RENAL PHYSIOLOGY (PART 3)

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Lec. 3

Mechanisms of Na+ Reabsorption

- Almost all *renal tubular cells* **reabsorb Na+ actively.**
- The reabsorption is driven by the **Na+ –K+ pump** located on the **basolateral membrane**, *which pumps Na+ into the paracellular spaces and lowers the intracellular Na+ concentration*.
- **However**, the *mechanisms of* ***Na+ transport*** *across the* ***apical membrane (luminal membrane)*** *differ in the different segments of the tubule.*

Mechanisms of Na+ Reabsorption

i. Unitransport of Na+ ions

ii. Sodium cotransport with organic substrates

iii. Na+ -H+ antiport with bicarbonate-chloride antiport

iv. Chloride-driven sodium transport

v. Sodium cotransport with chloride and potassium ions

vi. Sodium–chloride cotransport

Unitransport of Na+ ions

❖**occurs in the proximal tubule as well as in the collecting duct.**

- **It involves the following steps:-**

I. **Na+ is actively** transported by **Na+ –K+ ATPase** across the **basolateral surface**.

II. **Na+ passively** diffuses across the **luminal membrane** to restore intracellular electroneutrality and Na+ concentration.

III. **chloride (Cl–) passively** diffuses across the "**leaky" tight junctions** *to restore the transepithelial electrochemical balance.*

IV. The Na+ in the **basolateral spaces** largely enters the **peritubular capillaries** and **partly** leaks back into the tubule (through the leaky junctions).

Sodium cotransport with organic substrates

- occurs only in the **proximal tubule because** glucose, amino acids, and organic anions are reabsorbed completely in the **proximal tubule**.
- Both **glucose** and **amino acids** are **cotransported** with Na+ in the *proximal tubule*.
- The **organic anion** that is **cotransported** with Na+ is a dicarboxylate or a tricarboxylate organic anion.

- *Other organic ions are coupled to the transport of di/tricarboxylates and thereby are **indirectly coupled to Na+ transport**.*
- *For example, para-aminohippuric acid (PAH) is transported by a **PAH anion antiport** working together with a Na+ -di/tricarboxylate symporter.*

Na+ -H+ antiport with bicarbonate-chloride antiport

❖Occurs almost in **proximal tubule** .

- It involves the following steps:

1- Na+ is actively extruded across the basolateral surface, producing intracellular negativity.

2- Na+ diffuses inside across the luminal membrane along the electrochemical gradient with coupled *extrusion* of **H+** **(Na+ –H+ antiport)**. The **H+** is produced, along with **HCO3 –** , by the intracellular reaction of **CO2** with water. The electrical gradient persists

3- The **HCO3 –** either diffuses out across the basolateral surface to restore electroneutrality, or diffuses out across the luminal membrane with coupled entry of **Cl** (parallel HCO3 – –Cl– antiport).

❖*CL diffuses out across the basolateral surface to restore electroneutrality.*

❖Coupled extrusion of **H+** is **limited** by the intracellular availability of **H+** . Thus, it is increased by a **high PCO2** and decreased by **diamox** (carbonic anhydrase inhibitor), both of which affect **H+ production**.

❖**In alkalosis**, **H+** secretion **decreases**, and the **Na+ –H+ antiport** is **reduced**. Hence, Na+ reabsorption decreases in alkalosis.

❖Conversely, because **HCO3 – reabsorption** in the *proximal tubule* is **linked to Na+ reabsorption**, bicarbonate appears in the urine whenever Na+ reabsorption decreases in the proximal tubule, **resulting in slight acidosis**.

❖Hence, **diuretics** result in not only increased **Na+ excretion**, **but** also a *slight loss* of **bicarbonate** in the *urine* and *acidosis*.

