Physiology of Micturition

Hammam Mahmoud Alloh, M.D
Nephrologist (Al-Shifa & Aqsa Martyrs Hospitals)
Assistant Professor of Internal Medicine and Nephrology (IUG, AUG)

Introduction

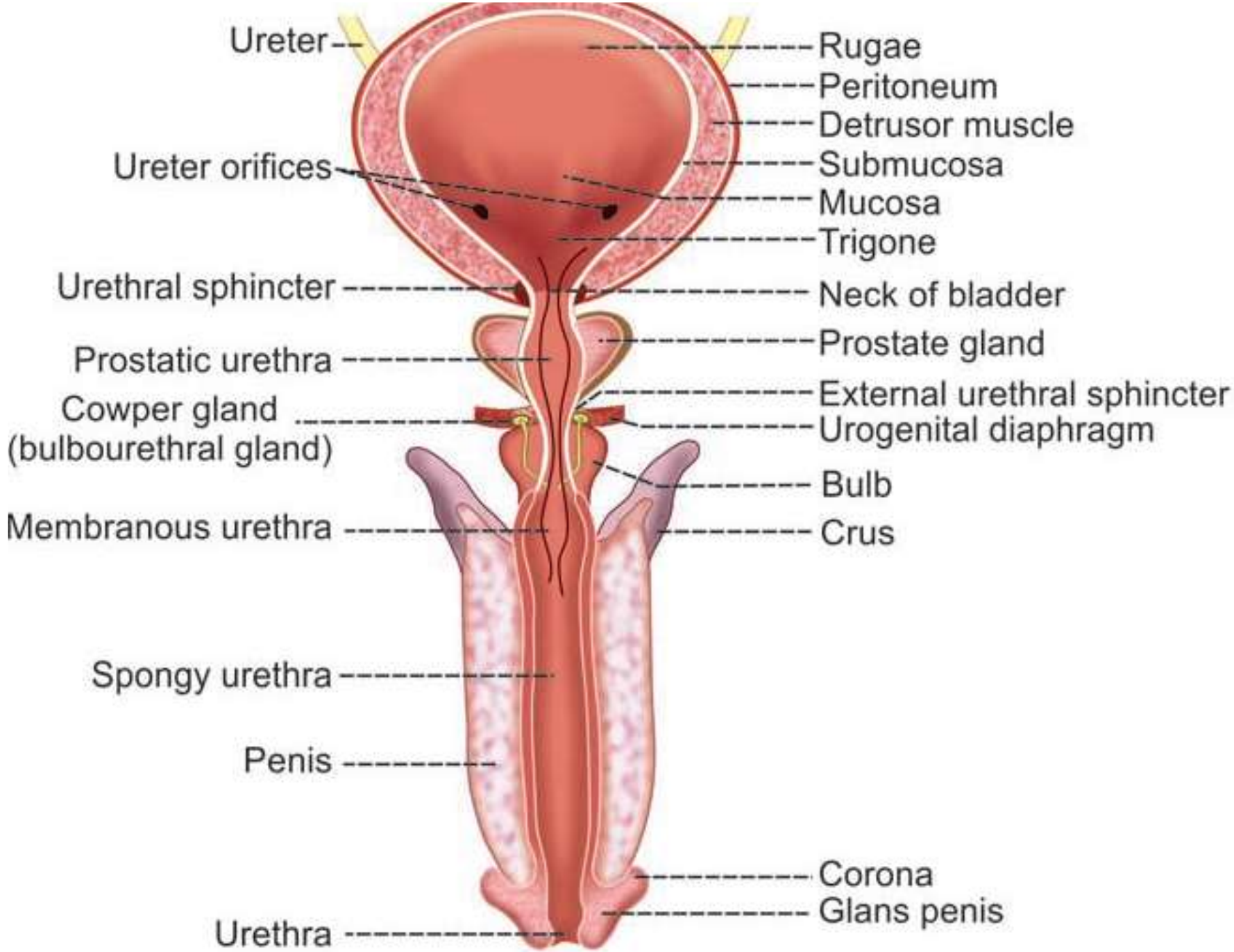
- Micturition is a process by which urine is voided from the urinary bladder
- It is a reflex process. However, in grown up children and adults, it can be controlled voluntarily
- The functional anatomy and nerve supply of urinary bladder are essential for understanding the process of micturition

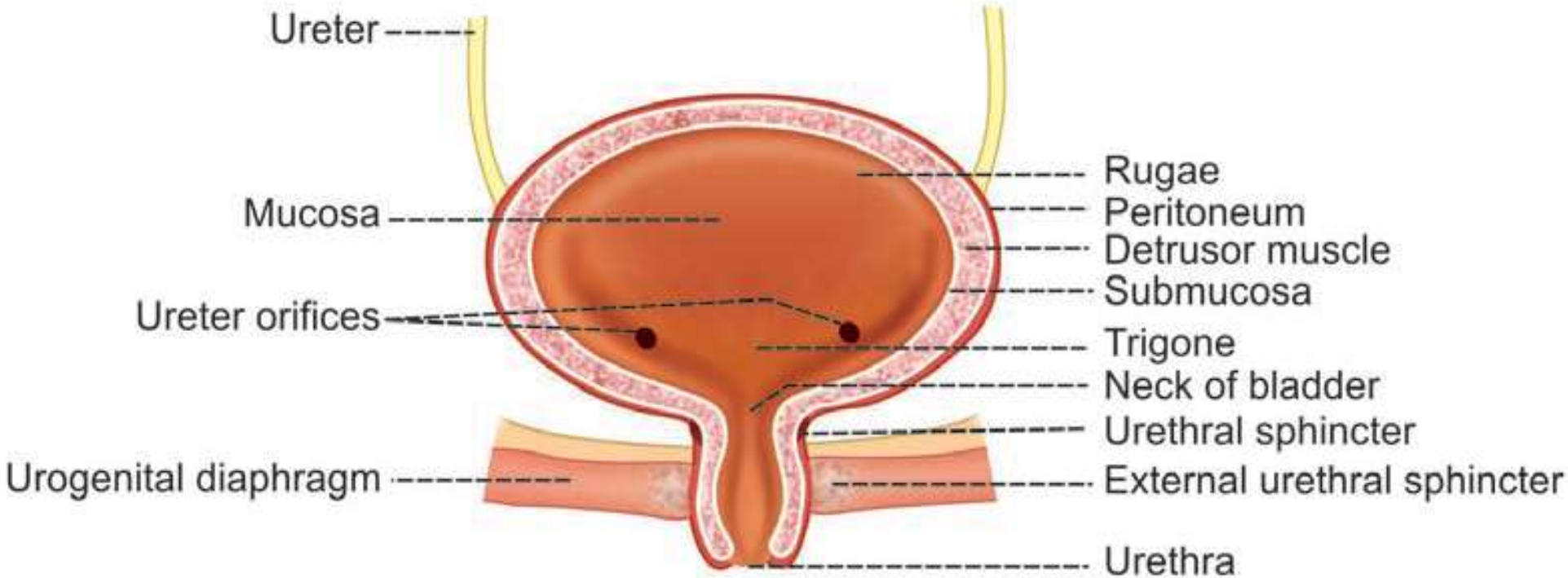
Urinary Bladder

- Urinary bladder is a triangular hollow organ located in lower abdomen
- It consists of a body and neck
- Wall of the bladder is formed by smooth muscle (Detrusor muscle)
- In empty bladder, the mucosa falls into many folds called rugae
- At the posterior surface of the bladder wall, there is a triangular area called trigone
- Lower part of the bladder is narrow and forms the neck
- It opens into urethra via internal urethral sphincter

Urethra

- Male urethra has both urinary function and reproductive function
- Female urethra has only urinary function
- So, male urethra is structurally different from female urethra


Ureter
Rugae
Peritoneum
Detrusor muscle
Ureter orifices
Submucosa
Mucosa
Trigone
Urethral sphincter
Neck of bladder
Prostate gland
Prostatic urethra
External urethral sphincter
Cowper gland
(bulbourethral gland)
Urogenital diaphragm
Bulb
Membranous urethra
Crus
Spongy urethra
Penis
Corona
Glans penis
Urethra


Ureter
Mucosa
Ureter orifices
Urogenital diaphragm
Rugae
Peritoneum
Detrusor muscle
Submucosa
Trigone
Neck of bladder
Urethral sphincter
External urethral sphincter
Urethra

Urethral Sphincters

- There are two urethral sphincters in urinary tract:

1. Internal urethral sphincter (thickening of detrusor muscle, innervated by autonomic nerve fibers, closes the urethra when bladder is emptied)

2. External urethral sphincter (circular skeletal muscle fibers, innervated by somatic nerve fibers)

Nerve Supply to urinary bladder and sphincters

- Urinary bladder and the internal sphincter are supplied by sympathetic and parasympathetic divisions of autonomic nervous system
- The external sphincter is supplied by the somatic nerve fibers
- Sympathetic nerve arise from L1 and L2 segments of spinal cords and supplies the detrusor muscle and internal sphincter thru the hypogastric nerve

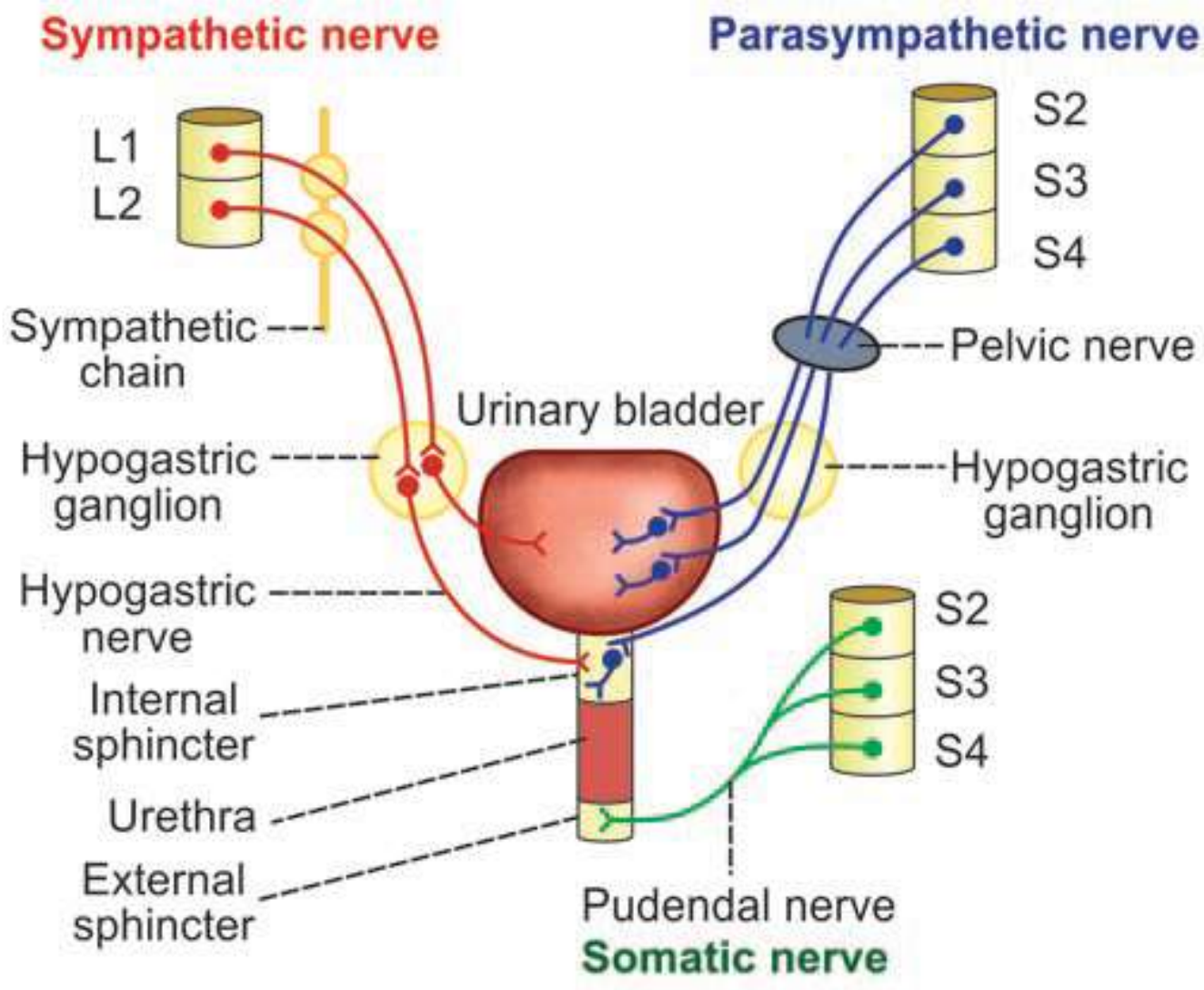
Nerve Supply to urinary bladder and sphincters

- Parasympathetic nerve arise from S2, S3 and S4 segments of spinal cord and supplies detrusor muscle and internal sphincter thru pelvic nerve
- External sphincter is innervated by the somatic nerve called pudendal nerve, which arises from S2, S3 and S4 segments

Functions of nerves supplying urinary bladder and sphincters

Nerve	On detrusor muscle	On internal sphincter	On external sphincter	Function
Sympathetic nerve	Relaxation	Constriction	Not supplied	Filling of urinary bladder
Parasympathetic nerve	Contraction	Relaxation	Not supplied	Emptying of urinary bladder
Somatic nerve	Not supplied	Not supplied	Constriction	Voluntary control of micturition

Nerve Supply to urinary bladder and sphincters



Filling of Urinary Bladder

- Urine is continuously formed by nephrons
- It flows into urinary bladder drop by drop through ureters
- When urine collects in the pelvis of ureter, the contraction sets up in pelvis
- This contraction is transmitted through rest of the ureter in the form of peristaltic wave
- **Peristaltic wave** usually travels at a velocity of 3 cm/second, at a frequency of 1 to 5 per minute

