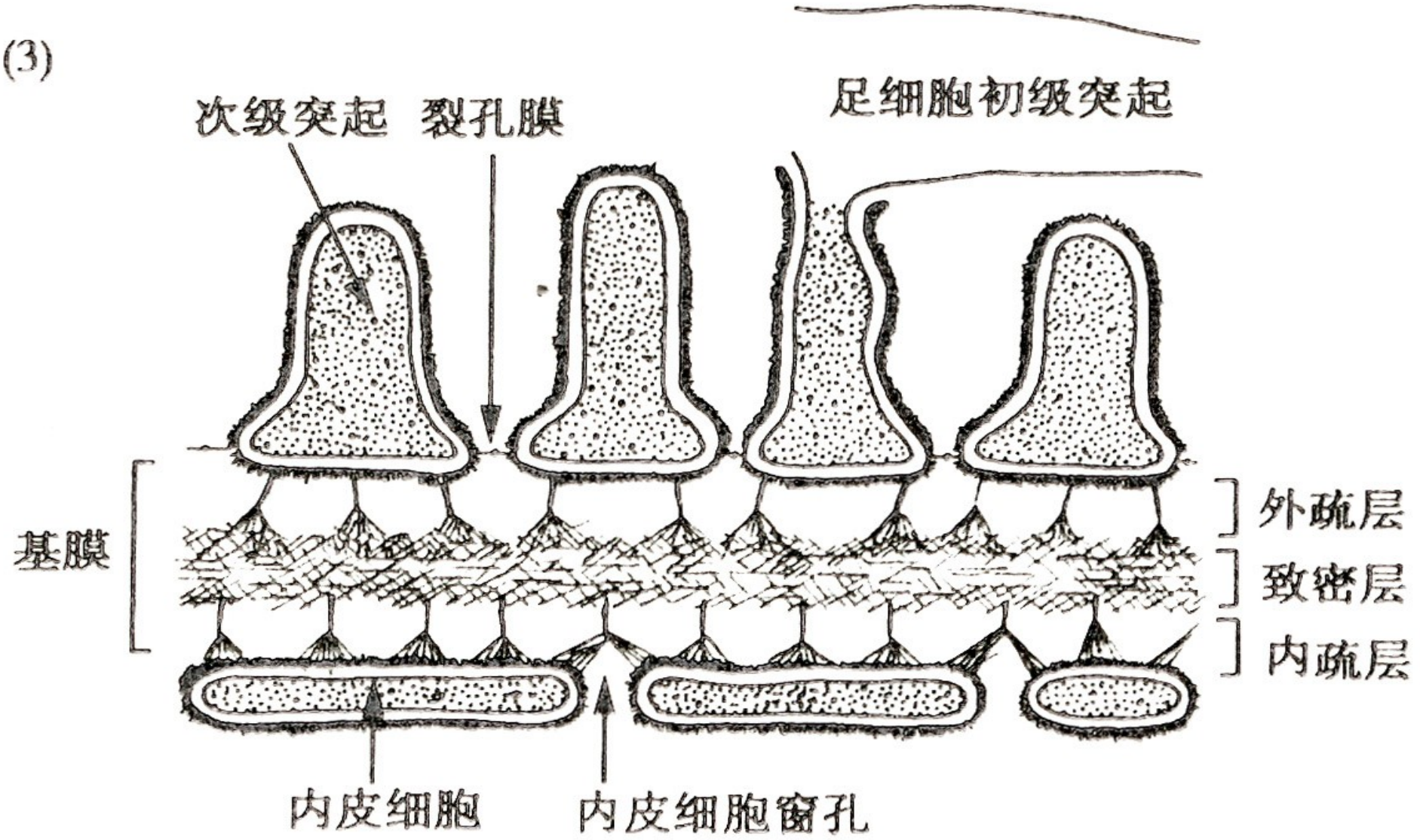
meshwork: meshes of 2~8 nm

negatively charged proteins ||

-- Foot processes of podocytes

filtration slit membrane (nephrin): 6~11 nm

(3)



Two barrier types:

Mechanical ~ : >4.2 nm

Electrical~: negatively charged, albumin

***Permeable to*:**

Water and small molecules, <2.0 nm

Positively charged molecules

Totally in adult, 2 kidneys have an area of

~1.5 m^2 (1.2 x 1.2)

2. Effective Filtration Pressure (EFP)

$$V = K_f * [(P_c + \pi_i) - (P_i + \pi_p)]$$

for interstitial fluid formation *(p141)*

$$SNGFR = K_f * [(P_{gl.cap} + \pi_{if}) - (P_{if} + \pi_{plasma})]$$

here, $\pi_{if} = 0$ (No protein in primary urine)

therefore,

$$EFP = P_{g.capillary} - P_{capsule} - \pi_{plasma}$$

glomerular capillary pressure ($P_{g.c.}$)

at the afferent end, ~45 mmHg

decreases on the way to the efferent end.

plasma colloid osmotic pressure (π_{plasma})

at the afferent end, ~25 mmHg

increases on the way to the efferent end.

hydrostatic pressure in Bowman's space ($P_{capsule}$)

usually constant, ~ 10 mmHg

ultra-fitration

ultra-filtrate or primary urine :

small molecules: G, aa, etc.

ions

protein : almost no

no reabsorption in glomerulus !

!!! π_{plasma} is the major variant !

when EFP =0, Filtration equilibrium

the Area on the efferent-side of the equ. point

==

the functional *reservation*

* Glomerular Filtration Rate (GFR)

the quantity of glomerular ultra-filtrate
formed by the both kidneys *per minute*.

125 ml/min, in normal adults
with a *body surface area* of 1.73 m^2 !

☞ BMR, Cardiac index, pulmonary ventilation…

inulin clearance ~ GFR

GFR derived :

Single Nephron GFR: micropuncture

* Filtration fraction (FF)

$$\frac{\text{GFR}}{\text{Renal Plasma Flow}} \times 100\%$$

normally 16% ~ 20%

RPF = renal blood flow * (1- hematocrit)

if GFR=125 ml/min, RPF=660 ml/min

then, FF= 19%

* filtration coefficient, K_f

definition: ml/sec/mmHg

area of filtration barrier

permeability

3. Factors affecting GFR

GFR = K_f * EFP

renal plasma flow

* Glomerular capillary pressure (hydrostatic)

a.Bp range 80~180 mmHg, GFR constant;

seen in blood loss, stress……

* Capsule pressure / usually stable;

severe ureteric kidney stones, or tumor ↑

* Plasma colloid osmotic pressure /usually stable;

too much saline,

albumin synthesis : end-stage of liver disease,

albumin loss: allergy, terminal kidney diseases ↓

** Renal plasma flow

changes filtration equilibrium:

the higher RBF is, the longer capillary filters

emergency /stress : renal sympathetic n. (+)

Note: the renal vascular smooth muscles are very sensitive to Ad/NE ☞p159

** Filtration coefficient

permeability & area of glomerular barrier

acute & chronic glomerulonephritis

Section 3

Transport Function of Renal Tubules and Collecting Ducts

Fine process of glomerular filtrate in and by renal tubules and collecting ducts

reabsorption

secretion

Filtrate formed :

125 ml/min * 24 * 60 min = 180 L (~3 * 60 kg)

24h Urine vol. : ~ 1.5 L

- **Active transport:** ATP consumption :

ion pumps : H^+pump, Na^+-K^+ pump, Ca^{2+} pump

secondary : Na^+- glucose, Na^+-amino acids : symport

K^+-Na^+-$2Cl^-$: symport

Na^+-H^+, Na^+-K^+ : antiport (exchange)

- **Passive transport:** no ATP consumption

diffusion, facilitated diffusion

solvent drag , *osmosis*

- endocytosis

Pathways (Cellular locations of those transporters)

apical membrane

baso-lateral m.