Chloride-driven sodium transport

- occurs in the **proximal tubule** alone.
- by the time the filtrate reaches the **proximal tubule** , the **chloride concentration** in the tubule is higher than in the peritubular capillary.
- **Cl–** therefore **diffuses passively** into the peritubular capillaries.
- *The passive diffusion of **Cl–** across the luminal membrane sets up an electrical gradient along which **Na+ diffuses in**.*

Sodium cotransport with chloride and potassium ions

❖is confined to the *ascending limb of Henle* **only.**

I. **Na+** is **actively** extruded across the **basolateral surface.**

II. **Na+ passively** diffuses **inside** with coupled *cotransport* of two Cl– ions and one K+ . This is termed the **Na+ /K+ –2Cl– cotransport system**.

III. **Two Cl–** and **one K+ ion** *diffuse out across the basolateral surface to restore electroneutrality*

IV. Due to the presence of "tight" **tight junctions**, **Na+** is **unable** to *leak back from the lateral spaces into the tubule.*

V. Some of the **K+** that enters the cell **leaks back** across the apical membrane into the **tubular lumen**.

❖*A group of diuretics called the loop diuretics **inhibit** the **Na+ / K+ –2Cl– system**. Loop diuretics include **furosemide** .*

Sodium–chloride cotransport

❖occurs in the **Distal tubule alone**.

❖It involves the following steps:-

I. **Na+** is actively extruded across the basolateral surface of the tubular cell.

II. **Na+** diffuses across the luminal membrane through **Na+ –Cl– cotransport**.

III. **The chloride** diffuses out into the basolateral spaces.

❖**Na+ -Cl- cotransport is inhibited** *by a group of compounds called the* benzothiazides.

❖*Thiazides therefore produce natriuresis with diuresis*.