Filling of Urinary Bladder

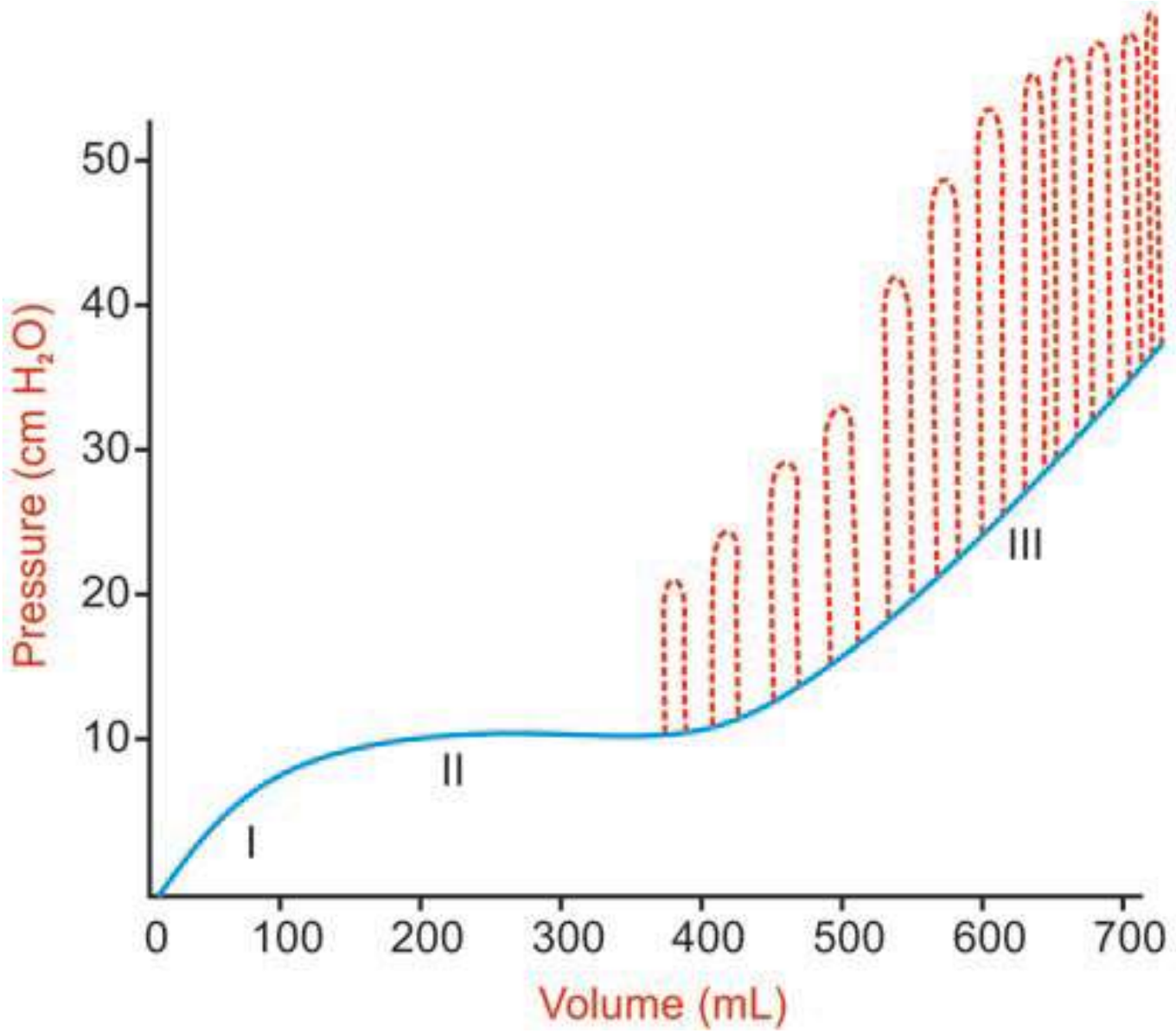
- At the entrance of ureters into urinary bladder, a valvular arrangement is present
- When peristaltic wave pushes the urine towards bladder, this valve opens towards the bladder
- The position of ureter and the valvular arrangement at the end of ureter prevent the back flow of urine from bladder into the ureter when the detrusor muscle contracts
- Thus, urine is collected in bladder drop by drop

Cystometrogram

- A reasonable volume of urine can be stored in urinary bladder without any discomfort and without much increase in intravesical pressure
- It is due to the adaptation of detrusor muscle
- This can be explained by cystometrogram
- Cystometry is the technique used to study the relationship between intravesical pressure and volume of urine in the bladder
- Cystometrogram is the graphical recording of pressure changes in urinary bladder in relation to volume of urine collected in it

Cystometrogram

Dotted lines indicate the contraction of detrusor muscle.



Cystometrogram

Cystometrogram shows three segments

-Segment I: when about 100 mL of fluid is collected, the pressure rises sharply to about 10 cm H2O

-Segment II: shows the plateau, because of adaptation of urinary bladder by relaxation (Laplace law, Pressure = Tension/Radius)

With 100 mL of urine and 10 cm H2O of intravesical pressure, the desire for micturition occurs.

When total volume rises beyond 400 mL, the pressure starts rising sharply

Cystometrogram

-Segment III: as the pressure increases with collection of 300 to 400 mL of fluid, the contraction of detrusor muscle becomes intense, increasing the urge for micturition

Voluntary control is possible up to volume of 600 to 700 mL at which the pressure rises to about 35 to 40 cm H2O

Above 40 cm H2O, contraction of detrusor muscle becomes more intense, and voluntary control of micturition is not possible

Now, pain sensation develops and micturition is a must at this stage.

Micturition Reflex

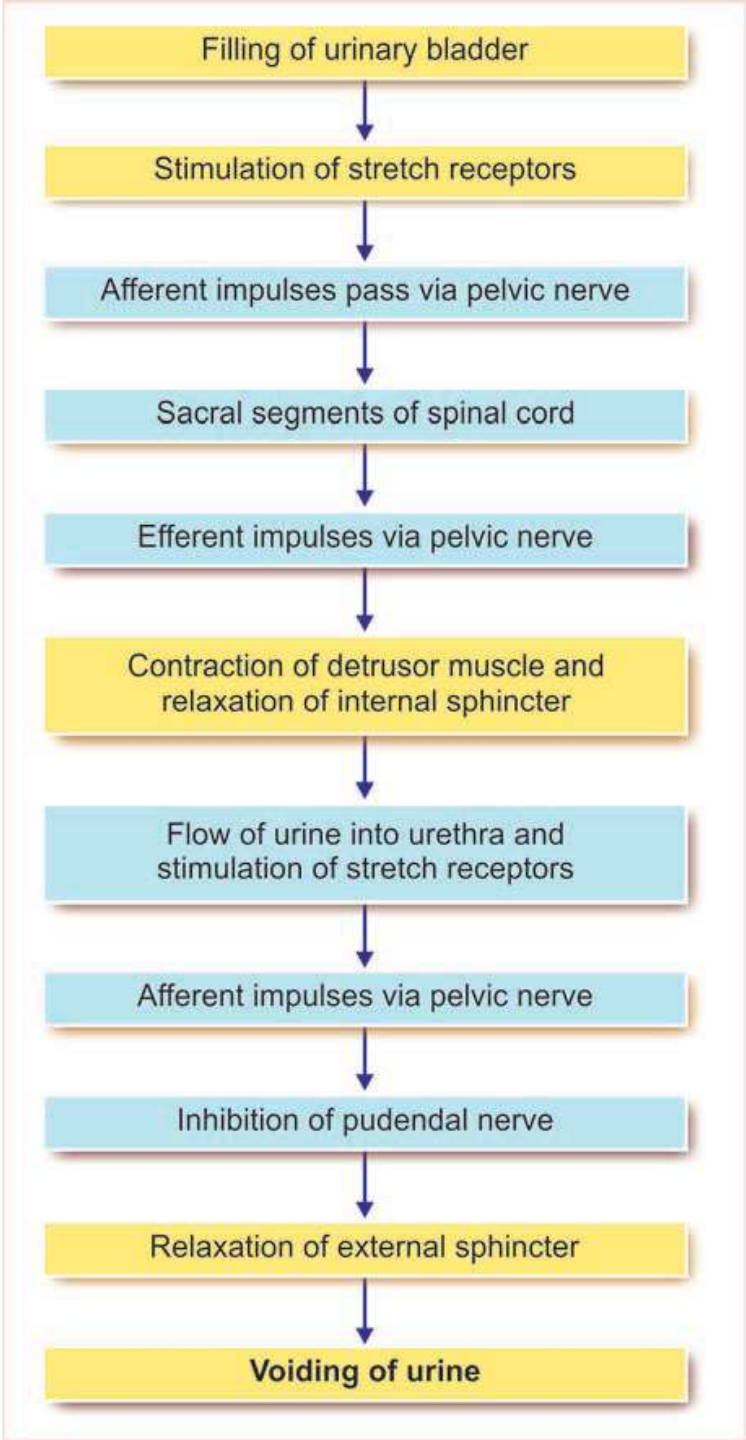
It is the reflex by which micturition occurs

It is elicited by the stimulation of stretch receptors situated on the wall of urinary bladder and urethra

When about 300 to 400 mL of urine is collected in the bladder, intravesical pressure increases, which results in stimulation of stretch receptors and generation of sensory impulses

Micturition reflex

-It is self regenerative (The cycle continues repeatedly until the force of contraction of bladder reaches the maximum and the urine is voided out completely)
-During micturition, the flow of urine is facilitated by the increase in the abdominal pressure due to the voluntary contraction of abdominal muscles



Higher Centers for Micturition

- Spinal centers for micturition are present in sacral and lumbar segments
- These are regulated by higher centers
- Higher center are of two types, inhibitory centers and facilitatory centers
- *Inhibitory centers* in midbrain and cerebral cortex inhibit the micturition by suppressing spinal micturition centers
- *Facilitatory centers* in pons facilitate micturition via spinal centers

Applied physiology

- Atonic neurogenic bladder (tabes dorsalis, spinal cord injury)
- Stroke causing urinary incontinence

Physiology of water and electrolytes balance

Hammam Mahmoud Alloh, M.D
Internist, Nephrologist (Al-Shifa & Aqsa Martyrs Hospitals)
Assistant Professor of Internal Medicine and Nephrology (IUG & AUG)

Water Balance

- We need water to live
- Therefore, we need to understand water balance physiology
- How is water distributed in our body?
- How does water shift between compartments/spaces?
- What does the kidney, and the body in general, do to maintain water balance (i.e. matching intake to output of water)

Total body water

- Equals 60% of body weight
- Percentage is highest in newborns and adult male individuals and lowest in adult female individuals (owing to increased proportion of body fat)
- Distribution of TBW

2/3 of TBW in ICF and 1/3 in ECF

Plasma volume represents ¼ of ECF

Interstitial fluid represents ¾ of ECF

Composition of ICF and ECF

Chemical	ICF	ECF
Na (mmol/L)	10	142
K (mmol/L)	140	4
Cl (mmol/L)	4	108
HCO3 (mmol/L)	10	24
Ca++ (mmol/L)	0.0001	2.4
Mg++ (mmol/L)	58	1.2
SO4 (mmol/L)	2	1
Phosphates (mmol/L)	75	4
Glucose (mg/dl)	0-20	90
Amino acids (mg/dl)	200	30
Protein (g/dl)	16	2

Measuring the volume of fluid compartments

- Dilution method

A known amount of a substance is given

Then, the volume of distribution of this substance is calculated according to the equation : Volume= Amount/Concentration

Example of substances used

-Tritiated water (distributes wherever water is found)

-Mannitol (a large molecule that cannot cross cell membrane, so it is used for ECF volume measurement)

-Evans blue dye (binds to albumin, so it remains confined to plasma compartment = intravascular compartment)

Example of Dilution method

- IV injection of 500mg Mannitol
- After 2-hour equilibration period, concentration of Mannitol in plasma is measured (3.2mg/100mL)
- During the equilibration period, 10% of Mannitol is excreted
- Patient's ECF volume is therefore calculated using V=A/C as

(500-50)/ 3.2 = 14.1 L

Substances used for measurement of major fluid compartments

- TBW: tritiated water, D2O, antipyrine
- ECF: Mannitol, inulin, thiosulfate, I-iothalamate
- Plasma: radioiodinated serum albumin (RISA), Evans blue dye
- Interstitial fluid: ECF-plasma volume
- ICF: TBW – ECF volume
- Blood volume: Cr-labelled RBCs, or calculated as plasma/(1-Hct)

Shift of water between compartments - Principles

- At steady state, ECF osmolarity = ICF osmolarity

To achieve this equality, water shifts between ECF and ICF

Solutes, such as NaCl and Mannitol, do not cross cell membranes and are therefore confined to ECF

Examples of water shifts between compartments

- Infusion of isotonic fluid (0.9% NaCl)

Represents iso-osmotic volume expansion

- Diarrhea – loss of isotonic fluid

Represents iso-osmotic volume contraction

- Excessive NaCl intake

Represents hyperosmotic volume expansion

- Sweating in a desert

Represents hyperosmotic volume contraction

Examples of water shifts between compartments

- Syndrome of inappropriate ADH secretion

Represents hypo-osmotic volume expansion

- Adrenocortical insufficiency

Represents hypo-osmotic volume contraction

Edema

- Excess fluid (water) in the tissues. It is either intracellular or extracellular
- Intracellular edema (increased ICF) occurs due to either

-depression of the metabolic systems of the tissues

-lack of adequate nutrition to the cells

In either case, Na that leaks into the cells, can no longer be pumped out, causing osmotic shift of water from ECF to ICF

Example: cerebral edema of hyponatremia

Edema

- Extracellular edema (increased ECF) results from either

-increase in capillary filtration

-failure of lymphatics to return fluid from interstitium to blood

Daily intake and output of water is balanced

- The total intakes of water and electrolytes must be carefully matched by equal outputs from the body, to prevent fluid volumes and electrolyte concentrations from increasing or decreasing
- The primary means of regulating output is by altering renal excretion
- Urine volume can be as low as 0.5L/day in a dehydrated person, or as high as 20L/day in a person who has been drinking large amounts of fluids

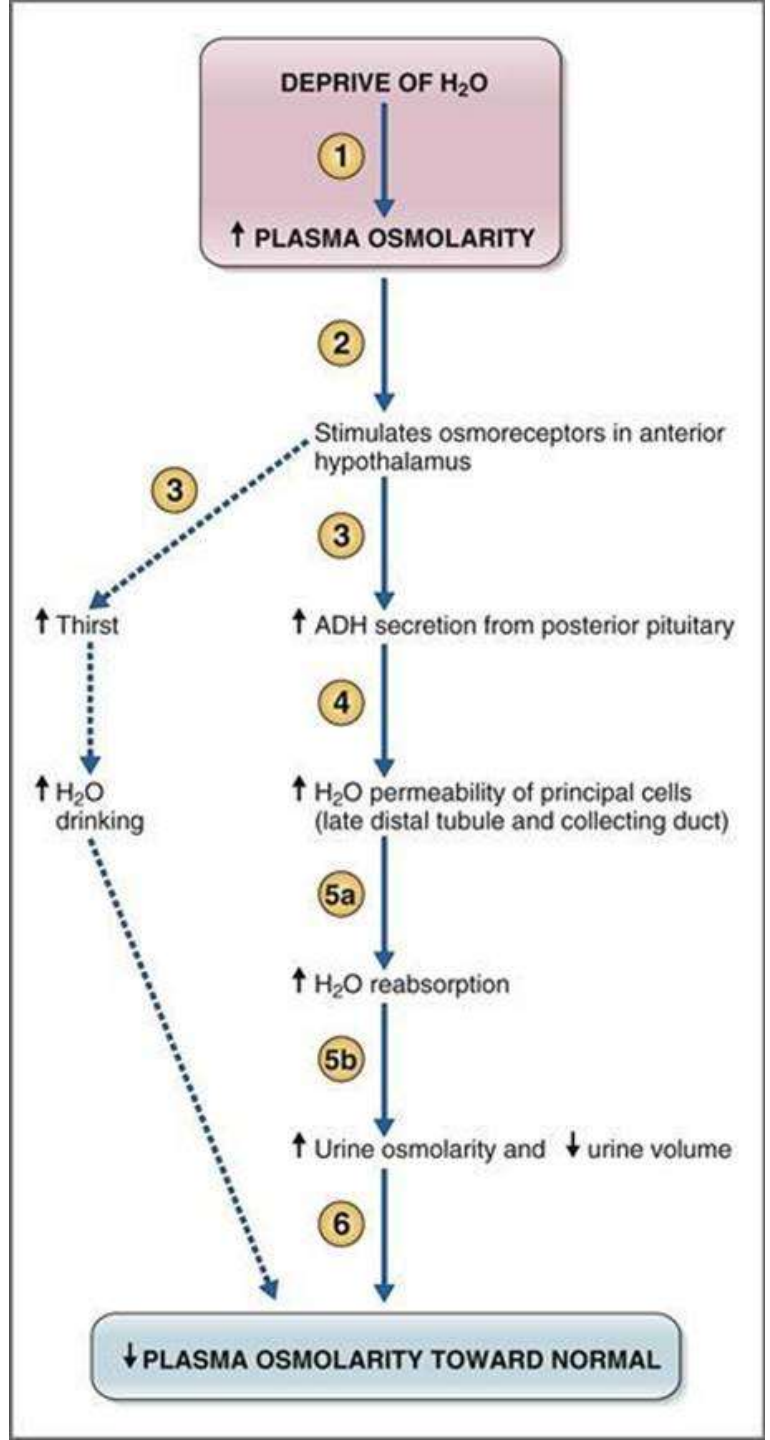
Parameter	Normal (ml/day)
Intake	
-fluids ingested	2100
-from metabolism	200
Total intake	2300
Output	
-Insensible skin loss	350
-Insensible lungs	350
-Sweat	100
-Feces	100
-Urine	1400
Total output	2300