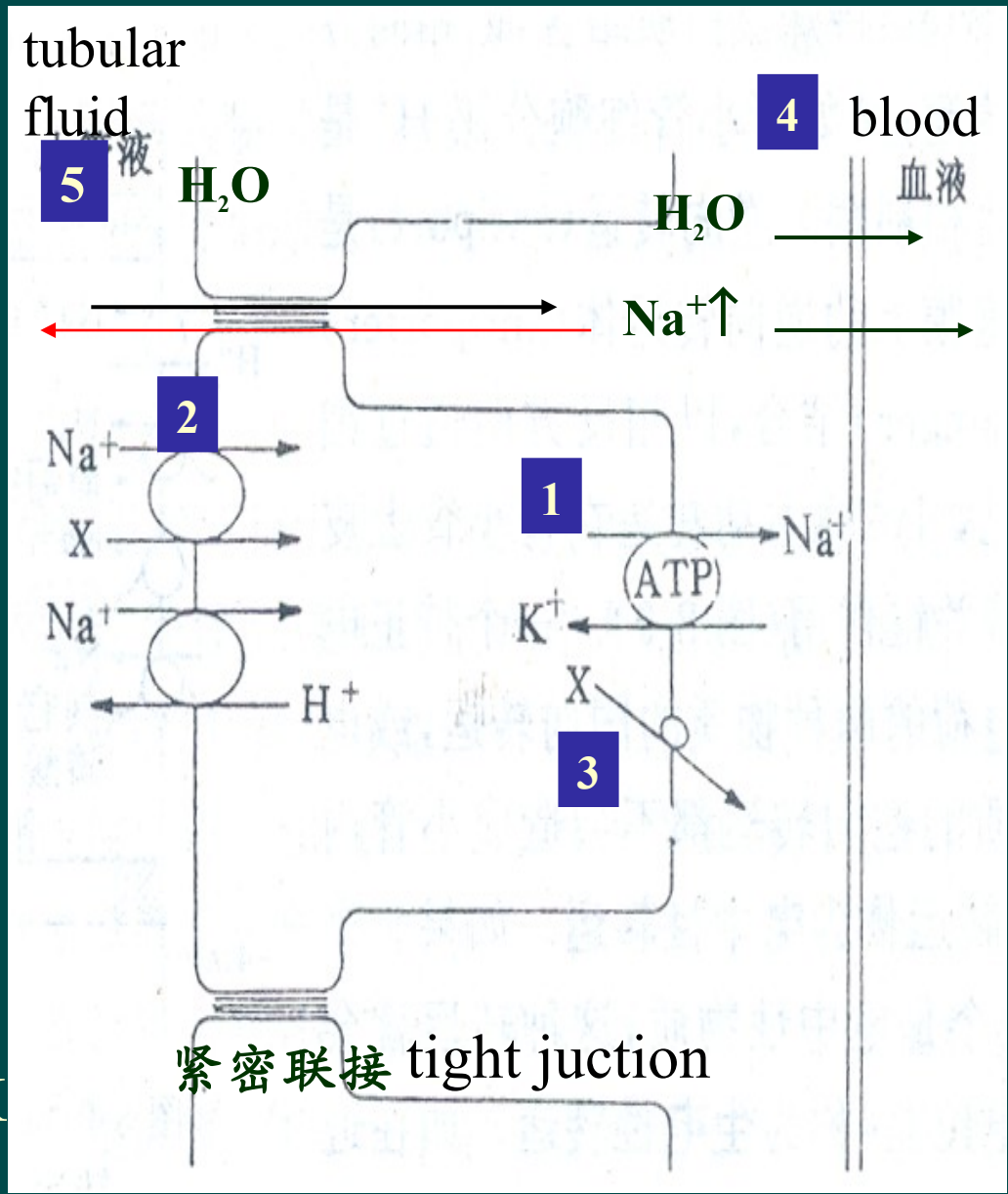
trans-cellular route

☞X

para-cellular route

tight junction

☞Na^+ leak



3.10 Reabsorption & secretion in renal tubules & collecting ducts

3.11 Reabsorption of Na^+, Cl^- , H_2O

Proximal tubule Loop of Henle Distal Tubule

70% of NaCl + H_2O :

2/3 *trans*-cellarly by initial PCT segment

1/3 *para*-cellularly, middle+distal segments

(1) NaCl (2) H_2O

✓ initial PT (early, mainly PCT)

*baso*lateral Na^+ pumps maintain a low $[Na^+]_i$

apical Na^+-G, Na^+-aa <u>symport</u> *p25*

apical Na^+ - H^+ <u>exchange</u> *(2ndary active)*

H^+ pump (active) *H^+ secretion*

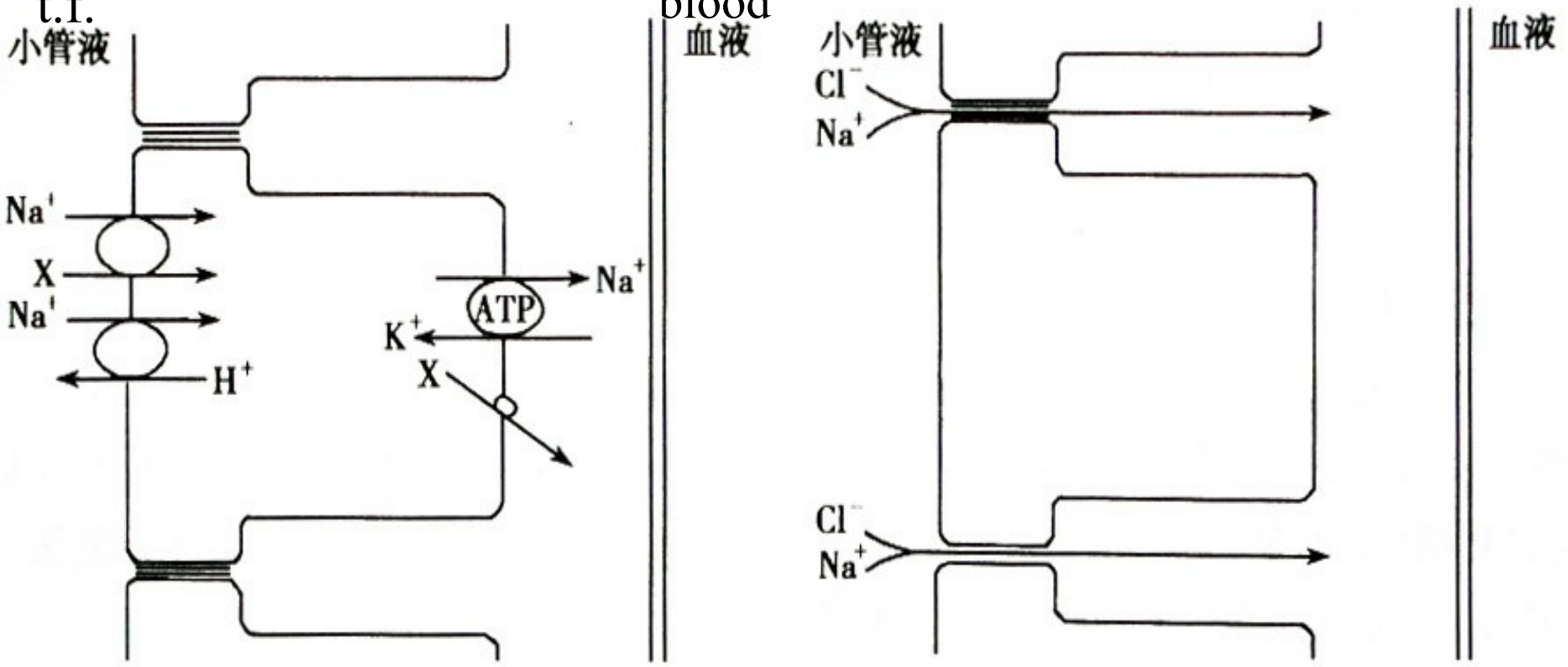
Na^+, G, aa reabsorbed

H_2O osmosis, H_2O solvent-drags other substances

H^+ helps HCO_3^- reabsorption,

Cl^- remains in tubular fluid.

t.f. blood



A 近球小管前半段 early PT

X 表葡萄糖、氨基酸、磷酸盐等

X= glucose etc.

B 近球小管后半段 later PT

图 8-8 近球小管重吸收 NaCl 示意图

✓ middle & distal PT

tubule fluid (t.f.) :
little G, aa, HCO_3^-

$[Cl^-]_{tf} >> [Cl^-]_{ECF}$

by 20~40%

*para*celluarly,

Cl^- : *t.f.* → *ECF* : *t.f.* positively-charged !

Na^+ : follows Cl^- (NaCl passive reabs.)

*trans*cellularly, (apical exchangers :)

Na^+-H^+ exchange : cytosol H^+ → *t.f.*

Cl^--HCO_3^- exchange : cytosol HCO_3^- → *t.f.*

t.f. Cl^- →cytosol →*ECF*

(basolateral Cl^--K^+ symporter)

PT: (1) NaCl (2) H_2O

follows osmolality gradient

*para*cellularly:

*trans*cellularly: aquaporin-1, AQP-1

solvent drags K^+, Ca^{2+}

Proximal tubule Loop of Henle Distal Tubule

Summary :

NaCl, H_2O , Ca^{2+} , K^+ 65~70%

Preferred reabsorption of HCO_3^- (to Cl^-)

the only segment that reabsorbs G

iso-osmotic reabsorption, *t.f. is* +-charged

3.11 Reabsorption of Na^+, Cl^- , H_2O

Proximal tubule **Loop of Henle** Distal Tubule

20% NaCl and 15% H_2O

25~30% K^+

20% Ca^{2+}

15% HCO_3^-

thick ascending limb

✓ Thin limbs :

in short:

Tubule fluid osmolality ≈

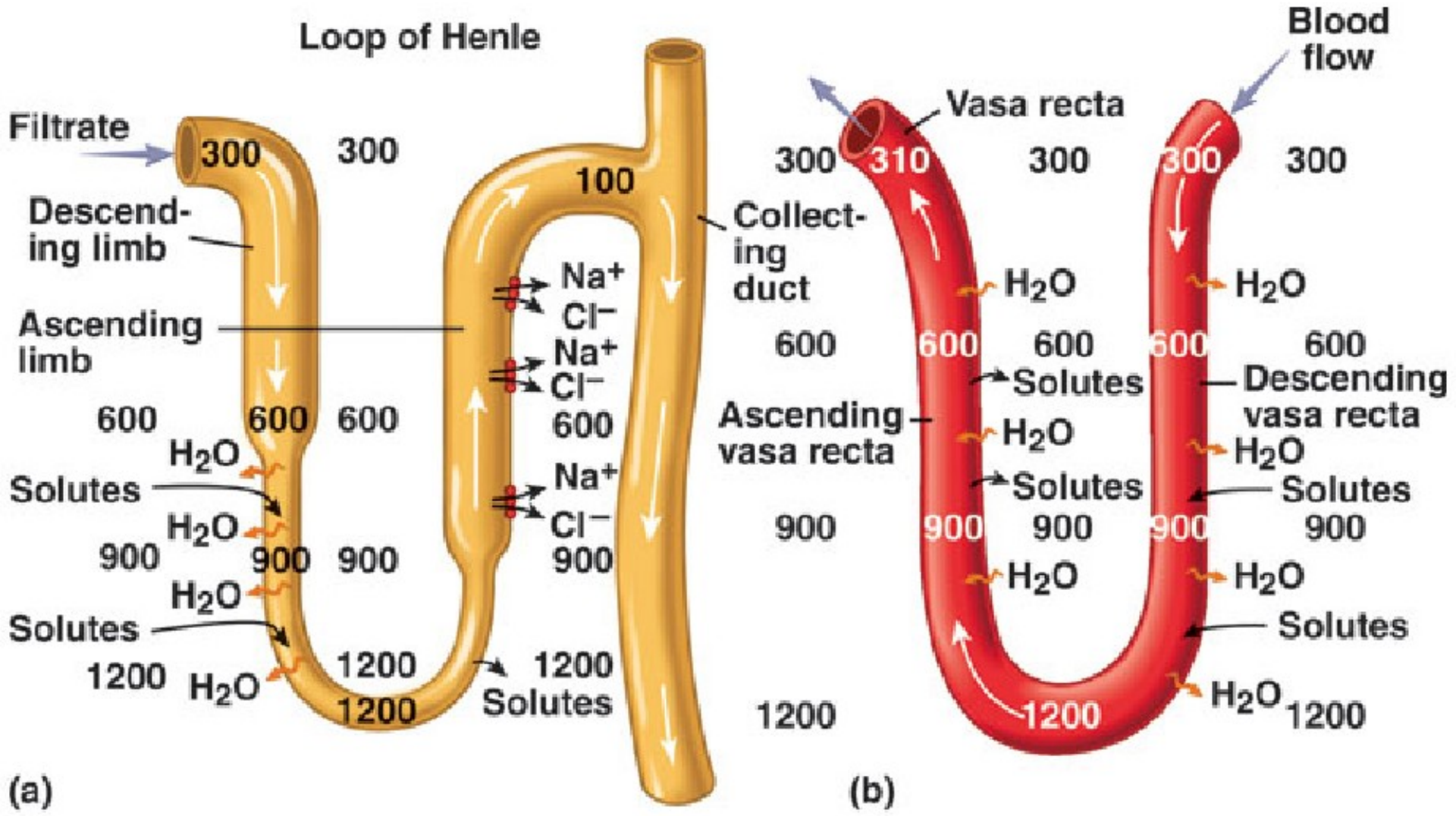
interstitial fluid (ECF) osmolality gradient

Thin descending limb: Na^+-*im*-, H_2O-permeable

Thin ascending limb: H_2O-*im*-, Na^+ -permeable

thin descending limb : AQP-1

Countercurrent Systems in the Kidney



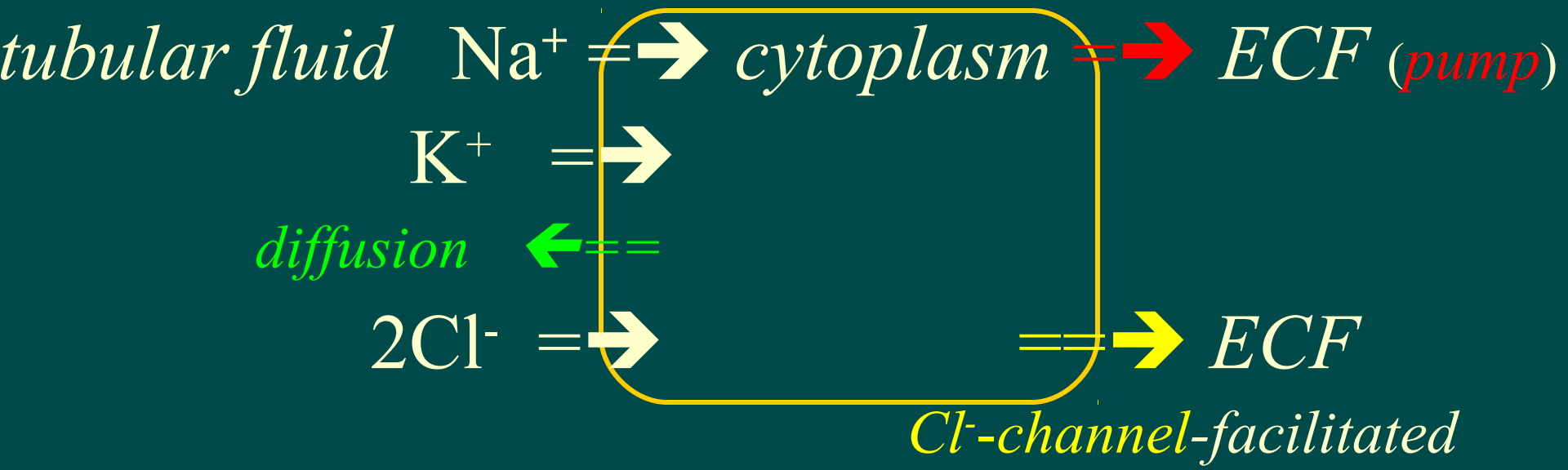
✓ Thick ascending limb

impermeable to H_2O

Epithelial cells :

apical Na^+-K^+-$2Cl^-$ symporter

basolateral Na^+-K^+ pump



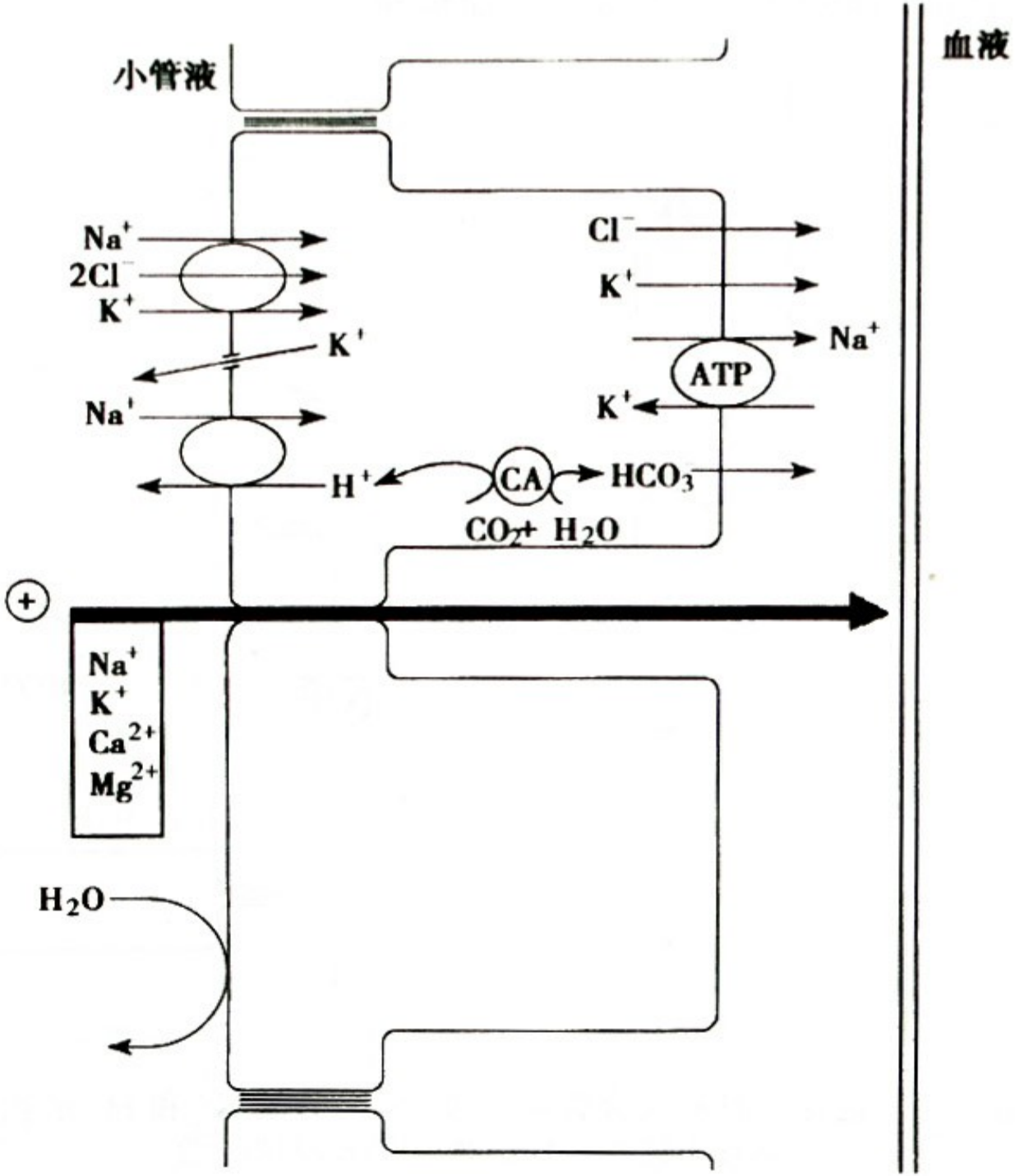


图 8-10

NaCl 在髓袢升支粗段中重吸收的机制

(引自 Berne, Levy, Physiology, 4th edition)

as results :