Factors Affecting Na+ Reabsorption

I. The apical sodium transport

II. The activity of the basolateral Na+ –K+ ATPase

III. and the Starling forces.

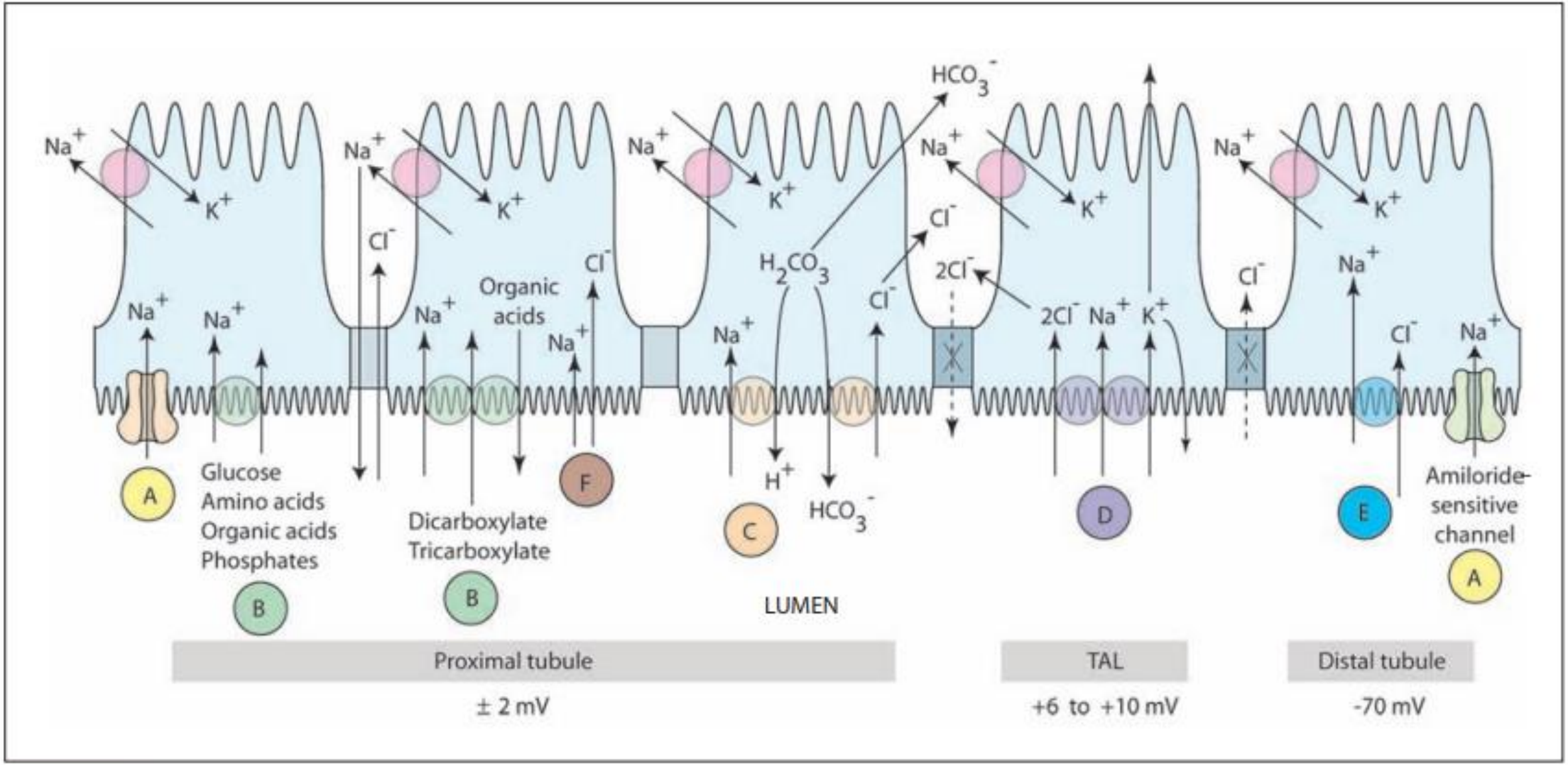


Fig. 55.2 Different mechanisms of tubular reabsorption of sodium ions. **(A)** Unitransport of Na^+; **(B)** Na^+ cotransport with non-Cl^-, non-H^+ substrates; **(C)** Na^+–H^+ exchange, usually with a parallel Cl^-–HCO_3^- uniport; **(D)** Na^+/K^+–$2Cl^-$ cotransport, **(E)** Na^+–Cl^- cotransport; and **(F)** chloride-driven Na^+ transport. TAL, thick ascending limb of the loop of Henle.

Coupling of Water Reabsorption to Na Reabsorption

❖**Water** *follows passively by* **osmosis**.

1- Na is transported from the **tubular lumen** to the **interstitial fluid** across the epithelial cells. Other solutes, such as glucose, amino acids, and HCO3 , whose reabsorption depends on Na transport, **also contribute** to **osmosis.**

2- The **removal of solutes** from the **tubular lumen** **decreases** *the local osmolarity of the tubular fluid adjacent to the cell* (i.e., **the local water concentration increases**).

At the same time, *the appearance of solute in the interstitial fluid just outside the cell* ***increases*** *the local osmolarity* (**i.e., the local water concentration decreases**).

3- The **difference** in *water concentration* **between** lumen and interstitial fluid **causes** *net diffusion of* ***water*** *from the lumen* ***across*** *the tubular cells' plasma membranes and/or tight junctions* ***into*** *the interstitial fluid*.

4- From there, **water**, **Na** , and **everything** else dissolved in the interstitial fluid **move together** by bulk flow into **peritubular capillaries** as the final step in reabsorption.