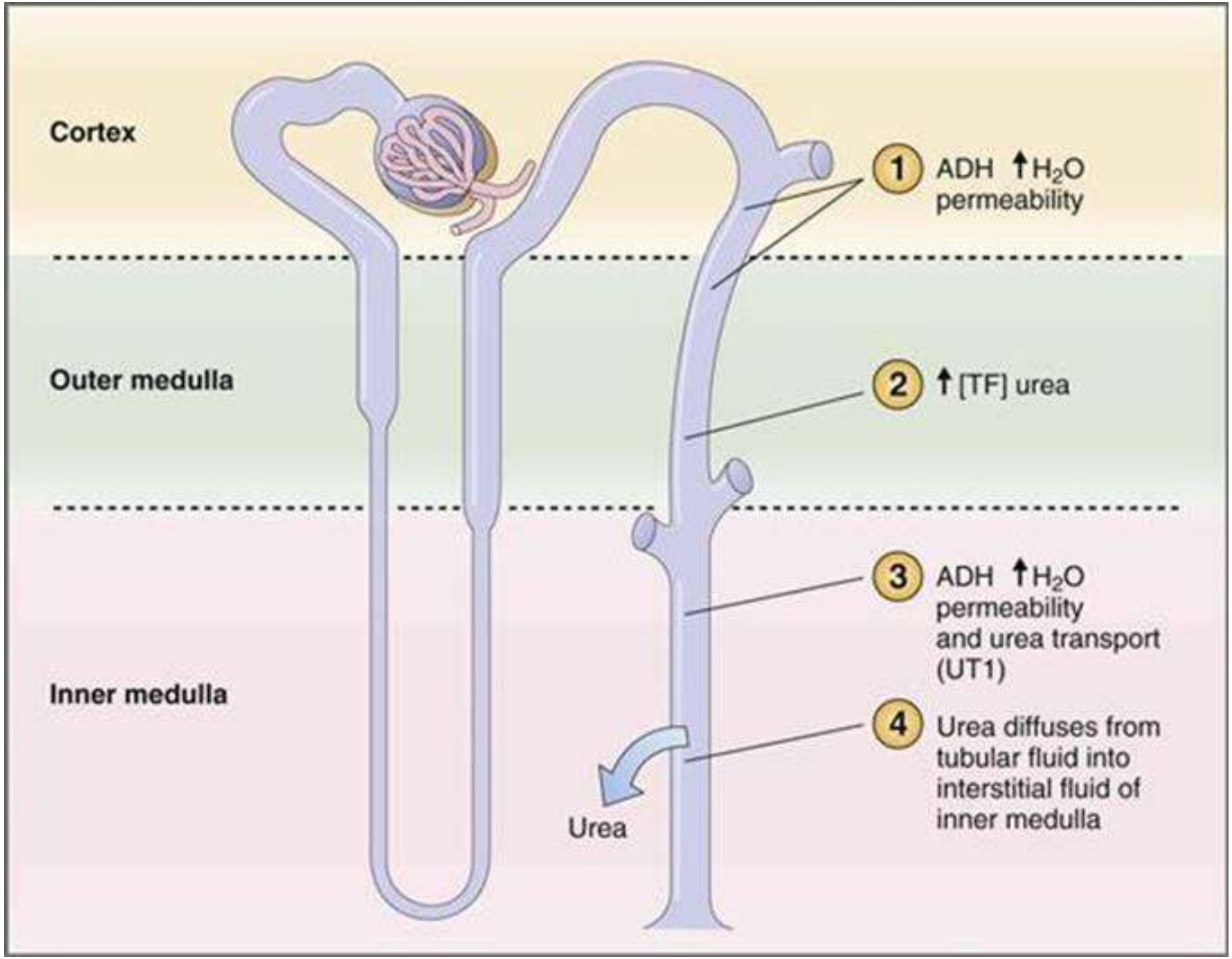
Regulation of plasma osmolarity

- Represents the response of the body, including the kidney, to water deprivation or increasing water intake
- Accomplished by varying the amount of water excreted in urine, which results in varying urine osmolarity (producing hyperosmotic/concentrated urine in response to water deprivation and producing hypoosmotic/dilute urine in response to increased water intake)

Response to water deprivation

- Water deprivation → increase in plasma osmolarity → stimulates osmoreceptors in anterior hypothalamus → increases secretion of ADH from posterior pituitary → increases water permeability of late distal tubule and collecting duct → increases water reabsorption → increases urine osmolarity and decreases urine volume → decreases plasma osmolarity toward normal
- This results in forming hyperosmotic urine, in which urine osmolarity > blood osmolarity
- A high corticopapillary osmotic gradient is required for the above mentioned pathway to occur (achieved by countercurrent multiplication and urea recycling and maintained by countercurrent exchange in the vasa recta)


DEPRIVE OF H_2O
1
↑ PLASMA OSMOLARITY
2
Stimulates osmoreceptors in anterior hypothalamus
3
3
↑ Thirst
↑ ADH secretion from posterior pituitary
4
↑ H_2O drinking
↑ H_2O permeability of principal cells (late distal tubule and collecting duct)
5a
↑ H_2O reabsorption
5b
↑ Urine osmolarity and ↓ urine volume
6
↓ PLASMA OSMOLARITY TOWARD NORMAL


Cortex
Outer medulla
Inner medulla
1 ADH ↑H_2O permeability
2 ↑ [TF] urea
3 ADH ↑H_2O permeability and urea transport (UT1)
4 Urea diffuses from tubular fluid into interstitial fluid of inner medulla
Urea

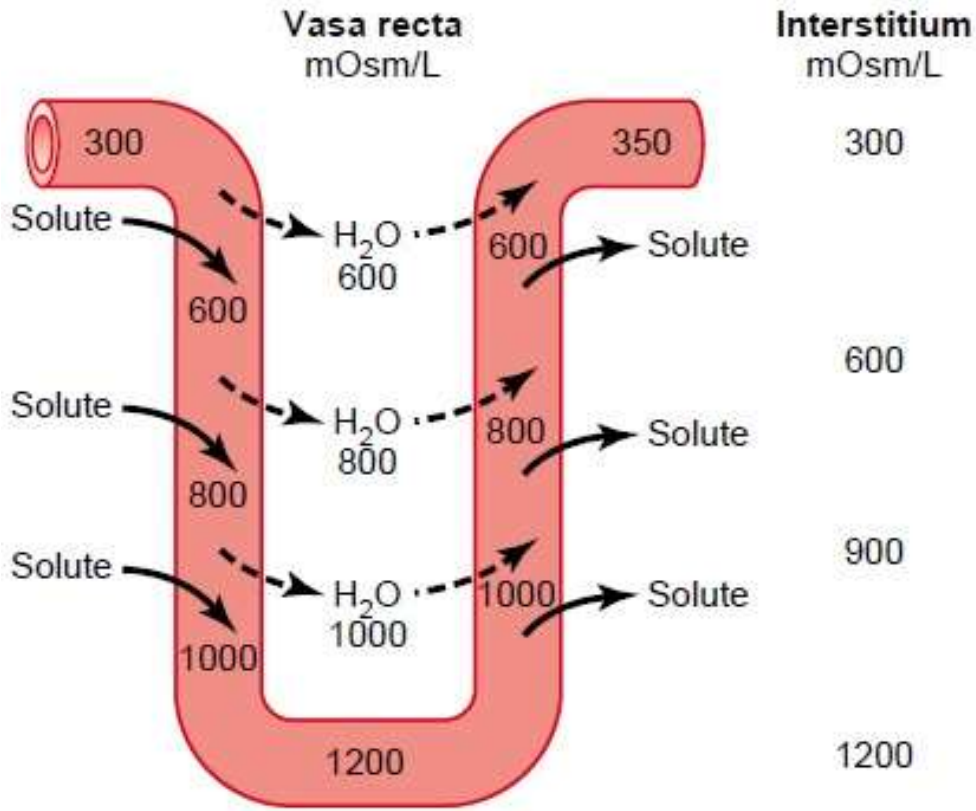
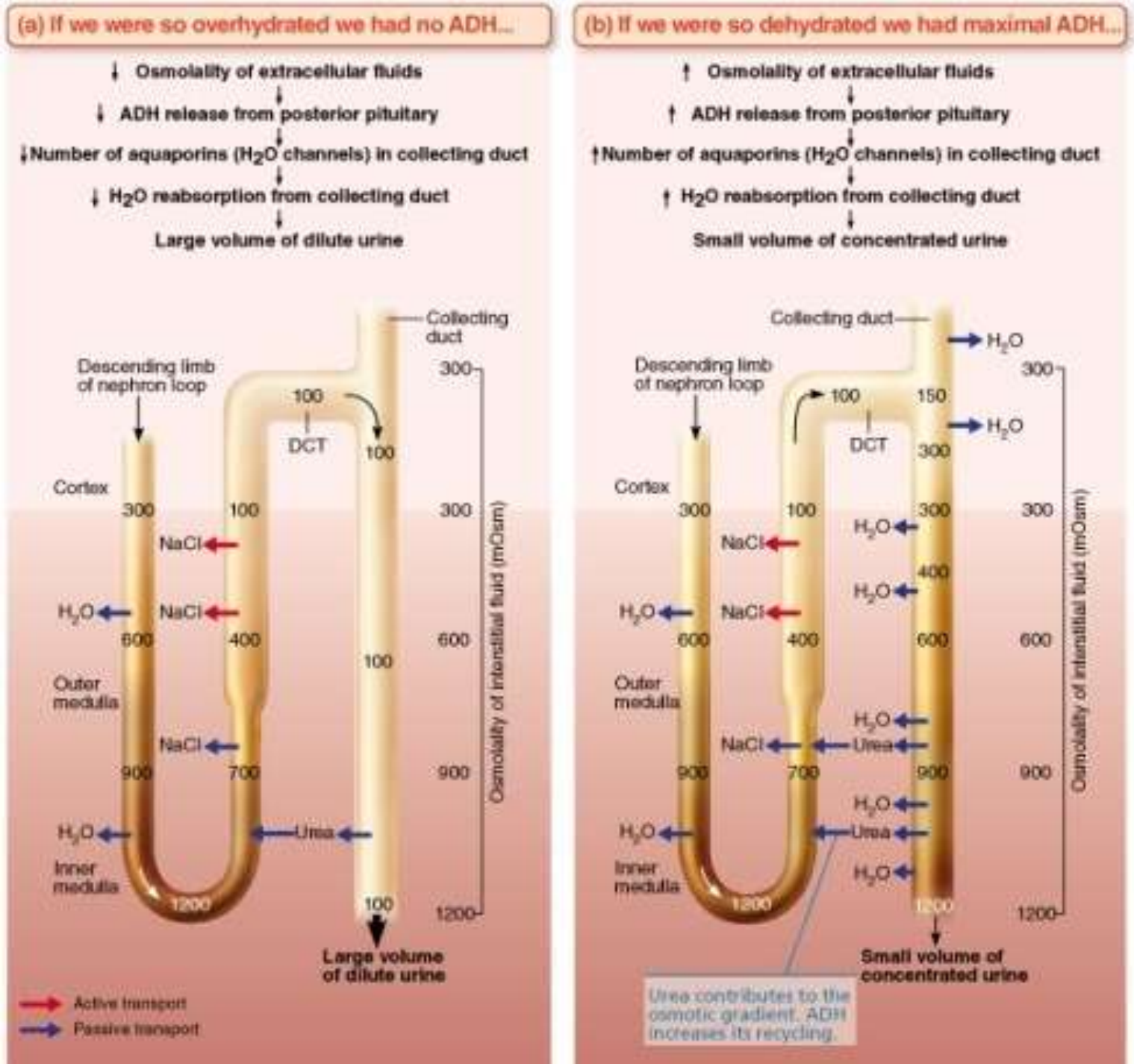


Figure 28–6

Countercurrent exchange in the vasa recta. Plasma flowing down the descending limb of the vasa recta becomes more hyperosmotic because of diffusion of water out of the blood and diffusion of solutes from the renal interstitial fluid into the blood. In the ascending limb of the vasa recta, solutes diffuse back into the interstitial fluid and water diffuses back into the vasa recta. Large amounts of solutes would be lost from the renal medulla without the U shape of the vasa recta capillaries. (Numerical values are in milliosmoles per liter.)

Response to water intake

- Water intake → decrease in plasma osmolarity → inhibits osmoreceptors in anterior hypothalamus → decreases secretion of ADH from posterior pituitary → decreases water permeability of late distal tubule and collecting duct → decreases water reabsorption → decreases urine osmolarity and increases urine volume → increases plasma osmolarity toward normal
- This results in forming hypo-osmotic urine, in which urine osmolarity < blood osmolarity


(a) If we were so overhydrated we had no ADH...
↓ Osmolality of extracellular fluids
↓ ADH release from posterior pituitary
↓ Number of aquaporins (H_2O channels) in collecting duct
↓ H_2O reabsorption from collecting duct
Large volume of dilute urine
Collecting duct
Descending limb of nephron loop
DCT
Cortex
Outer medulla
Inner medulla
NaCl
H_2O
Urea
300
100
600
400
900
700
1200
Osmolality of interstitial fluid (mOsm)
Large volume of dilute urine
Active transport
Passive transport
(b) If we were so dehydrated we had maximal ADH...
↑ Osmolality of extracellular fluids
↑ ADH release from posterior pituitary
↑ Number of aquaporins (H_2O channels) in collecting duct
↑ H_2O reabsorption from collecting duct
Small volume of concentrated urine
150
Small volume of concentrated urine
Urea contributes to the osmotic gradient. ADH increases its recycling.