* *tubular fluid* is positively-charged

* *buildup of* *ECF* osmotic gradient

solutes are actively reabsorbed, while

H_2O is **NOT** allowed to permeate :

t.f. osmolality becomes lower

i.f. osmolality becomes higher

furosemide (呋塞米，呋喃苯胺酸，速尿)

(loop diuretics)

ouabain (哇巴因)

Proximal tubule **Loop of Henle** Distal Tubule

Summary:

thin limbs:

$$t.f \text{ osmolality} \approx i.f. \text{ osmolality}$$

thick ascending limb :

Na^+-K^+-$2Cl^-$ symport

t. f. is positively-charged

furosemide

3.11 Reabsorption of Na^+, Cl^- , H_2O

Proximal tubule Loop of Henle **DT & CD**

~ 7% of filtrated NaCl		aldosterone
~ ? H_2O		ADH
~ ? K^+	{ reabsorption	aldosterone
	secretion	
9% Ca^{2+}		PTH, calcitonin, Vit. D_3
5%	HCO_3^-	

Initial Distal Convoluted Tubule:

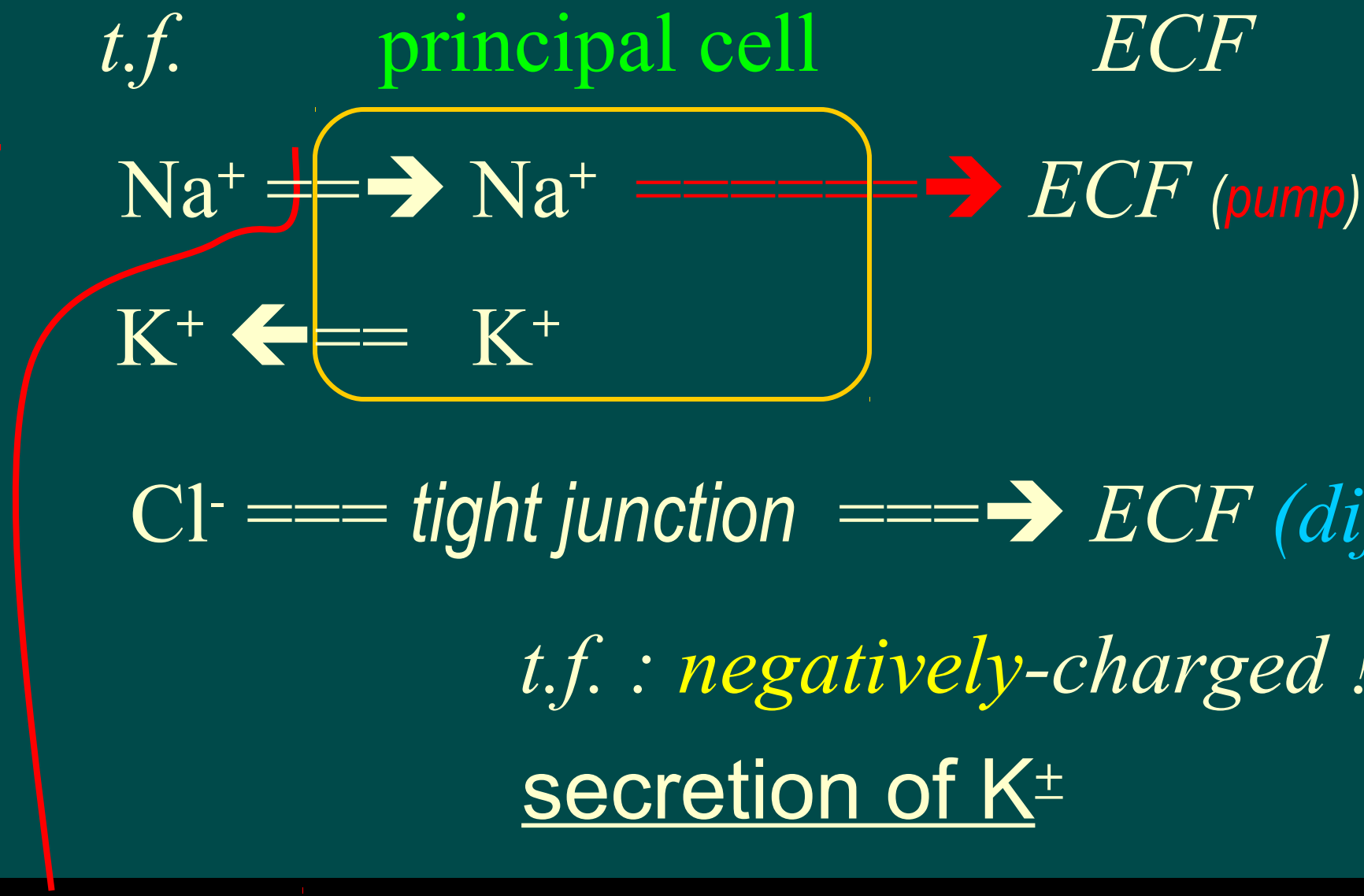
im-permeable to H_2O, *like thick ascending limb*

active NaCl reabsorption : Na^+-Cl^- symport

thiazide (噻嗪类， 如氢氯噻嗪) :

Na^+-Cl^- symporter (-)

distal DCT and collecting tubule :



H_2O reabsorption in CD:

principal cell :

the permeability to H_2O -- aqua-porins

水孔蛋白：水通道

AQP-2, AQP-3, AQP-4

ADH (anti-diuretic hormone, vasopressin)

Proximal tubule Loop of Henle **DT & CD**

Summary:

Na^+, H_2O, K^+, Ca^{2+} : hormone-controlled

Initial DCT : thiazide

distal DCT & CD : amiloride

t.f. is negatively-charged

secretion of NH_3, H^+, K^+ : interaction

3.12 Reabsorption of HCO_3^- and secretion of H^+ acid-base equilibrium

Proximal tubule Loop of Henle DT & CD

≈ 4320 mmol / day

80~85% proximal tubules

15% thick ascending limbs

5% distal tubules and collecting ducts

Preferred reabsorption of HCO_3^- (to Cl^-)

Secretion of H^+ in PT:

apical H^+-Na^+ exchanger (mostly)

apical H^+-ATPase (vacuolar-type, V-ATPase) (a little)

The ways leading to blood:

b-l. HCO_3^- - Na^+ symport 3:1 (→ *ECF*)

b-l. HCO_3^- - Cl^- exchange 1:1

CA, carbonic anhydrase 碳酸酐酶

Acetazolamide 乙酰唑胺

Proximal tubule Loop of Henle DT & CD

thick ascending segment only

Proximal tubule Loop of Henle **DT & CD**

DCT & CD intercalated cells :

HCO_3^- -H^+ handling cells

intercalated cells :

apical H^+-K^+-ATPase (parietal cells, stomach, p231

apical H^+-ATPase (vacuolar-type, V-ATPase)

H^+ : $+ HCO_3^-$ *(PT)*

$+ HPO_4^{2-} \rightarrow H_2PO_4^-$ *(DT,CD)*

$+ NH_3 \rightarrow NH_4^+$ *(PT,DT,CD)*

also, CD intercalated cells:

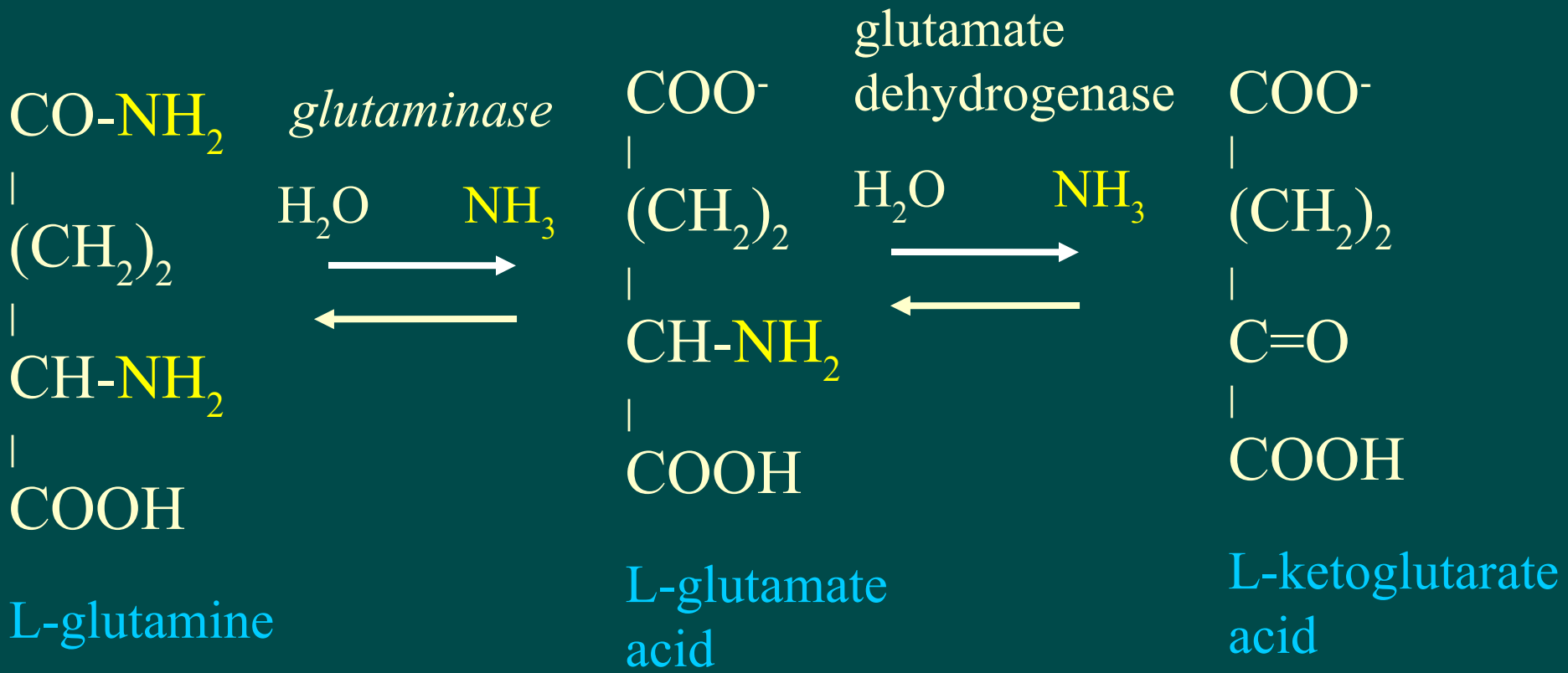
apical HCO_3^--Cl^- exchanger

b-l. proton pump 倒裝的

in *metabolic alkalosis*, to alkalize the urine

3.13 Secretion of NH_3 linked to H^+ & HCO_3^-

Formation of NH_3



intra-cellularly, $NH_3 + H^+ \leftrightarrow NH_4^+$

fates of NH_3

* simple diffusion (NH_3 is *lipid-soluble*)

* H^+ -Na^+ exchanger (H^+ *substituted by* NH_4^+)

thick ascending limb :

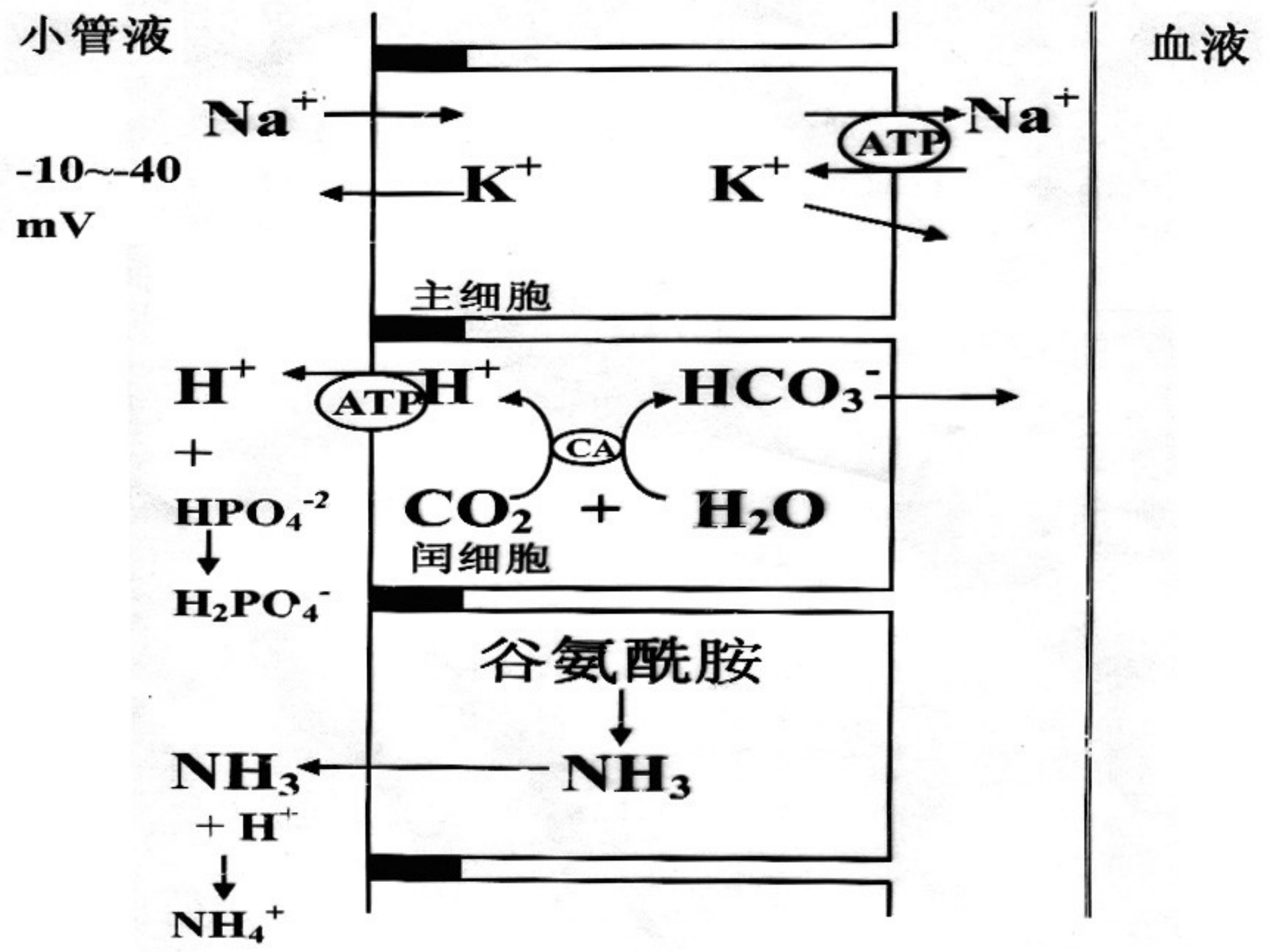
* Na^+-K^+-$2Cl^-$ symporter (K^+ *substituted by* NH_4^+)

collecting duct :

simple diffusion, in *t.f.* : $NH_3 + H^+ \rightarrow NH_4^+$

consequently, H^+ is in urine, HCO_3^- in blood

chronic acidosis : glutamine metabolism


小管液
血液
-10~-40
mV
Na^+
K^+
ATP
Na^+
K^+
主细胞
H^+
ATP
H^+
HCO_3^-
CA
+
HPO_4^{-2}
CO_2 + H_2O
闰细胞
$H_2PO_4^-$
谷氨酰胺
NH_3
NH_3
+ H^+
NH_4^+

4.14 Reabsorption and Secretion of K^+

PT: constant fraction … 65%~70%

Loop: 25%~30%

DT & CD : secretion+reabsorption

net excretion amount …

affected by hormones…

apical membrane: permeable to K^+

Na^+-K^+ pumps maintain high $[K^+]_i$,

tubular fluid voltage, H^+-K^+ pumps, *etc.*

K^+ : *DCT & CD*

principal cells : secretion ($[K^+]_{ECF}$, aldosterone, t.f. rate)

intercalated ~: reabsorption (H^+-K^+-ATPase)

aldosterone: retaining NaCl+H_2O,

excreting K^+

amiloride : K^+-sparing diuretics

acidosis // *hyper*-kalemia : H^+-K^+ exchange

H^+-K^+-ATPase

Summary:

secretion of NH_3 , H^+, K^+ :

we do not need too much, or supply is rich

their interaction is of great clinical importance

3.15 Reabsorption and excretion of Ca^{2+}

Plasma Ca^{2+}: 50% *free*, other half *conjunct*

Filtrated Ca^{2+}: 70% proximal tubule, parallel with Na^{+}

20% loop of Henle

9% distal & collecting tubules

<1% excreted

PT: 80% solvent drag (via tight junction)

20% *trans*-cellularly *b.-l.* pump+exchange

loop of Henle: only thick ascending limb

DT & CD: active transport

Ca^{2+} excretion // 钙磷代谢

regulated by:

parathyroid hormone, PTH : retaining Ca^{2+}

affected by

H_2O and Na^+ excretion

plasma pH : resorption ↑ in metabolic *acidosis*

3.16 Reabs. of glucose & amino acids

PT Only, *esp.* P. convoluted T.

Mechanism:

apical Na^+-G symporter (SGLT2) *(p25)*

D-glucose > L-glucose; phlorhizin (根皮甙)

b-l. glucose transporter 2 (GLUT2)

--- Amino acids : same, but more *specific* carriers

carrier numbers , saturation

When plasma [G] reaches 180 mg/100 ml…

Renal threshold for glucose

is referred to the plasma [G] at which glucose begins to appear in the urine.