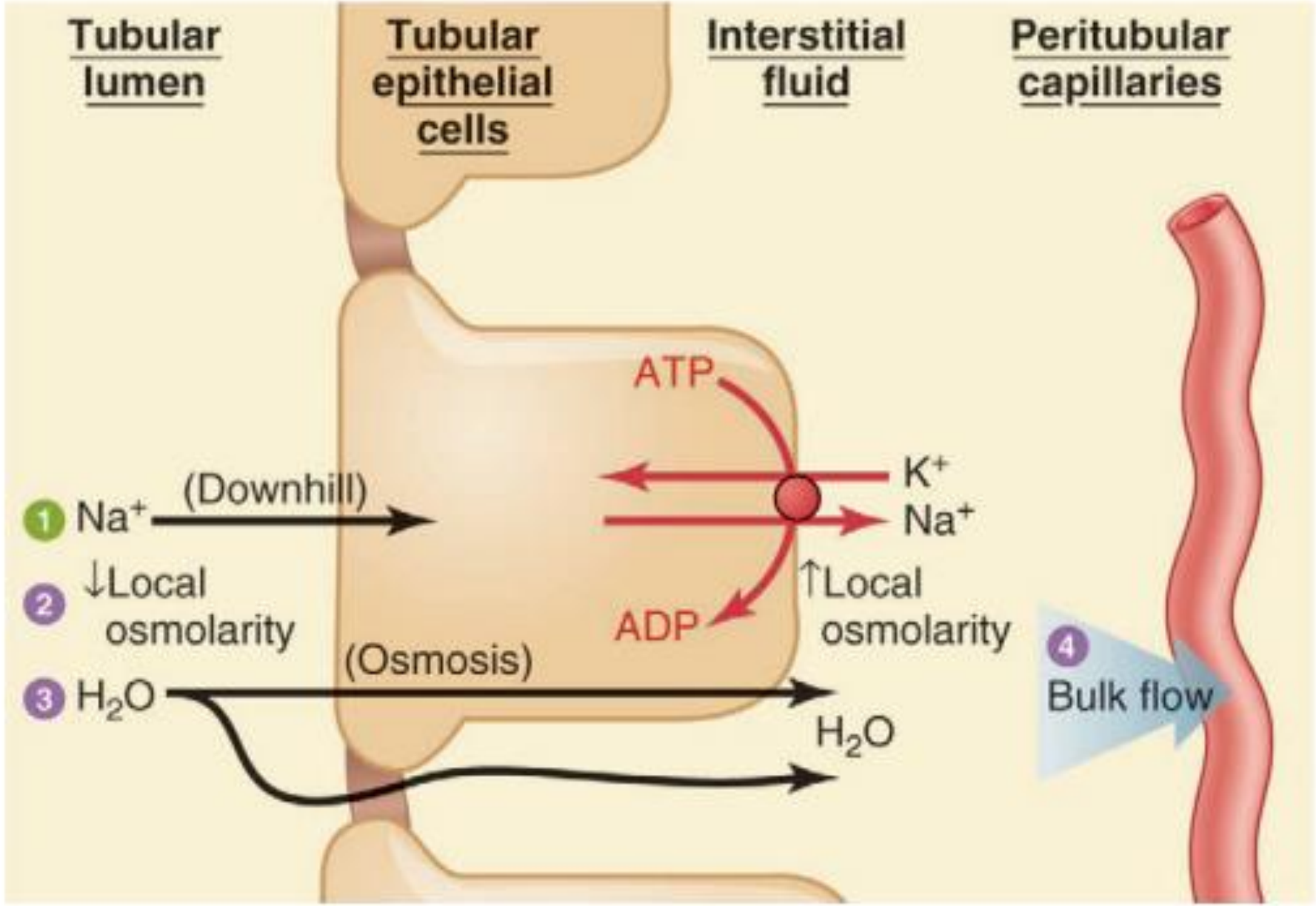


Figure 14.15 AP|R Coupling of water and Na^{1} reabsorption.

- **Water** movement across the tubular epithelium **can only occur** if the ***epithelium is permeable to water***.
- No matter how large its concentration gradient, **water** **cannot cross** *an epithelium* ***impermeable*** *to it.*
- **Water permeability** **varies** *from* ***tubular segment*** *to* ***segment*** **and** depends largely on the presence of **water channels**, called **aquaporins** , in the **plasma membranes**.

❖NOTE:

❖The **water permeability** of the **proximal tubule** is always **very high**, so this segment reabsorbs **water** molecules almost as rapidly as **Na**.

❖As a result, the proximal tubule reabsorbs large amounts of **Na** and **water** in the **same proportions**.

❖The **water permeability** of the **last portions** of the tubules, the cortical and medullary **collecting ducts**, can **vary greatly** *due to physiological control*.