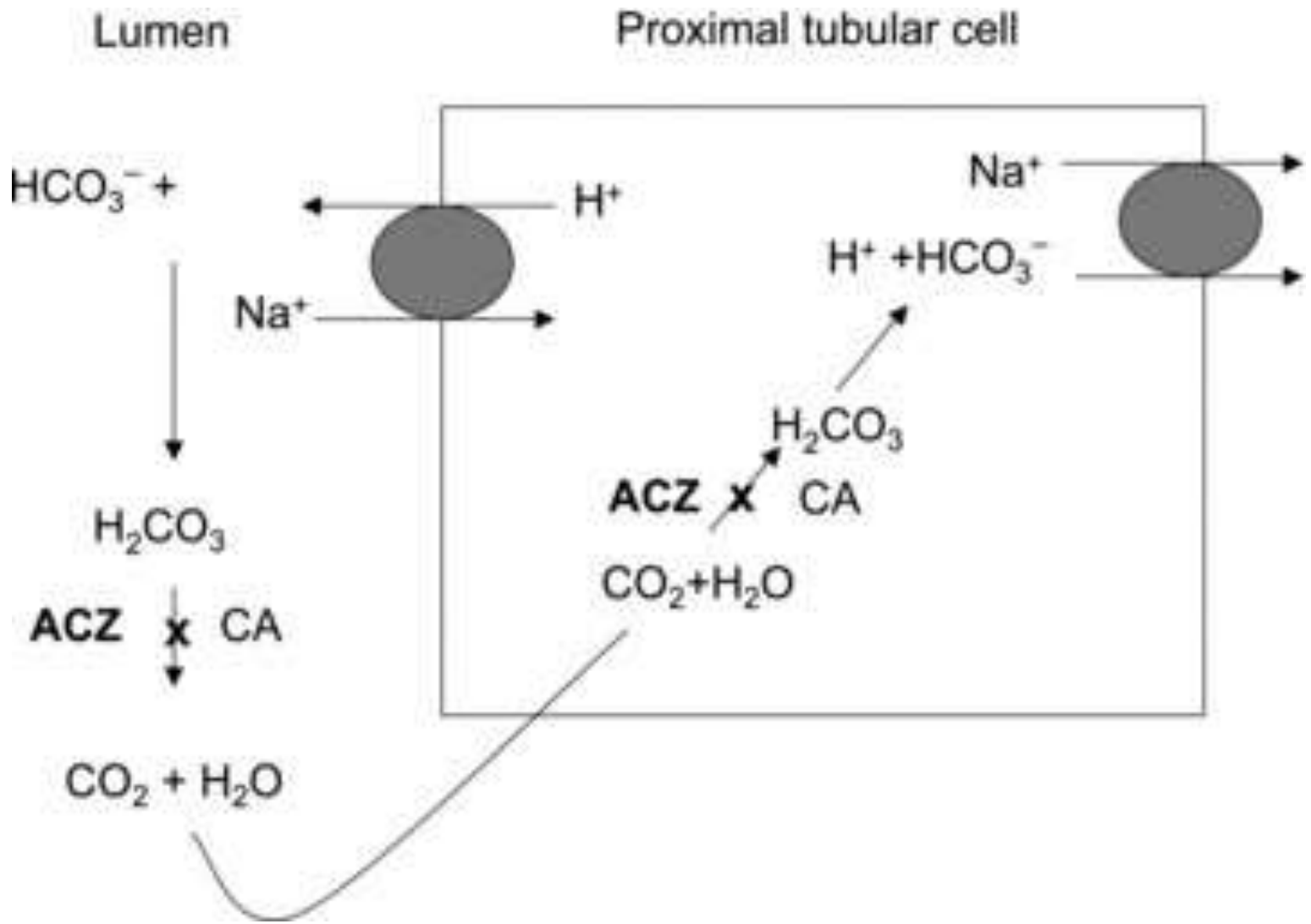
Renal sodium handling

- Na is freely filtered into Bowman's capsule
- Na is reabsorbed along the entire nephron, very little is excreted in urine (<1% of the filtered load)
- In PCT: 67% of filtered Na (and water) is reabsorbed

In early PCT, Na is reabsorbed by **cotransport** with water, bicarb, glucose, amino acids and phosphate, and by **countertransport** via Na-H exchanger

CAI, diuretics, act in early PCT and inhibit reabsorption of HCO_3

In late PCT, Na is reabsorbed with Cl


Lumen
Proximal tubular cell
HCO_3^- +
H^+
Na^+
Na^+
$H^+ + HCO_3^-$
H_2CO_3
ACZ x CA
CO_2+H_2O
H_2CO_3
ACZ x CA
$CO_2 + H_2O$

Renal sodium handling

- TAL:

25% of filtered Na is reabsorbed thru Na-K-2Cl cotransporter

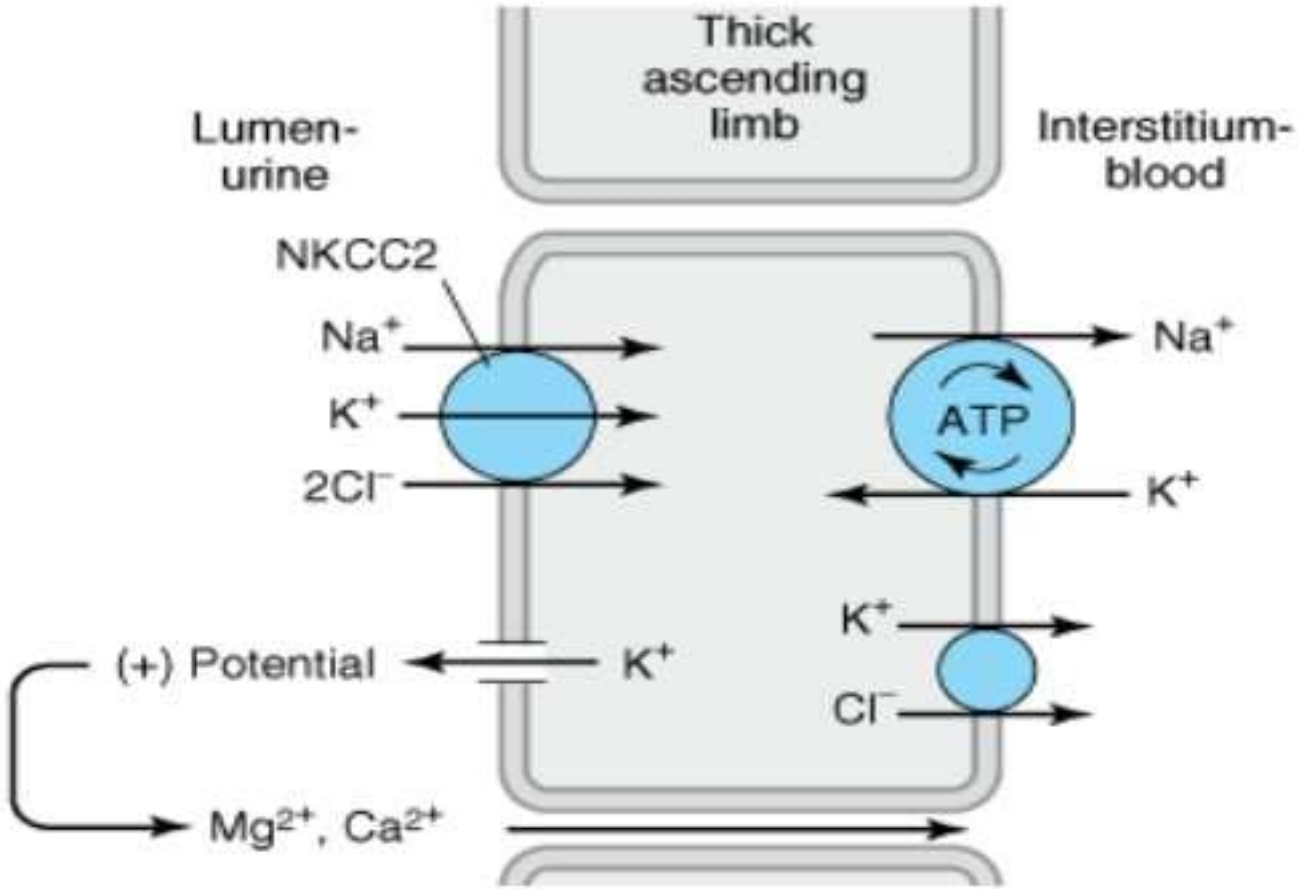
TAL is impermeable to water, therefore this is a diluting segment

Countercurrent system is attributed to this function

Some K diffuses back to the lumen, creating/maintaining positive charge in the lumen

Na-K-2Cl is the site of action of loop diuretics

Mechanism of Action of Loop Diuretic



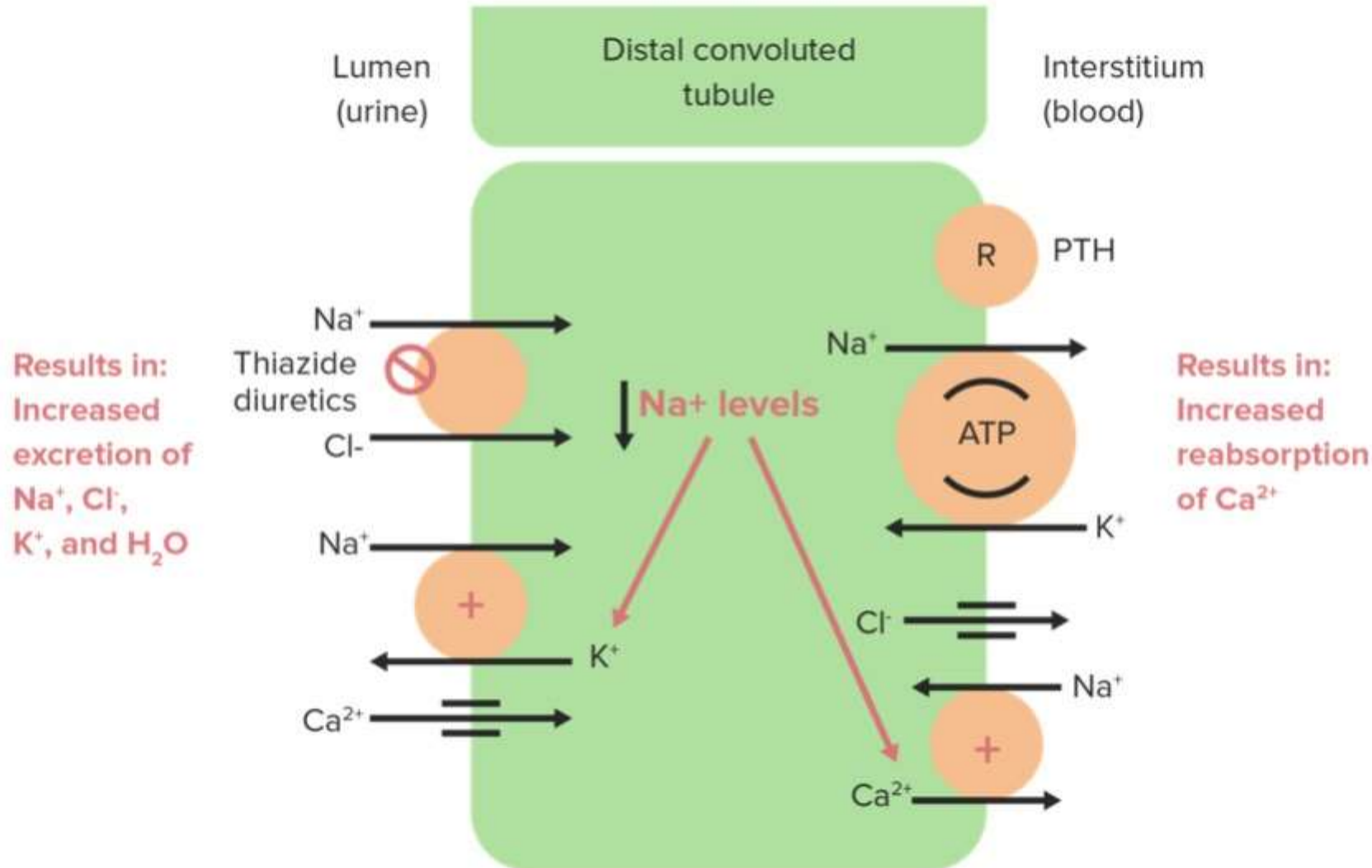
Renal sodium handling

- DT and CD reabsorb 8% of the filtered Na
- Early DT

Na is reabsorbed by Na-Cl cotransporter

This segment, similar to TAL, is impermeable to water, so causing further dilution to tubular fluid, it is called cortical diluting segment

Na-Cl cotransporter is the site of action of thiazide diuretics


Lumen
(urine)
Distal convoluted
tubule
Interstitium
(blood)
R
PTH
Na+
Thiazide
diuretics
Cl-
Na+ levels
Na+
ATP
K+
Results in:
Increased
excretion of
Na+, Cl-,
K+, and H2O
Na+
+
K+
Cl-
Na+
Ca2+
+
Ca2+
Results in:
Increased
reabsorption
of Ca2+