Maximal rate of transport for glucose ($T_{m\text{-}G}$)

plasma [G] reaches 300 mg/100 ml …

urine [G] parallel plasma [G]

male 375 mg/min, female 300 mg/min

heterogeneity of nephrons

3.17 other substances

- Urea UT1~4
  renal usage of this metabolite
- Creatinine
- Penicillin
- Phenol red
- Proteins : proteinuria

Summary

Ca^{2+} , K^{+} :

Glucose, aa, etc.

近端小管 （曲部、直部） 小管液 +

髓袢: 细段 （降支、升支）

远端小管 直部 +

远端小管 曲部、集合管 – –

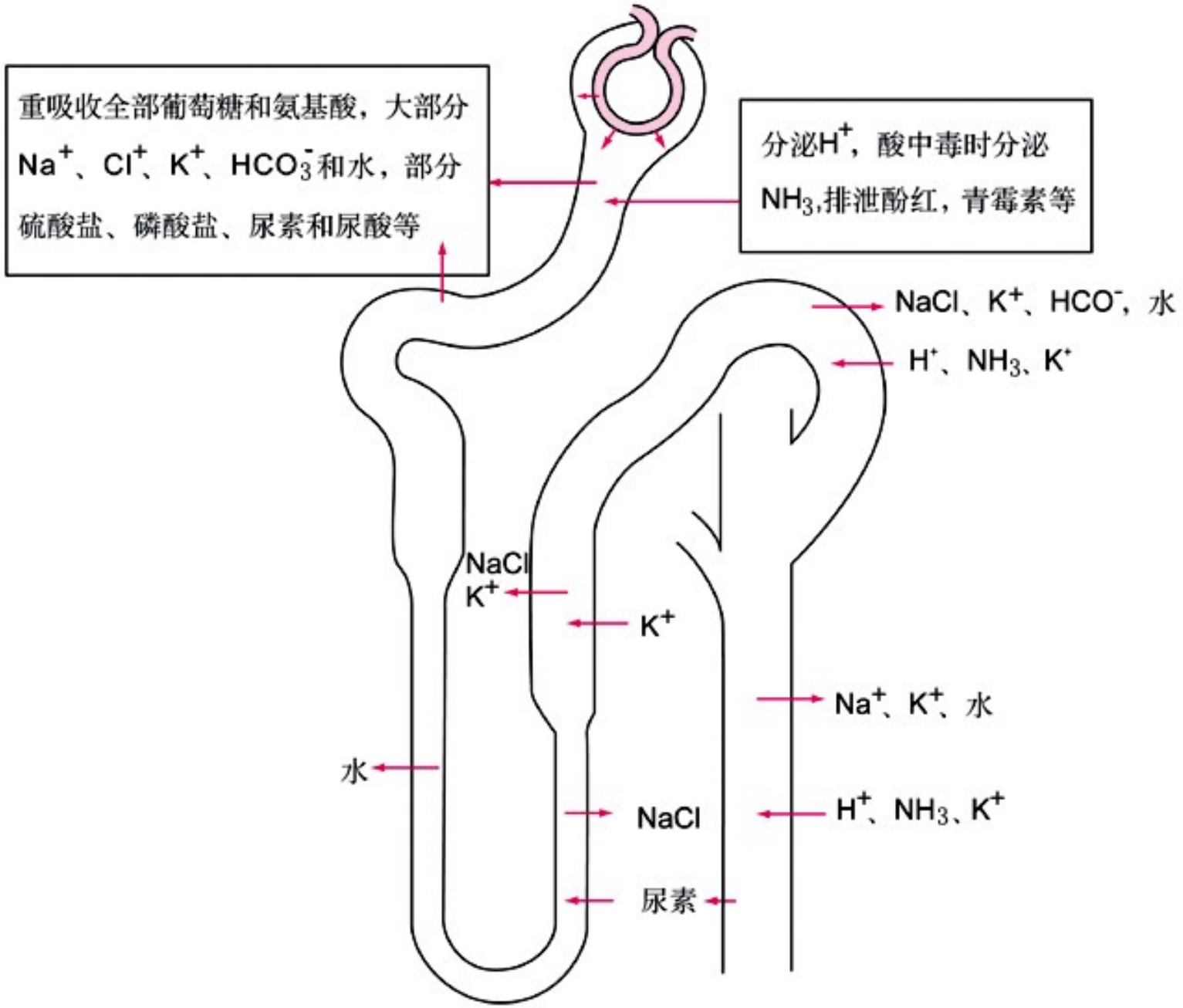


图8-14　肾小管和集合管的重吸收及其分泌作用示意图

PCT NaCl+H_2O 65~70%

the only segment that reabsorbs G

iso-osmotic reabsorption

loop of Henle

thin limbs *t. f.* osmolality ≈ *i. f.* osmolality

thick ascending limb active transport of Na^+-K^+-$2Cl^-$

impermeable to H_2O

DCT and CD

regulated reabsorption of NaCl+H_2O

Section 4

The Formation of Concentrated and Dilute Urines

Thick ascending limb : engine

DT & CD do concentration & dilution !

是 浓缩 和 稀释

发生的部位

4.20 Concentration

1200 mOsm/kgH_2O (4~5x plasma osmolarity)

(10,000 , *ie.* 33x in Australian hopping mouse)

(500, *ie.* 1.7x in beaver)

---- Removes waste and

prevents rapid dehydration

4.20 Concentration

4.30 The Medullary Hyperosmolarity :

the osmotic gradient

in the interstitial fluid

4.31 a little physics

Counter-Current System

and its applications in the kidney

Con-current system

Countercurrent systems in the kidney

* Create and maintain an osmolality gradient in the medullary interstitial fluid, which 'drains' H_2O from tubular fluid.

--- multiplication

* Take the reabsorbed H_2O+ solutes back to circulation:

1: with little disturbance to plasma osmotic p.

2: keep the gradient as it is.

--- exchange

4.31 Buildup of Osmotic gradient

1 segmental permeability to H2O and solutes

	H_2O	Na^+	Urea	action
TL d	perm.	im-.	im-.	*t.f.* concentrated
TL a	im-.	perm.	partial perm.	NaCl → ***i.f.***
				(partial) urea → *t.f.*
thick a	im-.	☯	im-.	NaCl → ***i.f.***
DCT	? ADH	☯	cortical im-.	NaCl → ***i.f.*** *(aldo)*
&			outer med.	*t.f.* urea concentrated
CD			inner med. perm.	NaCl → ***i.f.*** *(aldo)*
				(partial) urea → ***i.f.***