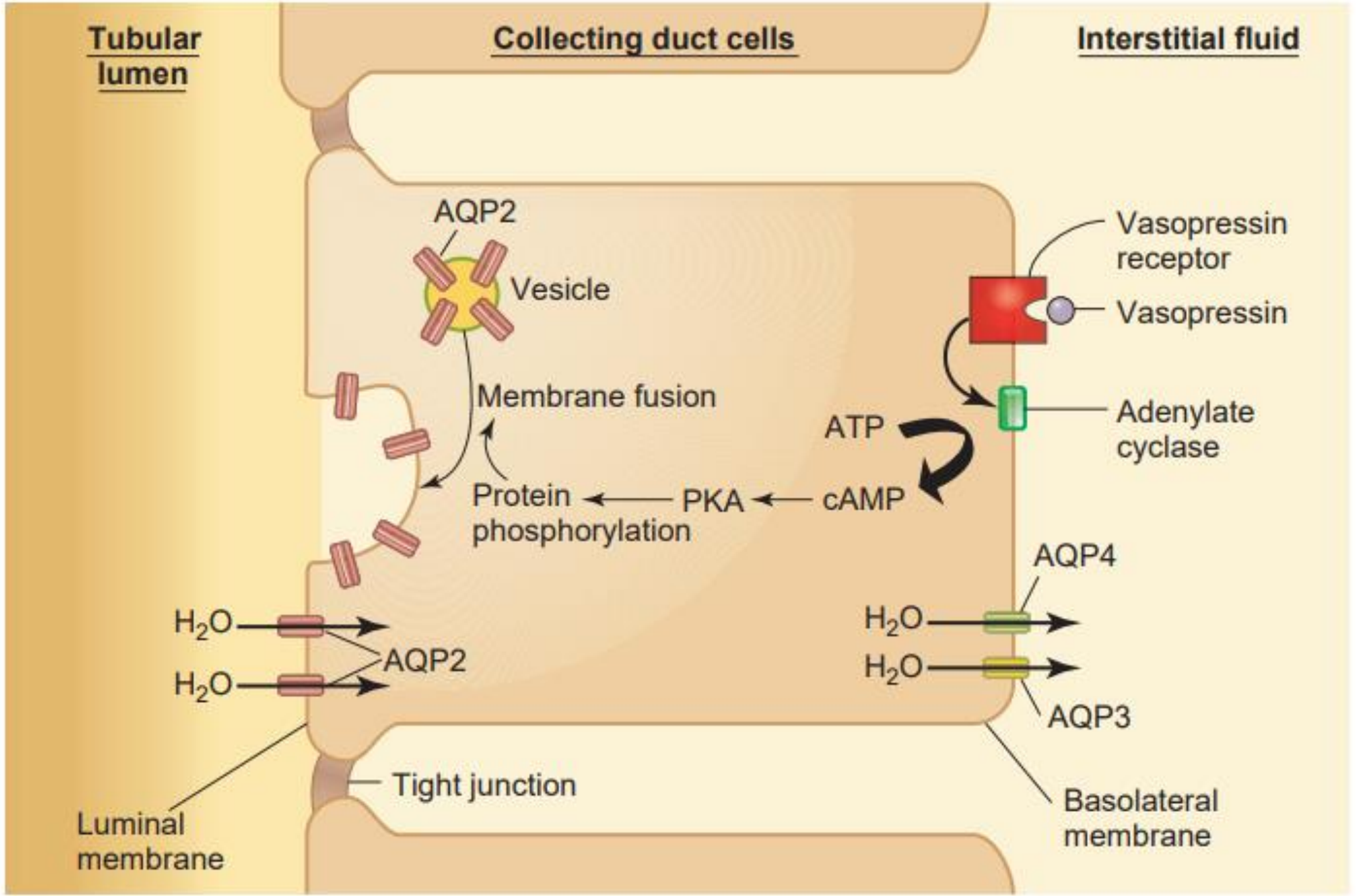
❖*These are the **only tubular segments** in which water permeability is under such control.*

Reabsorption of water in collecting duct

- *The major determinant of this **controlled permeability** and, therefore, of **passive water reabsorption** in the **collecting ducts** is* a peptide hormone secreted by the posterior pituitary gland and known as **vasopressin** , or **antidiuretic hormone (ADH).**
- **Vasopressin** stimulates the insertion into the **luminal membrane** of a particular group of **aquaporin water channels** made by the collecting-duct cells.
- More than 10 different aquaporins have been identified throughout the body, and they are identified as AQP1, AQP2,