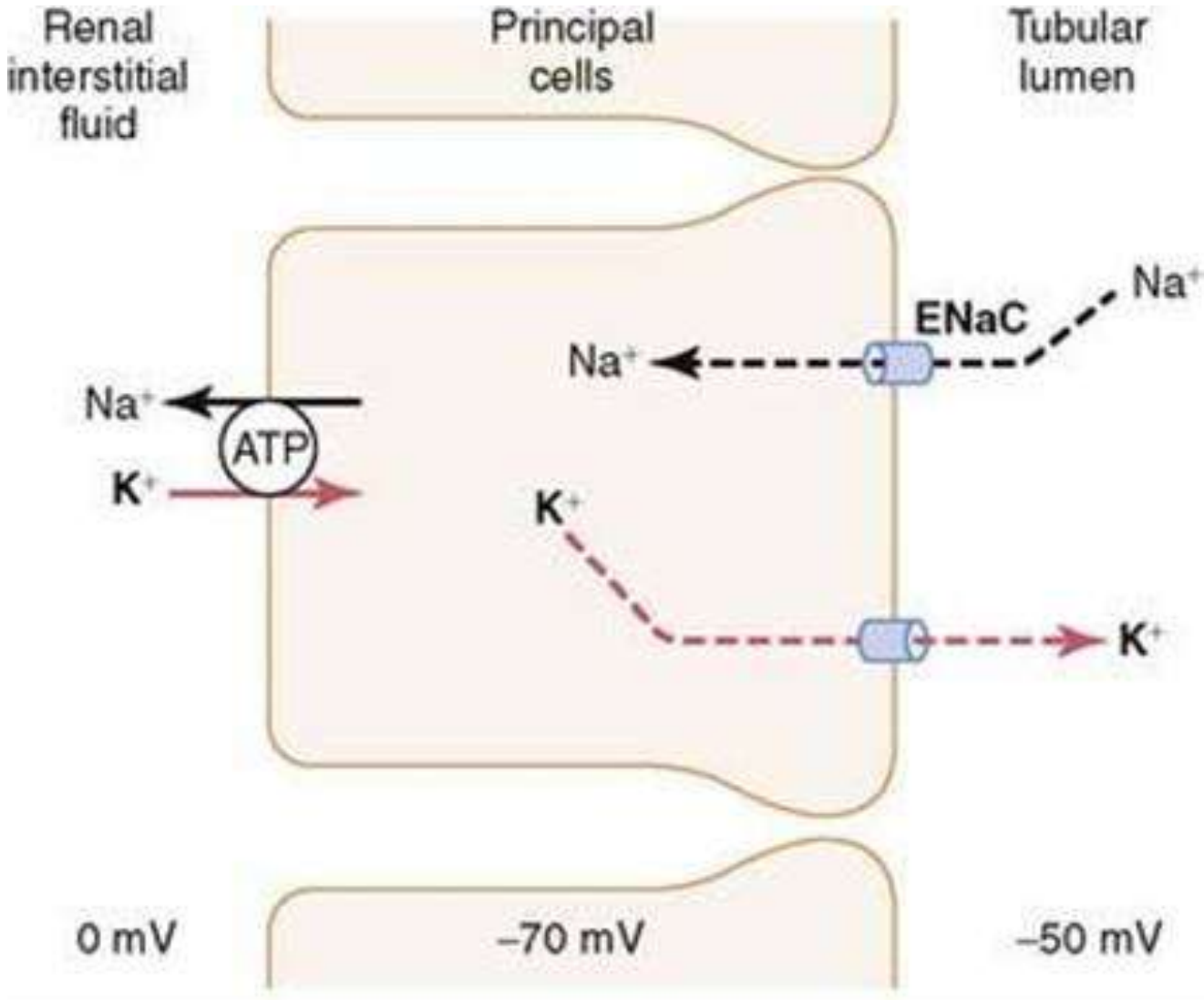
Renal sodium handling

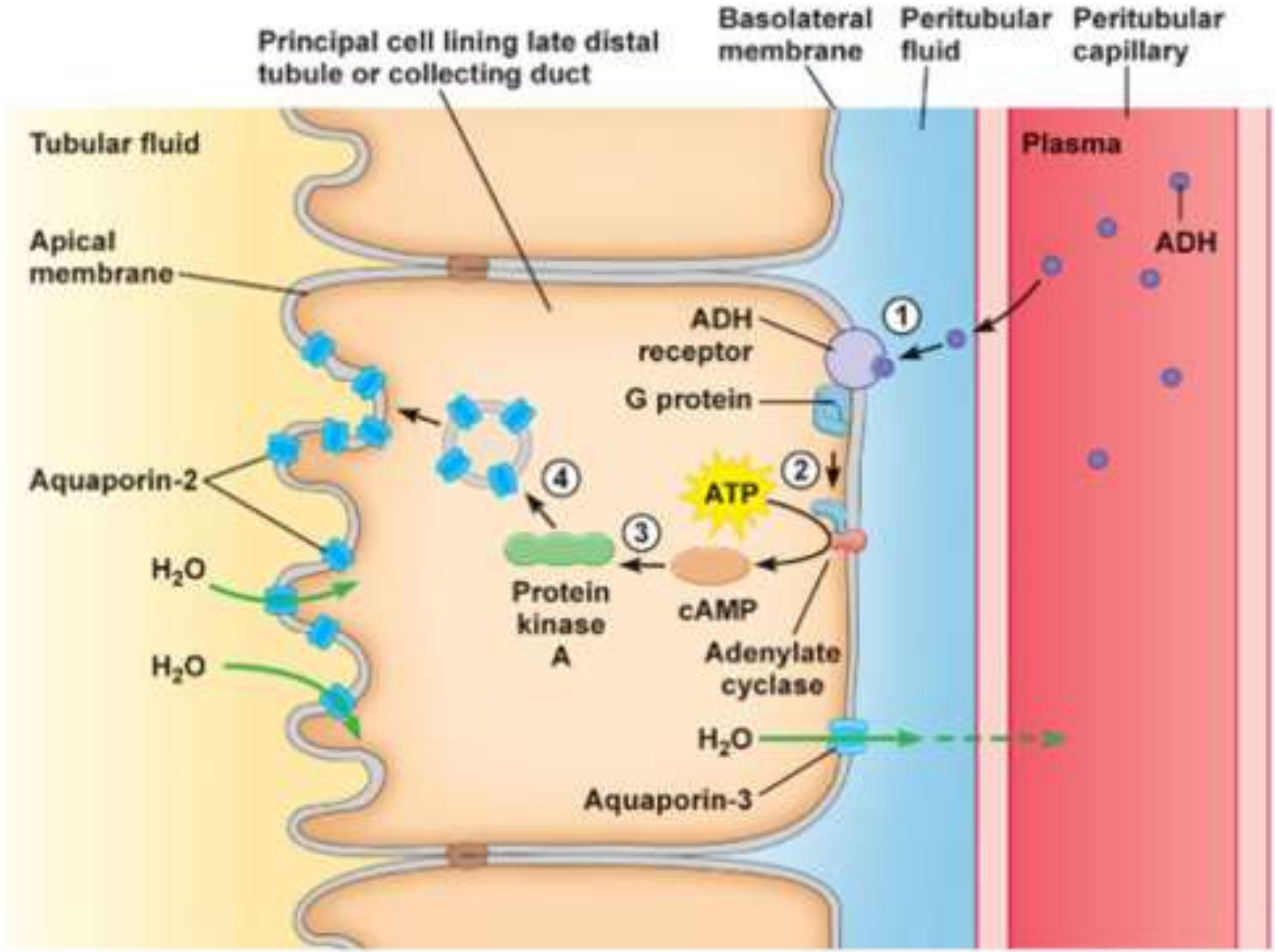
- Late DT and CD.

Principal cells: reabsorb Na and water, secrete K, induced by aldosterone

Principal cell is also the site of action of ADH causing increase in water permeability and absorption

Potassium-sparing diuretics decrease K secretion, by either directly antagonizing aldosterone receptor or effect

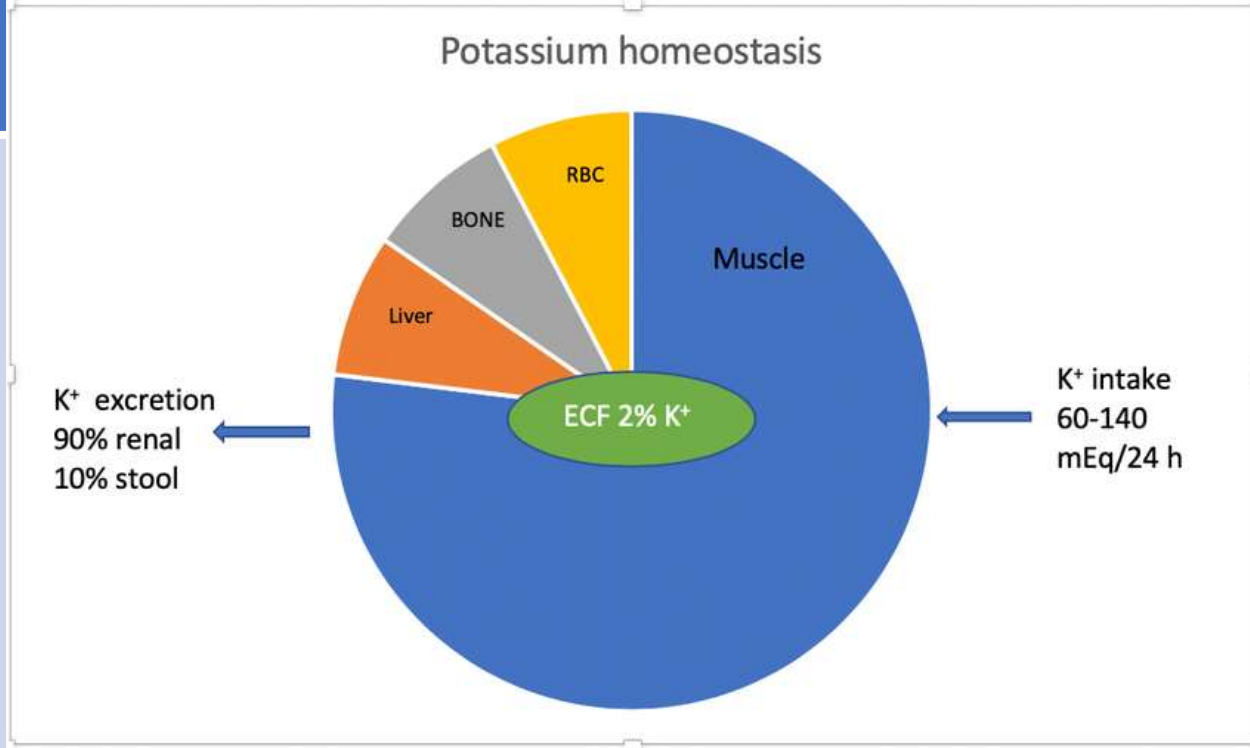

Renal interstitial fluid
Principal cells
Tubular lumen
Na+
ENaC
Na+
Na+
ATP
K+
K+
K+
0 mV
–70 mV
–50 mV


Principal cell lining late distal tubule or collecting duct
Basolateral membrane
Peritubular fluid
Peritubular capillary
Tubular fluid
Plasma
ADH
Apical membrane
ADH receptor
1
G protein
2
ATP
Aquaporin-2
4
3
H_2O
Protein kinase A
cAMP
Adenylate cyclase
H_2O
H_2O
Aquaporin-3

Potassium homeostasis

- Most of the body's K is located in the ICF
- A shift of K out of cells causes hyperkalemia
- A shift of K into cells causes hypokalemia
- Average daily K intake about 100 mEq/day
- 8-10% is excreted thru the gut (colonic secretion)
- 90-92% is excreted thru the kidney

Causes of shift of K out of cells	Causes of shift of K into cells
Insulin deficiency B-adrenergic antagonists Acidosis (H for K) Na/K pump inhibitors (digitalis) Exercise Cell lysis	Insulin B-adrenergic agonists Alkalosis



Renal potassium handling

- K is filtered, reabsorbed and secreted by the nephron
- Filtered: at the glomerulus
- Reabsorbed:

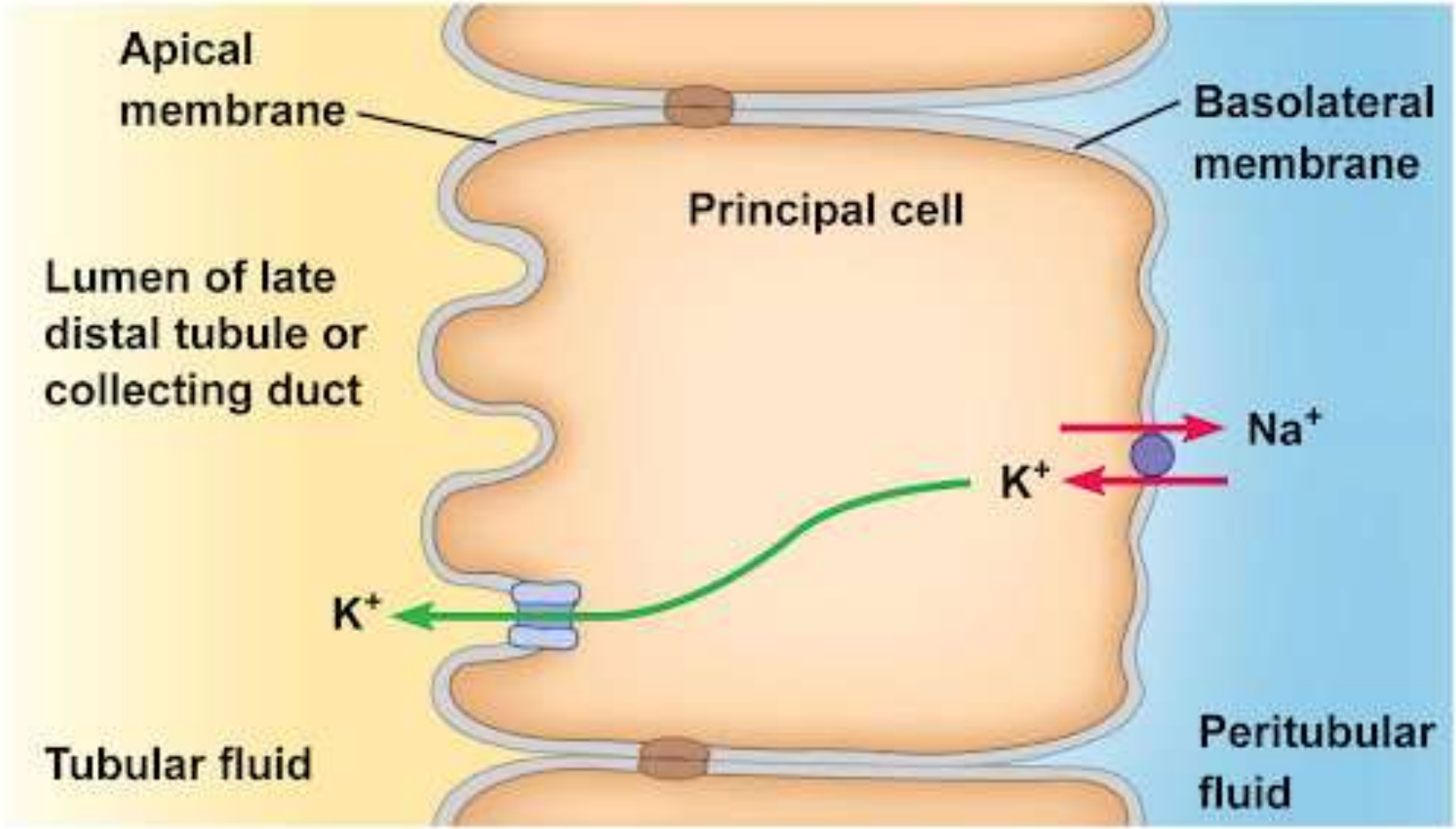
-PCT 67%, with Na and H2O

-TAL 20%, NaKCC2/Na-K-2Cl cotransporter

-DT and CD: H-K ATPase of alpha intercalated cells, with low potassium diet

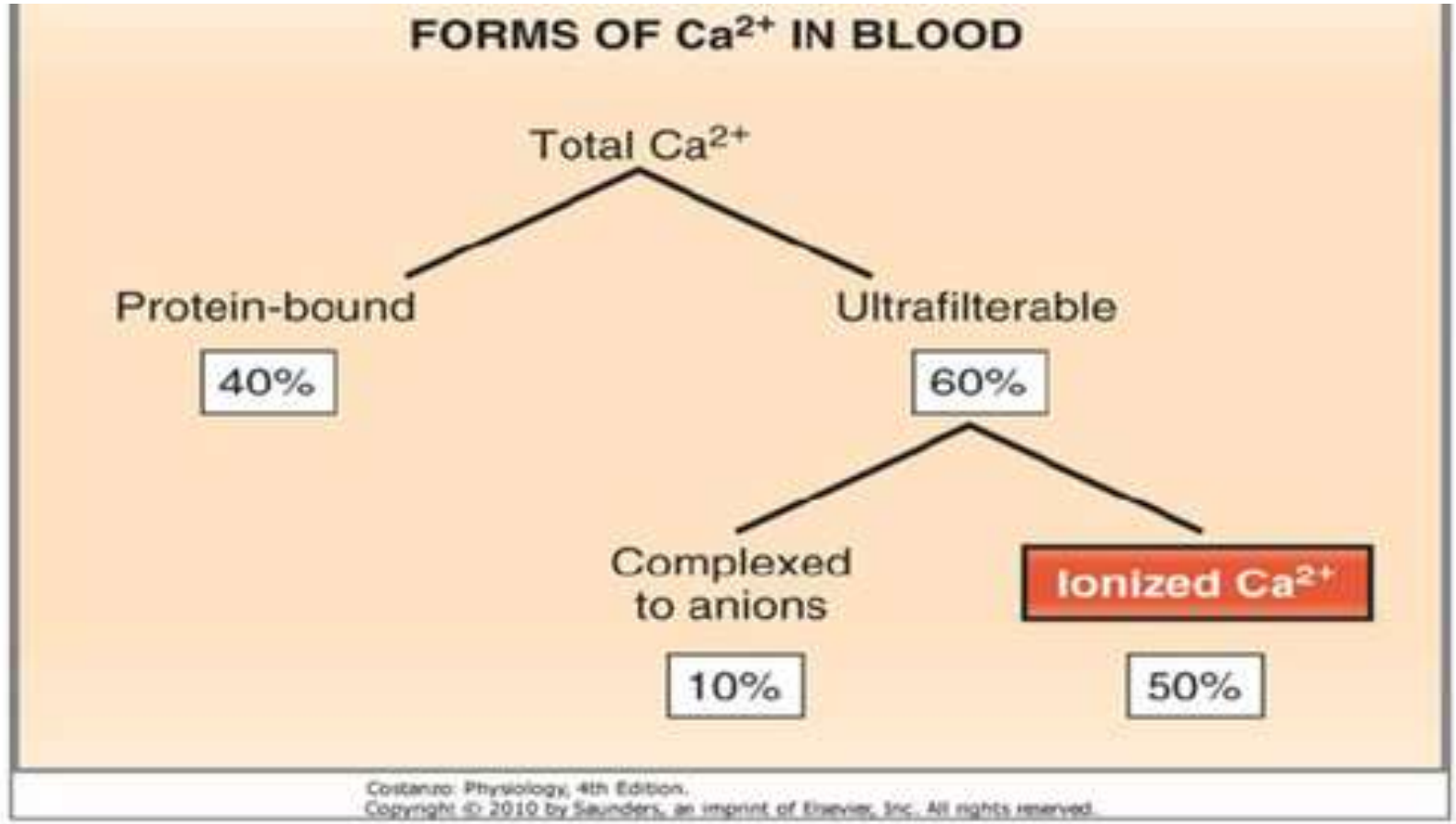
- Secreted

In the principal cells, of variable degree, depends on dietary potassium, aldosterone level, acid-base status, use of loop and thiazide diuretics, and urine flow rate


Apical membrane
Basolateral membrane
Principal cell
Lumen of late distal tubule or collecting duct
Na^+
K^+
K^+
Tubular fluid
Peritubular fluid

Calcium homeostasis

- Daily intake about 1000mg, net intestinal absorption about 200mg
- Bone contains 1000-1300 g of Ca (>99%)
- ECF content < 0.01% of total body store
- The kidney filters 10g/day, reabsorbs 98%, excretes 100-300 mg/day



Renal reabsorption of filtered calcium

- PCT: 60-70%, passive, coupled to Na reabsorption
- TAL: 20-25%, passive paracellular transport, inhibited by loop diuretics
- DCT and CD 15%: active process

PTH and thiazides increases Ca reabsorption in DCT

Serum calcium regulating mechanisms		
Site	**Increasing serum Ca**	**Decreasing serum Ca**
Intestine	Calcitriol	Excretion in bile
Bone	PTH: stimulates osteoclasts Met acidosis: stimulates Ca release from bone	Calcitonin inhibits osteoclasts
Kidney	PTH: Ca reabsorption DCT, activates vit D Volume depletion, thiazide Met alkalosis: increases reabsorption	Calcitonin decreases Ca reabsorption Volume expansion, loop diuretics Metabolic acidosis: decreases reabsorption
Serum	Acidosis: decreases albumin binding to Ca	Alkalosis: increases albumin binding to Ca

Magnesium homeostasis

- Intake about 350 mg/day
- Total body stores: 26g, 60% in bone, 40% in soft tissues, < 1% in ECF
- 70% of total plasma Mg is not protein-bound: filtered in kidney, >95% is reabsorbed
- Renal Mg reabsorption

PCT 20-30% passive

TAL 50-70% passive, paracellular

DCT: 5-10%

-in TAL, Mg and Ca compete for reabsorption, hypercalcemia increases Mg excretion and hypermagnesemia increases Ca excretion

Phosphate homeostasis

- Phosphorus (P) always present in combination with other elements, as organic and inorganic phosphate (inorganic is the fraction measured in ECF)
- Daily intake around 1000 mg/day
- GI absorption: 60-80% of dietary load
- Total body stores around 900 g, 85% in bone, 15% in soft tissues, 0.01% in ECF
- Renal handling: 85% of filtered phosphate is reabsorbed in PCT
- 15% of filtered phosphate is excreted
- PTH inhibits phosphate reabsorption (phosphaturic)

Renal Physiology

Acid-Base Regulation

Hammam Mahmoud Alloh, M.D
Internist, Nephrologist (Al-Shifa & Aqsa Martyrs Hospitals)
Assistant Professor of Internal Medicine and Nephrology (IUG, AUG)

Introduction

- In this chapter, we consider the various mechanisms that contribute to the regulation of H+ concentration, with special emphasis on control of renal H+ handling, and excretion of bicarbonate ions (HCO3-), one of the key components of acid-base control systems in the body fluids

H+ CONCENTRATION IS PRECISELY REGULATED

- Precise H+ regulation is essential, why? It affects all enzyme systems of the body. Changes in H+ concentration alter virtually all cell and body functions
- Compared with other ions, the H+ concentration of the body fluids normally is kept at a low level. It averages only 0.00004 mEq/L
- Equally important, the normal variation in H+ concentration in extracellular fluid is only about one millionth as great as the normal variation in sodium ion. This emphasizes the importance of precise regulation of H+ concentration

ACIDS AND BASES—THEIR DEFINITIONS AND MEANINGS

- Acids: molecules containing hydrogen atoms that can release hydrogen ions in solutions

Examples: HCl ionizes in water and releases H+ and Cl-, H_2CO_3 ionizes in water and releases H+ and HCO_3^-

- Bases: ions or molecules that can accept an H+

Examples: HCO_3^- can accept H+ to become H_2CO_3, plasma proteins

Normal H+ Concentration and pH of Body Fluids and Changes That Occur in Acidosis and Alkalosis

- Blood H+ concentration is normally maintained within tight limits around a normal value of about 40 nEq/L
- Normal variations are only about 3 to 5 nEq/L
- Because H+ concentration normally is low, and because these small numbers are cumbersome, it is customary to express H+ concentration on a logarithm scale, using pH units

$$pH = \log \frac{1}{[H^+]} = -\log[H^+]$$

- For example, normal [H+] is 40 nEq/L (0.00000004 Eq/L). Therefore, the normal pH is

$$pH = -\log[0.00000004]$$
$$pH = 7.4$$

- From this formula, one can see that pH is inversely related to the H+ concentration; therefore, a low pH corresponds to a high H+ concentration and a high pH corresponds to a low H+ concentration
- Because the normal pH of arterial blood is 7.4, a person is considered to have *acidosis* when the pH falls below this value and *alkalosis when* the pH rises above 7.4
- The lower limit of pH at which a person can live more than a few hours is about 6.8, and the upper limit is about 8.0

Table 31-1 pH and H^+ Concentration of Body Fluids

	H^+ Concentration (mEq/L)	pH
Extracellular fluid		
Arterial blood	4.0×10^{-5}	7.40
Venous blood	4.5×10^{-5}	7.35
Interstitial fluid	4.5×10^{-5}	7.35
Intracellular fluid	1×10^{-3} to 4×10^{-5}	6.0-7.4
Urine	3×10^{-2} to 1×10^{-5}	4.5-8.0
Gastric HCl	160	0.8

DEFENDING AGAINST CHANGES IN H+ CONCENTRATION: BUFFERS, LUNGS, AND KIDNEYS

- Three primary systems regulate the H+ concentration in the body fluids to prevent acidosis or alkalosis:

(1) the *chemical acid-base buffer systems of the body fluids*

(2) the *respiratory center,* which regulates the removal of CO2, and

(3) the *kidneys,* which can excrete either acid or alkaline urine

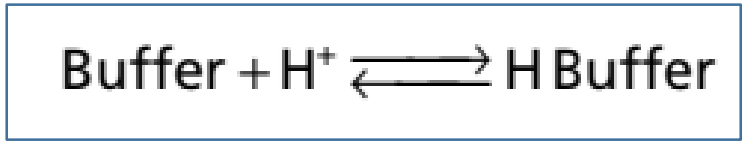
- When there is a change in H+ concentration, the *buffer systems* of the body fluids react within seconds to minimize these changes

Buffer systems do not eliminate H+ from or add H+ to the body but only keep them tied up until balance can be re-established

- The second line of defense, the *respiratory system,* acts within a few minutes to eliminate CO_2 and, therefore, H_2CO_3 from the body
- Although the kidneys are relatively slow to respond compared with the other defenses, over a period of hours to several days, they are by far **the most powerful of the acid-base regulatory systems**

BUFFERING OF H+ IN THE BODY FLUIDS

- A buffer is any substance that can reversibly bind H+



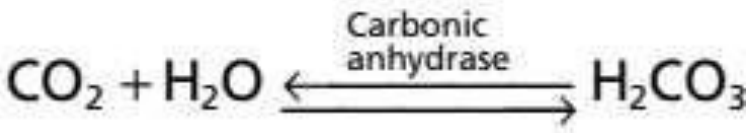
- When the H+ concentration increases, the reaction is forced to the right and more H+ binds to the buffer
- Conversely, when the H+ concentration decreases, the reaction shifts toward the left and H+ is released from the buffer
- The importance of the body fluid buffers can be quickly realized if one considers that 80 mEq of H+ is either ingested or produced each day by metabolism, whereas the H+ concentration of the body fluids normally is only about 40nEq/L
- Without buffering, the daily production and ingestion of acids would cause lethal changes in body fluid H+ concentration

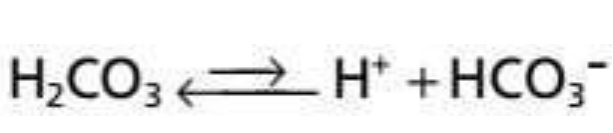
BICARBONATE BUFFER SYSTEM

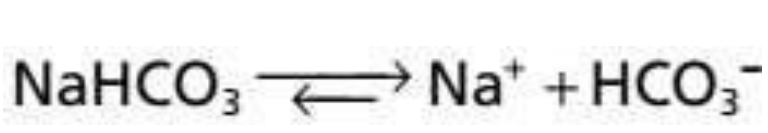
- It consists of a water solution that contains two ingredients:

(1) a weak acid, H2CO3, and

(2) a bicarbonate salt, (NaHCO3)

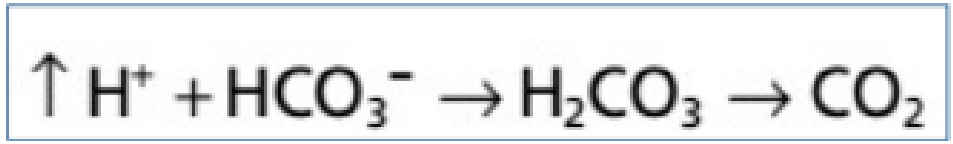






Buffering acid by bicarbonate buffer system

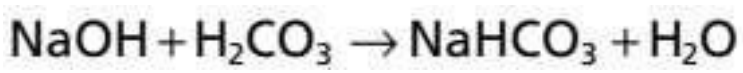
- When a strong acid such as HCl is added to the bicarbonate buffer solution, the increased H+ released from the acid (HCl → H+ + Cl-) is buffered by HCO3-

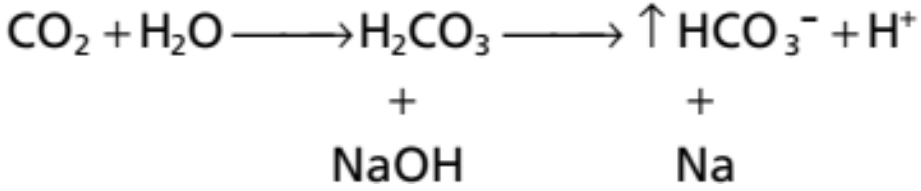


- From these reactions, one can see that H+ from the strong acid HCl reacts with HCO3- to form the very weak acid H2CO3, which in turn forms CO2 and H2O
- The excess CO2 greatly stimulates respiration, which eliminates the CO2 from the extracellular fluid

Buffering base by bicarbonate buffer system

- The opposite reactions take place when a strong base, such as sodium hydroxide (NaOH), is added to the bicarbonate buffer solution





- The net result, therefore, is a tendency for the CO2 levels in the blood to decrease, but the decreased CO2 in the blood inhibits respiration and decreases the rate of CO2 expiration.
- The rise in blood HCO3- that occurs is compensated for by increased renal excretion of HCO3-

The Bicarbonate Buffer System Is the Most Important Extracellular Buffer

- The bicarbonate buffer system is the most powerful extracellular buffer in the body
- This is mainly due to the fact that the two elements of the buffer system, HCO_3^- and CO_2, are regulated, respectively, by the kidneys and the lungs
- As a result of this regulation, the pH of the extracellular fluid can be precisely controlled by the relative rate of removal and addition of HCO_3^- by the kidneys and the rate of removal of CO_2 by the lungs

PHOSPHATE BUFFER SYSTEM

- Although the phosphate buffer system is not important as an extracellular fluid buffer, it plays a major role in buffering renal tubular fluid and intracellular fluids
- The main elements of the phosphate buffer system are H2PO4- and HPO4-
- When a strong acid such as HCl is added to a mixture of these two substances, the hydrogen is accepted by the base HPO4- and converted to H2PO4-

$$HCl + Na_2HPO_4 \rightarrow NaH_2PO_4 + NaCl$$

- When a strong base, such as NaOH, is added to the buffer system, the OH- is buffered by the H2PO4- to form additional amounts of HPO4- & H2O

$$NaOH + NaH_2PO_4 \rightarrow Na_2HPO_4 + H_2O$$

- *the phosphate buffer is especially important in the tubular fluids of the kidneys* for two reasons: (1) phosphate usually becomes greatly concentrated in the tubules, thereby increasing the buffering power of the phosphate system, and (2) the tubular fluid usually has a considerably lower pH than the extracellular fluid does

- *The phosphate buffer system is also important in buffering intracellular fluid* because the concentration of phosphate in this fluid is many times that in the extracellular fluid
- Also, the pH of ICF is lower than that of ECF

PROTEINS ARE IMPORTANT INTRACELLULAR BUFFERS

- The buffer systems within the cells help prevent changes in the pH of extracellular fluid but may take several hours to become maximally effective
- Approximately 60 to 70% of the total chemical buffering of the body fluids is inside the cells, and most of this buffering results from the intracellular proteins
- However, except for the red blood cells, the slowness with which H+ and HCO3- move through the cell membranes often delays for several hours the maximum ability of the intracellular proteins to buffer extracellular acid-base abnormalities