2 *Counter*current multiplication

Solutes, *esp.* NaCl and Urea

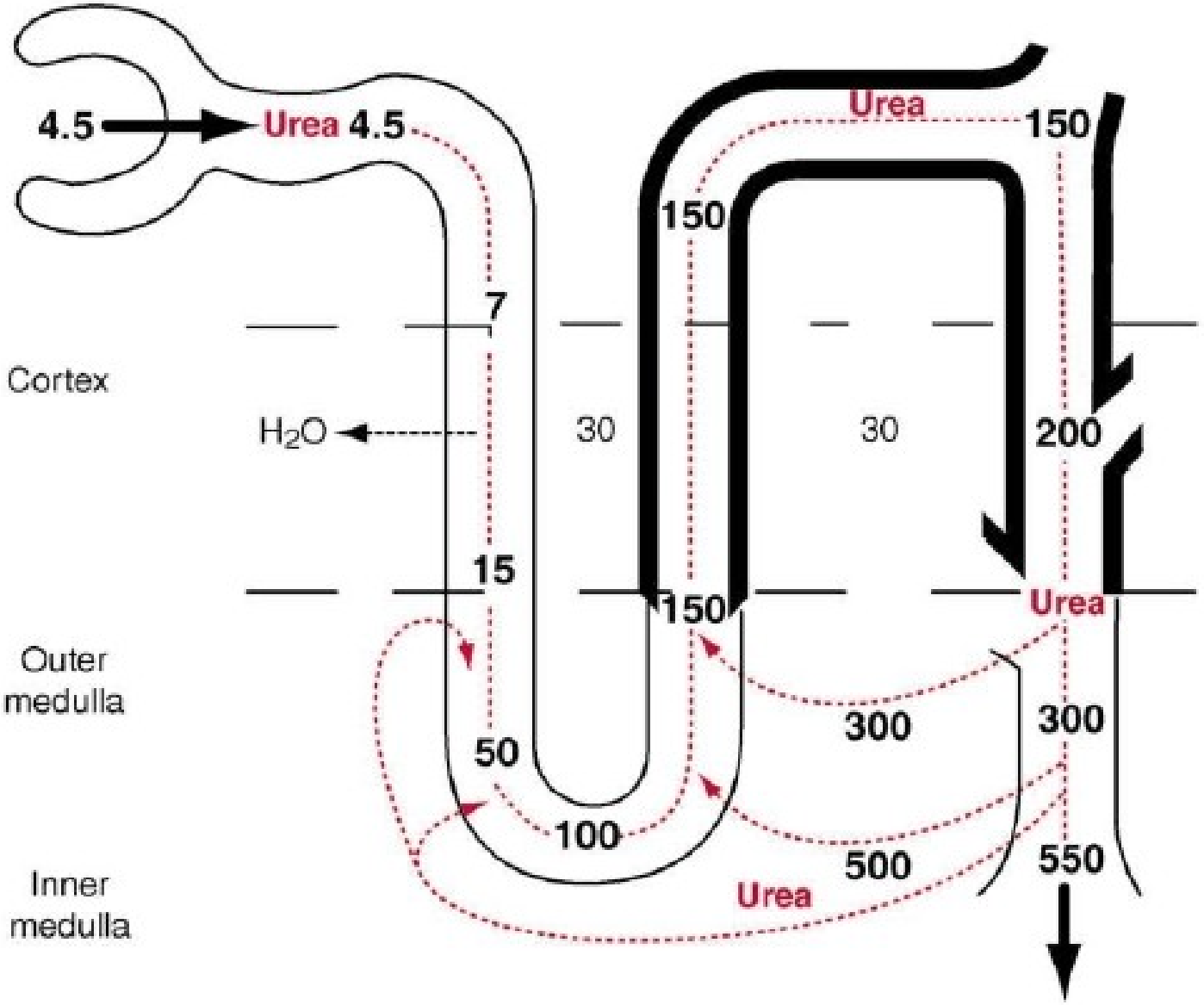
are "trapped" in the medulla

Mechanism:

multipliction

urea recycling

Recirculation of urea absorbed from medullary collecting duct into interstitial fluid.



The hyperosmolality is the driving force for H_2O reabsorption

how can H_2O be taken back to circulation ?

4.40 *Vasa Recta* prevent

the medullary hyperosmolality

from being dissipated !

U-shape *Vasa Recta* : countercurrent exchanger

{ take away <u>certain amount</u> of solute+ H_2O

maintains the hyperosmolality

blood flow in *Vasa Recta*

If large, large amount of solutes is taken away,
osmotic gradient becomes lower,
…

If small, …

Vasa recta bring blood to
inner medulla structures

Summary

Homeostasis and urine concentration and dilution

DT & CD dilute and concentrate urine

medullary osm. gradient is the driving force

buildup of osm. Gradient :

outer med. : active transport of solutes by thick ascending segment

inner med. : segmental permeability to urea and NaCl...

urea recycling

vasa recta : take back, maintaining gradient, blood supply

Section 5

Regulation of Urinary Formation

Auto-regulation
Nervous regulation
Humoral regulation

5.1 *Autoregulation*

5.10 Osmotic diuresis:

Solute concentration in tubular fluid

NaCl

glucose : tubular fluid osmotic pressure

diabetes millitus : *poly*uria

mannitol, sucrose, urea

5.11 *Glomerulo*-tubular balance

PT reabsorbs 65-70% of load of salt+water .

------- constant fraction reabsorption

Mechanism: plasma oncotic pressure
in capillary neighboring PCT

Relevance: relative constant NaCl+H_2O excretion

5.12 *Nervous regulation*

1. Renal Sympathetic Nerve

innervates renal vessels

tubules (proximal and distal)

juxtaglomerular apparatus

NE:

* afferent/efferent a. contract → GFR ↓ (α)
* renin release ↑ (β)
* NaCl + H_2O reabsorption ↑ in *PT* & *loop* (α)

5.12 Nervous regulation

2 Reflex

肾交感紧张之改变

- Blood volume

^ cardiopulmonary receptor (vBp) → X →…

^ baroreceptor (aBp) → IX, X → …

- Renorenal reflex

5.13 *Humoral regulation*

1. Vasopressin, VP

pp ~159~

anti-diuretic hormone, ADH or
arginine vaso-pressin, AVP

* Synthesis and storage :

Supra-optic + *para*-ventricular nuclei

Carrier: neurophysin

*hypo*thalamo-*hypo*physial tract ➔ *hypo*physis

* Receptors and Targets

V_1 receptor : vascular smooth muscles → Bp ↑

V_2 receptor : epithelial cells of DCT & CD

V_2 (+) → G_s (+) → cAMP ↑ → PKA (+) →

apical AQP-2 ↑ → H_2O permeability ↑ →

water reabsorbed ↑ (urine volume ↓)

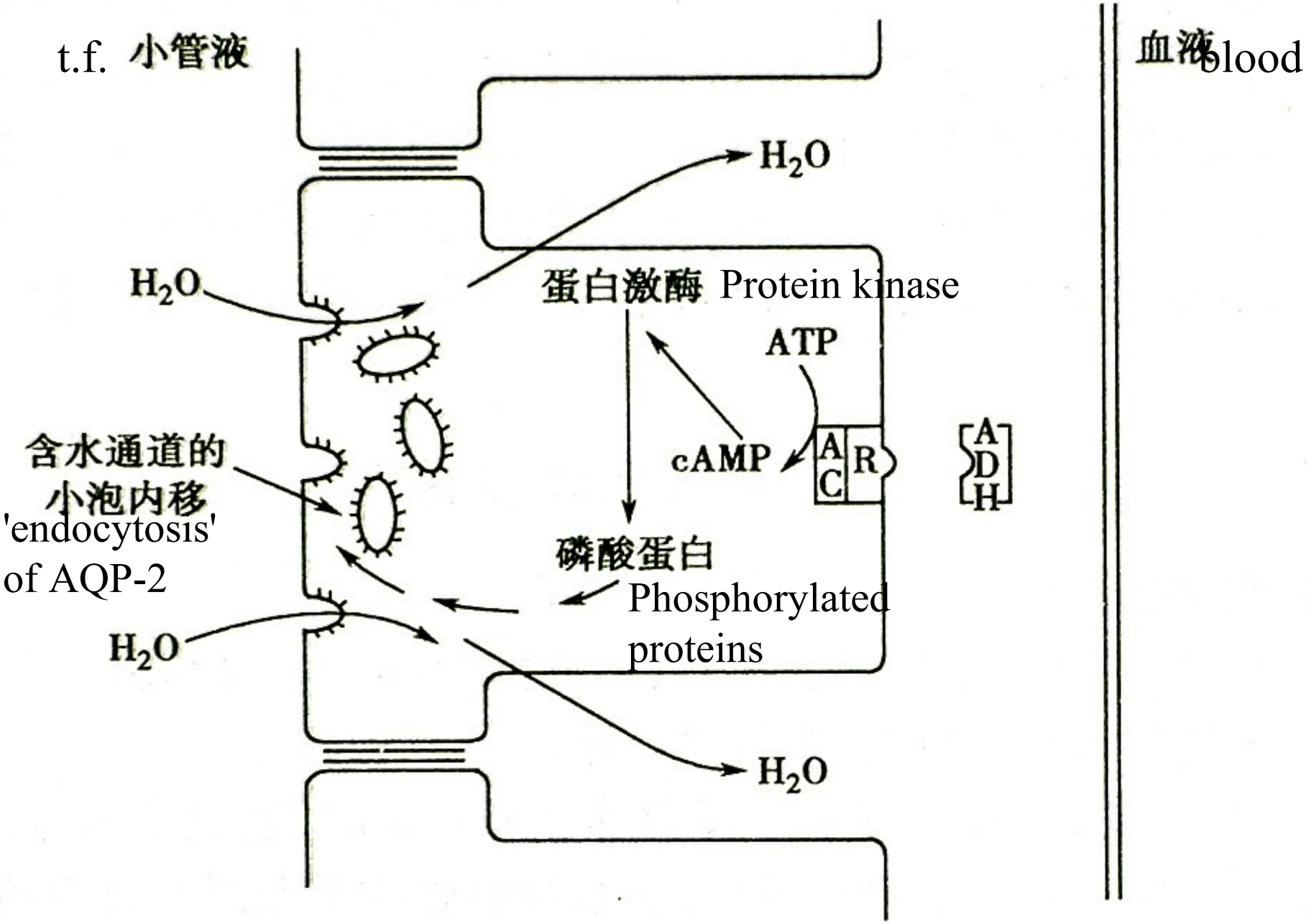


图 8-15　血管升压素的作用机制示意图

* Regulation of ADH release

- *ECF* (crystal) osmolality

  280~290 mOsm/kgH_2O

  threshold : 275~290 ***set point***

  plasma [ADH] : 0~4 pg/ml

  <u>thirst</u> : plasma osmolality 289~307

  : plasma [ADH] > 5 pg/ml

osmo-receptor

hypothalamus

AV3V, antero-ventral region of the 3rd ventricle

(OVLT, organum vasculosum of the lamina terminalis)

NaCl, mannitol, sucrose, glucose, urea

Water loss → plasma osmolality ↑ → osmoreceptor (+)…

water load → …

water diuresis

- Blood volume

  ^ cardiopulmonary receptor (vBp) → X →…

  ^ baroreceptor (aBp) → IX, X → …

  not as sensitive as brain osmoreceptor : 5~10%

  but reset set point !