- When **vasopressin** from the blood **enters** the **interstitial fluid** and binds to its **receptor** on the **basolateral membrane**, the intracellular production of the second-messenger cAMP is increased.
- *This activates the enzyme cAMP-dependent protein kinase* (also called protein kinase A, or PKA), which, in turn, phosphorylates proteins that **increase the rate** of **fusion of vesicles containing AQP2 with the luminal membrane**.
- This **leads to an increase** in the **number of AQP2s inserted** into the luminal membrane from vesicles in the cytosol.
- This allows an increase in the **diffusion** of ***water down its concentration gradient across the luminal membrane into the cell.***

- **Water** then diffuses through **AQP3** and **AQP4 water channels** on the **basolateral membrane** into the **interstitial fluid** and **then enters the blood**.
- (*The basolateral AQPs are not regulated by vasopressin*.)
- In the presence of a **high plasma concentration** of **vasopressin**, the **water permeability** of the ***collecting ducts*** increases dramatically.
- Therefore, passive water reabsorption is maximal and the final urine volume is small—**less than 1%** of the **filtered water.**


Tubular lumen
Collecting duct cells
Interstitial fluid
AQP2
Vesicle
Membrane fusion
Vasopressin receptor
Vasopressin
Adenylate cyclase
ATP
cAMP
PKA
Protein phosphorylation
AQP4
H_2O
H_2O
AQP2
H_2O
H_2O
AQP3
Tight junction
Luminal membrane
Basolateral membrane

- Without vasopressin, the water permeability of the collecting ducts is **extremely low** because the number of **AQP2s** in the luminal membrane is minimal and very little water is reabsorbed from these sites.
- Therefore, a large volume of water remains behind in the tubule to be excreted in the urine.
- This increased urine excretion resulting from low vasopressin is termed **water diuresis** .
- **Diuresis simply** *means a large urine flow from any cause*.

- The **disease diabetes insipidus** , which is **distinct** from the **other kind of diabetes** (diabetes mellitus, or "sugar diabetes"), illustrates the consequences of **disorders** of the **control** of or **response** to *vasopressin*.
- **Diabetes insipidus** *is caused by the failure of the posterior pituitary gland to release vasopressin* (central diabetes insipidus) *or the inability of the kidneys to respond to vasopressin* (nephrogenic diabetes insipidus).
- **Regardless** of the type of diabetes insipidus, the permeability to water of the collecting ducts **is low** even if the patient is dehydrated. A constant water diuresis is present that can be as much as **25 L/day**; in such extreme cases, it may not be possible to replenish the water that is lost due to the diuresis, and the disease may lead to **death** *due to dehydration and very high plasma osmolarity*.

- Note that in water diuresis, there is an **increased urine flow but not** an **increased solute excretion**.
- In all other cases of diuresis, termed **osmotic diuresis** , *the increased urine flow is the result of a primary increase in solute excretion*. For example, failure of normal **Na reabsorption** causes both increased **Na excretion** and **increased water excretion**, **because**, *as we have seen, water reabsorption is dependent on solute reabsorption.*
- Another example of **osmotic diuresis** occurs in people with uncontrolled **diabetes mellitus**; **in this case**, *the glucose that escapes reabsorption because of the huge filtered load retains water in the lumen, causing it to be excreted along with the glucose.*

Summary of The regulation and function of aquaporins (AQPs) in the medullary-collecting-duct cells

- **Vasopressin** binding to its receptor increases intracellular cAMP via activation of a Gs protein and subsequent activation of adenylate cyclase. cAMP increases the activity of the enzyme protein kinase A (PKA). PKA increases the phosphorylation of specific proteins that increase the rate of the fusion of vesicles (containing AQP2) with the luminal membrane. *This leads to an increase in the number of AQP2 channels in the luminal membrane*. This allows increased passive diffusion of water into the cell. Water exits the cell through AQP3 and AQP4, which are not vasopressin sensitive.