RESPIRATORY REGULATION OF ACID-BASE BALANCE

- The second line of defense against acid-base disturbances is control of extracellular fluid CO_2 concentration by the lungs
- About 1.2 mol/L of dissolved CO_2 normally are in the extracellular fluid, corresponding to a PCO_2 of 40 mmHg
- An increase in ventilation eliminates CO_2 from extracellular fluid and reduces the H^+ concentration
- Conversely, decreased ventilation increases CO_2, thus also increasing H^+ concentration in the extracellular fluid

- If the rate of metabolic formation of CO_2 increases, the PCO_2 of the extracellular fluid is increased.
  Conversely, a decreased metabolic rate lowers the PCO_2.
- Therefore, changes in either pulmonary ventilation or the rate of CO_2 formation by the tissues can change the extracellular fluid PCO_2

Efficiency of Respiratory Control of H+ Concentration

- Respiratory control cannot return the H+ concentration all the way back to normal when a disturbance outside the respiratory system has altered pH.
- Ordinarily, the respiratory mechanism for controlling H+ concentration is approximately 50 to 75 % effective
- Example: if the pH is suddenly decreased by adding acid to the ECF and pH falls from 7.4 to 7.0, the respiratory system can return the pH to a value of about 7.2 to 7.3. This response occurs within 3 to 12 minutes

Buffering Power of the Respiratory System

- *Respiratory regulation of acid-base balance* *is a physiological type of buffer system* because it acts rapidly and keeps the H+ concentration from changing too much **until** the slowly responding kidneys can eliminate the imbalance
- In general, **the overall buffering power of the respiratory system is one to two times as great as the buffering power of all other chemical buffers in the extracellular fluid combined**

Impairment of Lung Function Can Cause Respiratory Acidosis

- an impairment of lung function, such as severe emphysema, decreases the ability of the lungs to eliminate CO_2, which causes a buildup of CO_2 in the extracellular fluid and a tendency toward *respiratory acidosis.*
- Also, the ability to respond to metabolic acidosis is impaired because the compensatory reductions in PCO_2 that would normally occur by means of increased ventilation are blunted.
- In these circumstances, the kidneys represent the sole remaining physiologic mechanism for returning pH toward normal after the initial chemical buffering in the extracellular fluid has occurred

RENAL CONTROL OF ACID-BASE BALANCE

- The kidneys control acid-base balance by excreting either acidic or basic urine
- If more H+ is secreted than HCO3− is filtered, there will be a net loss of acid from the extracellular fluid. Conversely, if more HCO3− is filtered than H+ is secreted, there will be a net loss of base
- Each day the body produces about 80 mEq of nonvolatile acids, mainly from the metabolism of proteins (*nonvolatile* because they are not H2CO3, therefore, cannot be excreted by the lungs)

- The kidneys must also prevent the loss of bicarbonate in the urine
- Each day the kidneys filter about 4320 mEq of HCO_3^- (180 L/day × 24 mEq/L)
- Almost all this is reabsorbed from the tubules, thereby conserving the bicarbonate buffer system
- Because HCO_3^- must react with a secreted H^+ to form H_2CO_3 before it can be reabsorbed, 4320 mEq of H^+ must be secreted each day just to reabsorb the filtered HCO_3^-
- Then an additional 80 mEq of H^+ must be secreted to rid the body of the nonvolatile acids produced each day (4320 with HHCO3 + 80 H = 4400H)

- When there is a reduction in the extracellular fluid H+ (alkalosis) the kidneys secrete less H+ and fail to reabsorb all the filtered HCO_3^-, thereby increasing the excretion of HCO_3^-
- In acidosis, the kidneys secrete additional H+ and do not excrete HCO_3^- into the urine but, which is added back to the extracellular fluid

- Thus, the kidneys regulate extracellular fluid H+ concentration through three fundamental mechanisms:

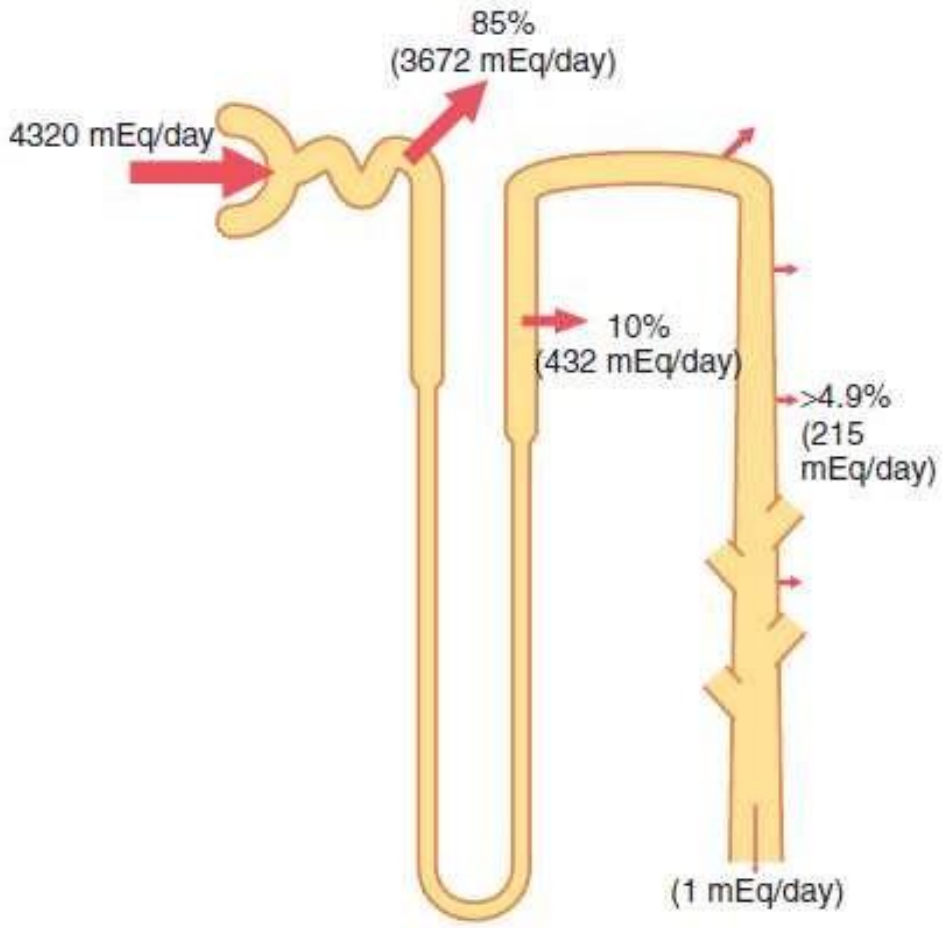
(1) secretion of H+,

(2) reabsorption of filtered HCO_3^-, and

(3) production of new HCO_3^-

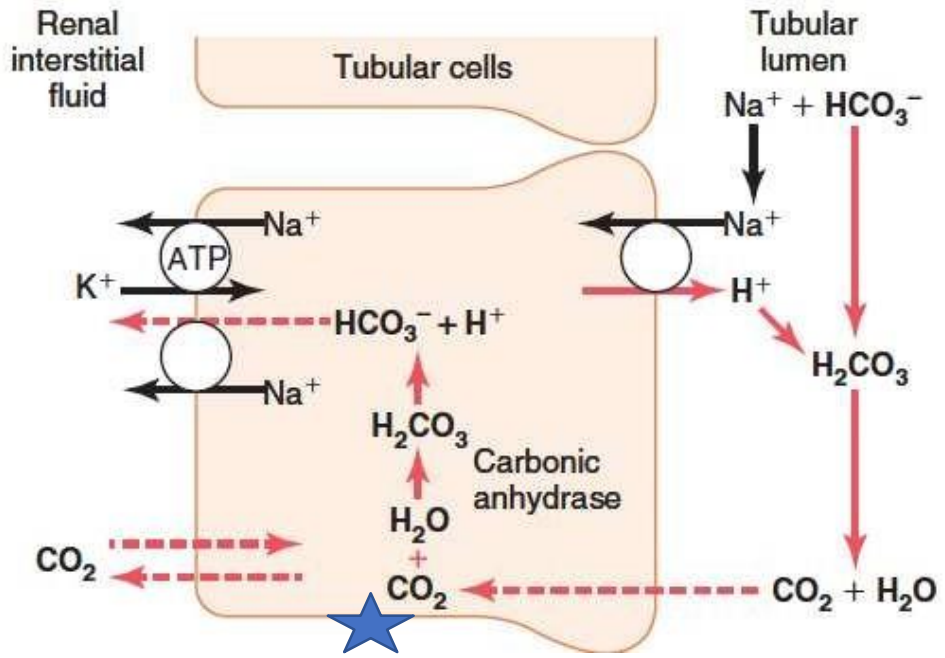
SECRETION OF H+ AND REABSORPTION OF HCO3− BY THE RENAL TUBULES

- H+ secretion and HCO3− reabsorption occur in virtually all parts of the tubules except the descending and ascending thin limbs of the loop of Henle
- For each HCO3− reabsorbed, a H+ must be secreted



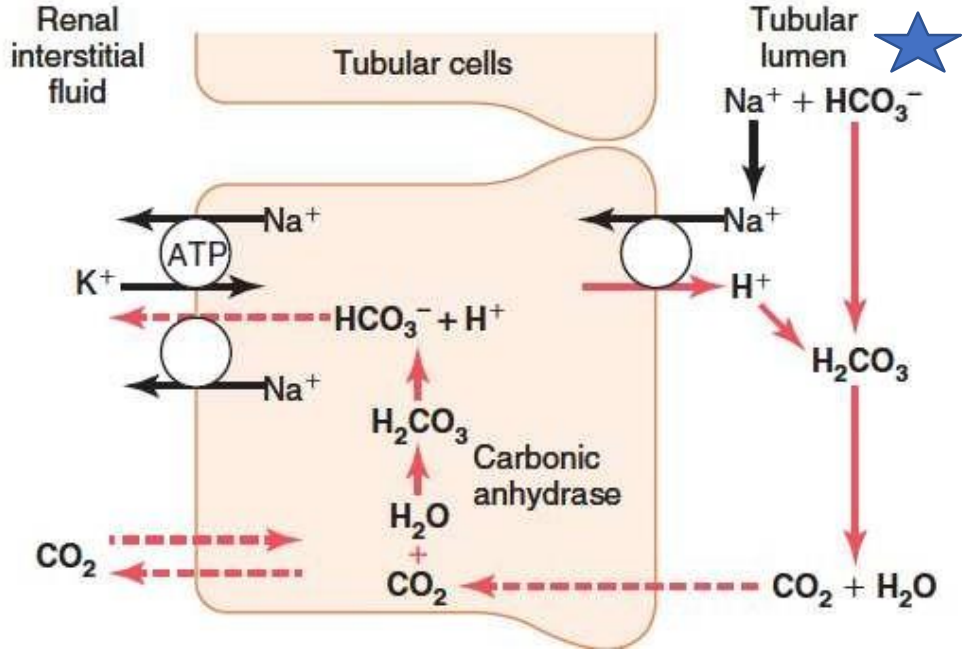
H+ IS SECRETED BY SECONDARY ACTIVE TRANSPORT IN THE EARLY TUBULAR SEGMENTS

- The epithelial cells of the proximal tubule, the thick segment of the ascending loop of Henle, and the early distal tubule all secrete H+ into the tubular fluid by sodium-hydrogen counter-transport
- This mechanism, however, does not establish a very high H+ concentration in the tubular fluid; the tubular fluid becomes very acidic only in the collecting tubules and collecting ducts



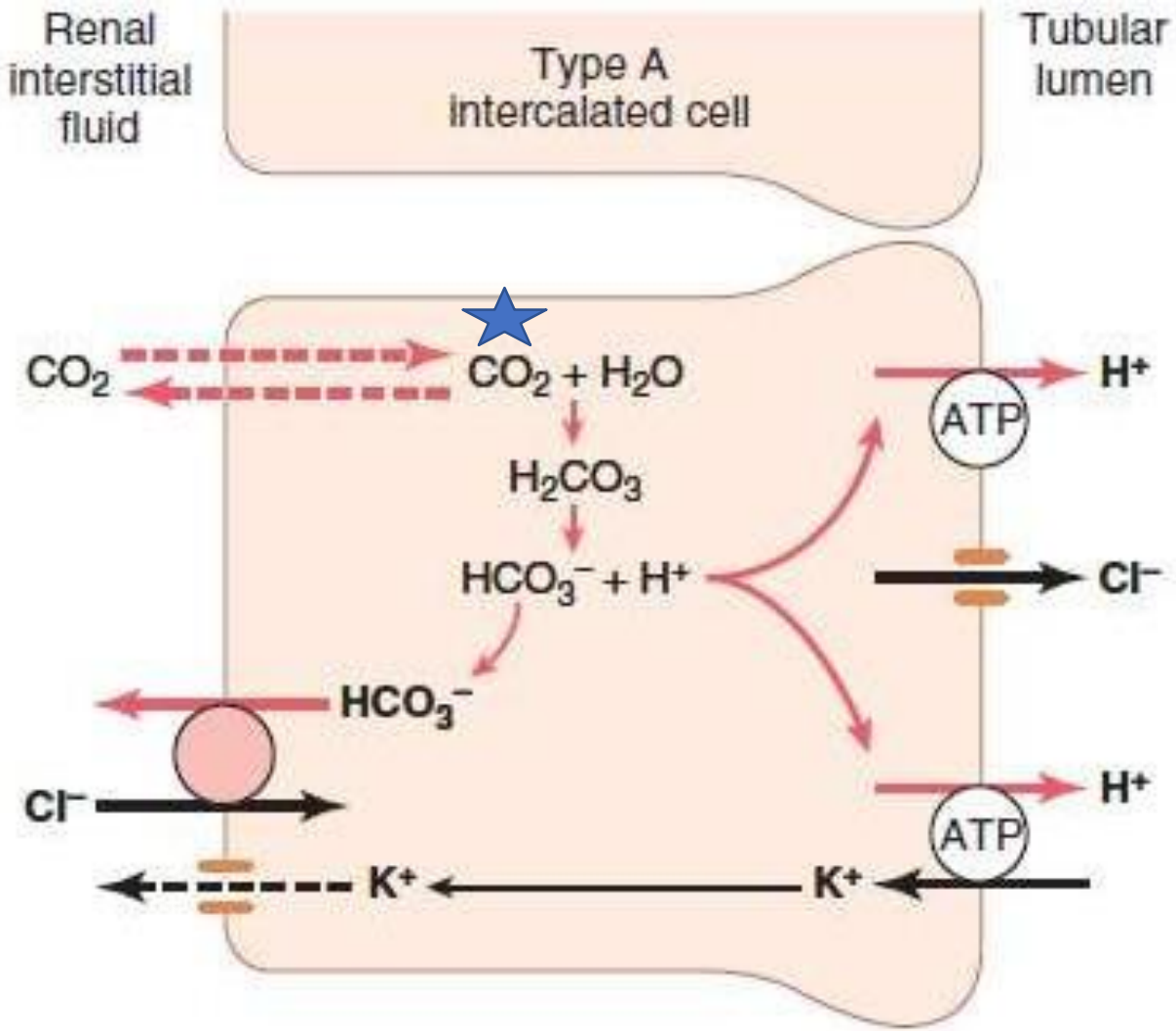
FILTERED HCO3− IS REABSORBED BY INTERACTION WITH H+ IN THE TUBULES

- The transport of HCO3 across the basolateral membrane is facilitated by two mechanisms: (1) Na+-HCO3− co-transport in the proximal tubules and
- (2) Cl−-HCO3− exchange in the late segments of the proximal tubule, the thick ascending loop of Henle, and the collecting tubules and ducts