- Other factors

  nausea, stress, AT-II, *hypo*glycemia, nicotine, morphine ethanol (alcohol), ANP

2. RAAS

pp ~159

systemic RAAS, local RAS

> Final Common Pathway for blood pressure regulation

Renin
Angiotensin
Aldosterone
system

> *Other important components:*

ACE, Angiotensin-Converting Enzyme
HSD11β2, 11-β HydroxySteroid Dehydrogenase type II

Angiotensin II *Ang-II* *on urine formation*

- directly :
  - Reabsorption of NaCl in Proximal T. ↑
  - GFR changes due to contraction of
    - afferent / efferent arterioles
    - mesangial cells
- indirectly :
  - Aldosterone synthesis+secretion
  - ADH (and ACTH) release:
    - NO, PGs formation
  - NE (sympathetic) release

↑ thirst → behaviors

Aldosterone

p529

Adrenal cortex

steroid, the major *mineralo*-corticoid

Mechanism: cytoplasmic receptor
Aldosterone-induced protein

Effects:

de novo synthesis of apical Na^+ channel
ATP supply for basolateral Na^+-K^+-ATPase
basolateral Na^+-K^+-ATPase (+)

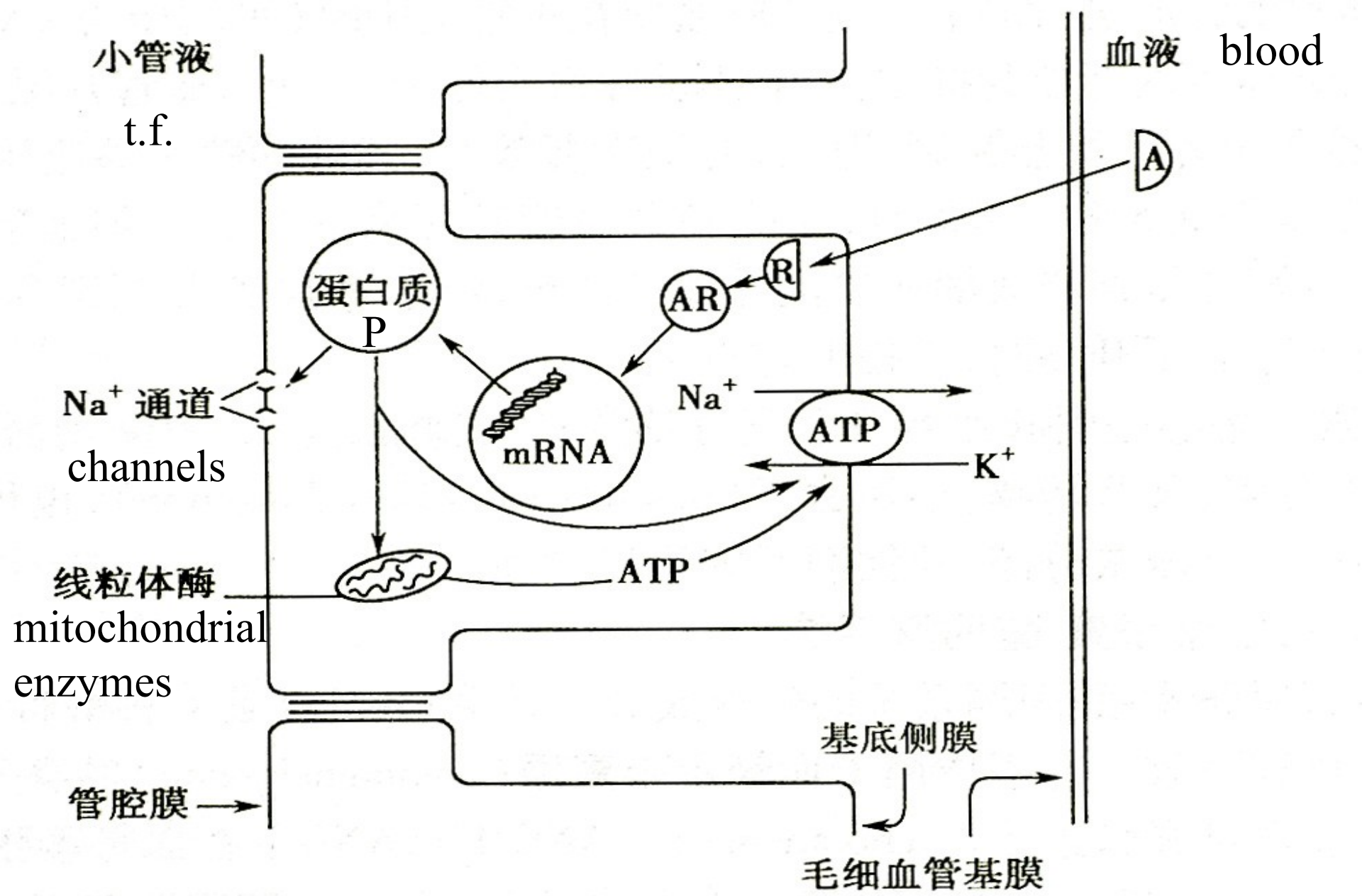


图 8-17 醛固酮作用机制的示意图

A：醛固酮；R：受体

Proteins synthetized *de novo*

Renin : Regulation of release

Juxtaglomerular apparatus

j-g. cells : perfusion stretch ⬇

macula densa : Na^+ flow in *DCT* ⬇

Nervous

renal sympathetic n.: j.-g. cells: β-receptor

Humoral

Ad, NE, local PGE_2 , PGI_2 stimulate

AT-II, ADH, ANP, endothelin, NO inhibit

5.13 Humoral regulation

3. Atrial natriuretic peptide, ANP *p ~159*

Atrial cardiac muscle cells, 28-aa

BNP (brain-type)

CNP (C-type)

Receptors : NPR<u>A</u>, NPR<u>B</u>, NPR<u>C</u>

A, B with *guanylyl cyclase* (GC) → *cGMP* ⇧

C contains no intracellular GC and

is thought to clear natriuretic peptides

http://herkules.oulu.fi/isbn9514252721/html/c368.html

Kidney:

Afferent a. :

cGMP → $[Ca^{2+}]_i$ ⇩ → dilates → GFR ⇧

CD:

apical Na^+ channel (-) → Na^+ excretion ⇧

J.-g. cells: renin release ⇩

Adrenal cortex:

aldosterone secretion ⇩ $Na^+ + H_2O$ ⇧

Brain: :

ADH release ⇩ H_2O excretion ⇧

Extraglomerular mesangial cells contract Kf dec

Regulation :

Atrial distension : ⇧ (posture changes)

Ach, NE, CGRP ⇧ (calcitonin gene-related p.)

Section 6

Clearance

Useful substance :

inulin 菊粉（糖）

endogenous creatinine 内生肌酐

PAH (*para*-amino-hipp-uric acid)

对 氨基 马 尿 酸

diodrast 碘锐特

1. Definition and Calculation

The **equivalent volume** of plasma from which a *specific substance* is completely cleared (excreted) by **both** kidneys within 1 minute.

Measurements and culculation:

U_X : conc. in urine mg/100ml

V : urine vol. per minute ml/min

P_X : conc. in plasma mg/100ml

$$P_X * C_X = U_X * V \quad \text{ml/min}$$

2. Applications : *to quantify kidney function*

1. Clearance can be used to estimate GFR

* *inulin* **clearance** : (the "gold standard")

- freely filtered, not reabsorbed or secreted;

* *endogenous creatinine* **clearance** :

plasma creatinine level is stable if :

- no ingestion of meats
- avoid of violent physical activity

the *secreted* + *reabsorbed* amount is small…

2. applications :

C_{Inulin} >= *true GFR*

20~40 yrs old normal : ml/(min*1.73m^2)

male : 127~130

female : 118~120

factors : physical activities, stress, ingestion,

circadian rhythm, age, pregnancy etc.

2. Clearance can be used to estimate RBF

PAH, diodrast

- both are filtered and secreted;
- renal venous concentration ~ 0

$C_X * P_X = U_X * V$ here,

$C_X \approx$ <u>effective RPF</u>

take *blood supply* into consideration: the "true" RPF

take *hematocrit* into consideration : RBF

PAH : filtered + secreted;

conc. in renal venous blood ≈ 0 (Not 0 !)

take *blood supply* into consideration:

extraction ratio: $E_{PAH} \approx$ 91%

the "true" RPF $= C_{PAH} / E_{PAH}$

take *hematocrit* into consideration : R B F

3. Deducing renal tubule function

net tubular secretion : if $C_X > C_{Inulin}$

eg. $C_{PAH} > C_{Inulin}$

net tubular reabsorption : if $C_X < C_{Inulin}$

eg. $C_{glucose} < C_{Inulin}$

qualify only; free substance only

urea : diffusion, without <u>maximum</u>

PAH, glucose : active transport

if plasma conc. is *high enough*,

<u>maximal</u> rate of transport

4. Free-water clearance, C_{H2O}

solute-free water

concentrated / dilute urines
adjust their osmolality, = plasma osmolality

Clearance of total solute :

Osmolar clearance : C_{osm}

$C_{osm} * P_{osm} = V * U_{osm}$ *(ml)*

$C_{H2O} = V - C_{osm}$:

if negative: free-water reabsorption, ➔ T^{c}_{H2O}

ADH determines tububular conservation of water

Section 7

Micturition