PRIMARY ACTIVE SECRETION OF H+ IN THE INTERCALATED CELLS OF LATE DISTAL AND COLLECTING TUBULES

- Beginning in the late distal tubules and continuing through the remainder of the tubular system
- occurs in special types of cells called the type A intercalated cells
- Although it accounts for only about 5 % of the total H+ secreted, this mechanism is important in forming maximally acidic urine
- In the proximal tubules, H+ concentration can be increased only about 3-4 folds and the tubular fluid pH can be reduced to only about 6.7
- However, H+ concentration can be increased as much as 900-fold in the collecting tubules, which can reduce urine pH to maximally acidic (4.5)


Renal interstitial fluid
Type A intercalated cell
Tubular lumen
CO_2
$CO_2 + H_2O$
H_2CO_3
$HCO_3^- + H^+$
HCO_3^-
Cl^-
K^+
H^+
ATP
Cl^-
H^+
ATP
K^+

COMBINATION OF EXCESS H+ WITH PHOSPHATE AND AMMONIA BUFFERS IN THE TUBULE GENERATES "NEW" HCO3 –

- When H+ is secreted in excess of the HCO3– filtered into the tubular fluid, only a small part of the excess H+ can be excreted in the ionic form (H+) in the urine
- This is because the minimal urine pH is about 4.5, corresponding to an H+ concentration of 0.03 mEq/L
- Thus, for each liter of urine formed, a maximum of only about 0.03 mEq of free H+ can be excreted
- To excrete the 80 mEq of nonvolatile acid formed by metabolism each day, about 2667 liters of urine would have to be excreted if the H+ remained free in solution

- The excretion of large amounts of H+ in the urine is accomplished primarily by combining the H+ with buffers in the tubular fluid
- The most important buffers are phosphate buffer and ammonia buffer
- when there is excess H+ in the extracellular fluid, the kidneys not only reabsorb all the filtered HCO_3^- but also generate new HCO_3^- (from phosphate and ammonia buffers), thereby helping to replenish the HCO_3^- lost from the extracellular fluid in acidosis

PHOSPHATE BUFFER SYSTEM CARRIES EXCESS H+ INTO THE URINE AND GENERATES NEW HCO3−

- The phosphate buffer system is composed of HPO4= and H2PO4−
- Although phosphate is not an important extracellular fluid buffer, it is much more effective as a buffer in the tubular fluid
- Under normal conditions, much of the filtered phosphate is reabsorbed and only 30 to 40 mEq/day are available for buffering H+. Therefore, much of the buffering of excess H+ in the tubular fluid in acidosis occurs through the ammonia buffer system

- There is one important difference in this sequence of H+ excretion from that discussed previously.
- In this case, the HCO3− that is generated in the tubular cell and enters the peritubular blood represents a net gain of HCO3−by the blood, rather than merely a replacement of filtered HCO3-
- *Therefore, whenever an H+ secreted into the tubular lumen combines with a buffer other than HCO3−, the net effect is addition of a new HCO3− to the blood*

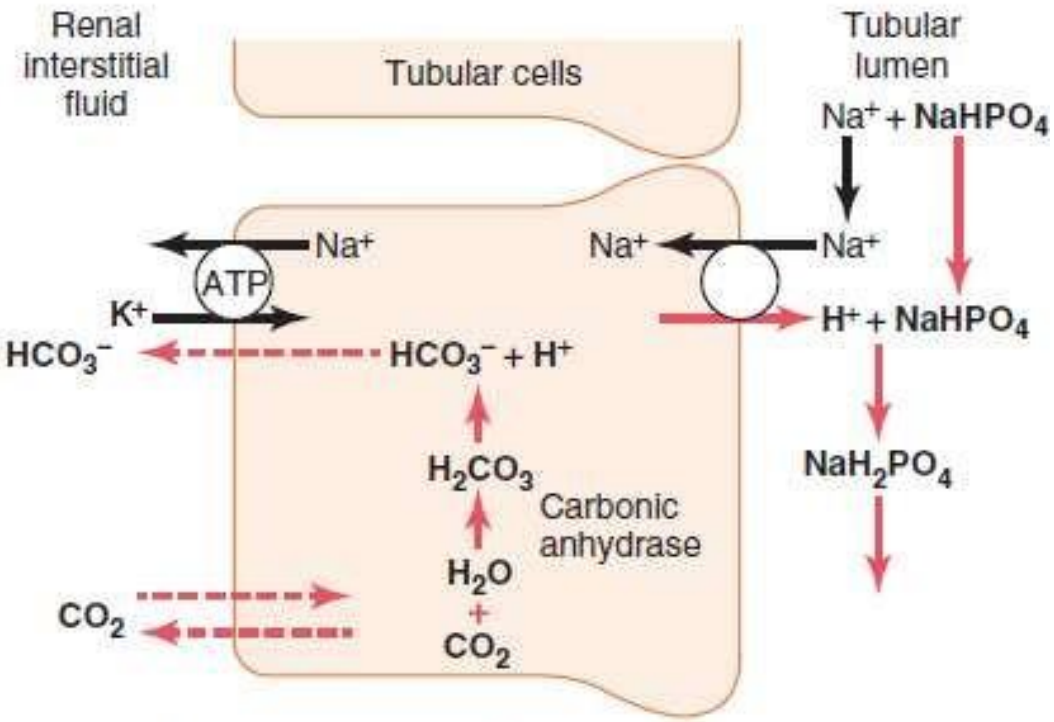


Figure 31-7. Buffering of secreted H^+ by filtered phosphate ($NaHPO_4$). Note that a new HCO_3^- is returned to the blood for each $NaHPO_4$ that reacts with a secreted H^+.

EXCRETION OF EXCESS H+ AND GENERATION OF NEW HCO3− BY THE AMMONIA BUFFER SYSTEM

- A second buffer system in the tubular fluid that is even more important quantitatively than the phosphate buffer system is composed of ammonia (NH3) and the ammonium ion (NH4+)
- Ammonium ion is synthesized from glutamine, which comes mainly from the metabolism of amino acids in the liver
- The glutamine delivered to the kidneys is transported into the epithelial cells of the proximal tubules, thick ascending limb of the loop of Henle, and distal tubules

- For each molecule of glutamine metabolized in the proximal tubules, two NH4+ are secreted into the urine and two HCO3 − are reabsorbed into the blood
- *TheHCO3− generated by this process constitutes new HCO3−*

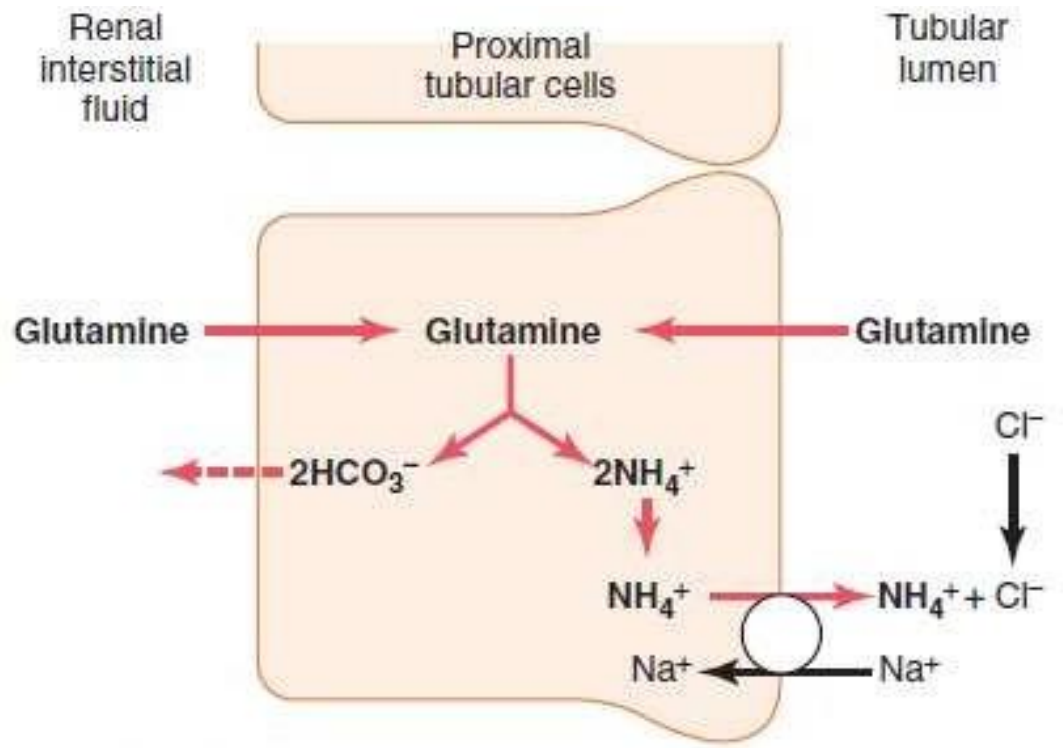


Figure 31-8. Production and secretion of ammonium ion (NH_4^+) by proximal tubular cells. Glutamine is metabolized in the cell, yielding NH_4^+ and bicarbonate. The NH_4^+ is secreted into the lumen by a sodium-NH_4^+ exchanger. For each glutamine molecule metabolized, two NH_4^+ are produced and secreted and two HCO_3^- are returned to the blood.

In the collecting tubules, the addition of NH4+ to the tubular fluids occurs through a different mechanism

For each NH4+ excreted, a new HCO3– is generated and added to the blood

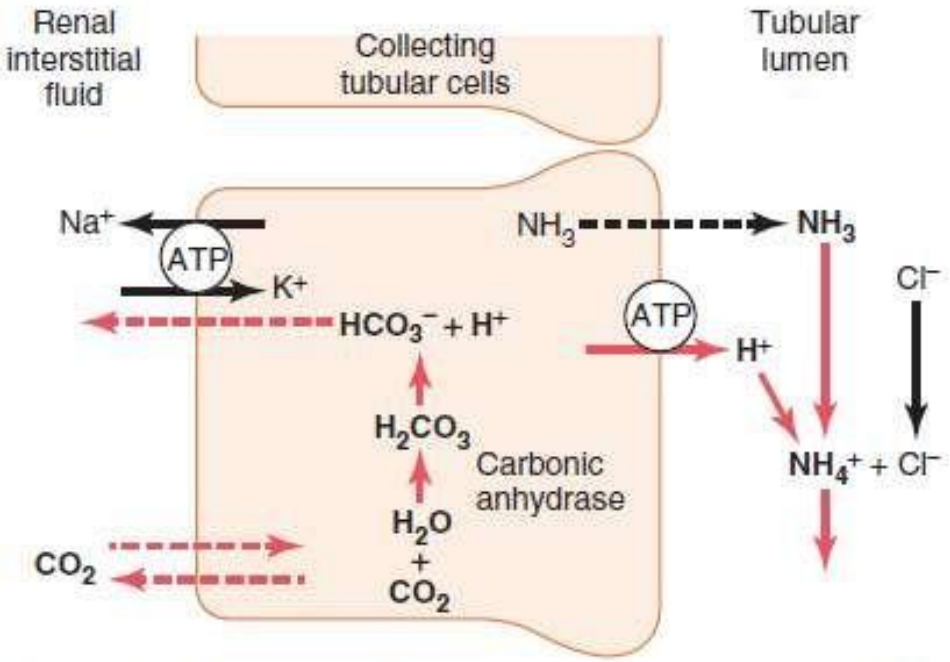


Figure 31-9. Buffering of hydrogen ion secretion by ammonia (NH_3) in the collecting tubules. Ammonia diffuses into the tubular lumen, where it reacts with secreted H^+) to form NH_4^+, which is then excreted. For each NH_4^+ excreted, a new HCO_3^- is formed in the tubular cells and returned to the blood.

Chronic Acidosis Increases NH4+ Excretion

- Under *normal conditions*, the amount of H+ eliminated by the ammonia buffer system accounts for about 50 % of the acid excreted and 50 percent of the new HCO3− generated by the kidneys
- with *chronic acidosis*, the rate of NH4+ excretion can increase to as much as 500 mEq/day
- *Therefore, with chronic acidosis, the dominant mechanism by which acid is eliminated is excretion of NH4+*
- This process also provides the most important mechanism for generating new bicarbonate during chronic acidosis

REGULATION OF RENAL TUBULAR H+ SECRETION

- The most important stimuli for increasing H+ secretion by the tubules in acidosis are

(1) an increase in PCO2 of the extracellular fluid in respiratory acidosis

(2)an increase in H+ concentration of the extracellular fluid *(decreased pH)* in respiratory & metabolic acidosis

In acidosis

There is an increase in the rate of H+ secretion:

- The increased PCO2 raises the PCO2 of the tubular cells, causing increased formation of H+ in the tubular cells, which in turn stimulates the secretion of H+.
- The second factor that stimulates H+ secretion is an increase in extracellular fluid H+ concentration (decreased pH) in respiratory and metabolic acidosis

In alkalosis

- The tubular cells usually respond to a decrease in H+ concentration (alkalosis) by reducing H+ secretion.

The decreased H+ secretion results from

(1)decreased extracellular PCO_2, as occurs in respiratory alkalosis, or

(2)from a decrease in H+ concentration per se, as occurs in both respiratory and metabolic alkalosis.

Table 31-2 Plasma or Extracellular Fluid Factors That Increase or Decrease H^+ Secretion and HCO_3^- Reabsorption by the Renal Tubules

Increase H^+ Secretion and HCO_3^- Reabsorption	Decrease H^+ Secretion and HCO_3^- Reabsorption
↑ P_{CO_2}	↓ P_{CO_2}
↑ H^+, ↓ HCO_3^-	↓ H^+, ↑ HCO_3^-
↓ Extracellular fluid volume	↑ Extracellular fluid volume
↑ Angiotensin II	↓ Angiotensin II
↑ Aldosterone	↓ Aldosterone
Hypokalemia	Hyperkalemia

Table 31-3 Characteristics of Primary Acid-Base Disturbances

	pH	H^+	PCO_2	HCO_3^-
Normal	7.4	40 mEq/L	40 mm Hg	24 mEq/L
Respiratory acidosis	↓	↑	↑↑	↑
Respiratory alkalosis	↑	↓	↓↓	↓
Metabolic acidosis	↓	↑	↓	↓↓
Metabolic alkalosis	↑	↓	↑	↑↑

The primary event is indicated by the double arrows (↑↑ or ↓↓). Note that respiratory acid-base disorders are initiated by an increase or decrease in PCO_2, whereas metabolic disorders are initiated by an increase or decrease in HCO_3^-.