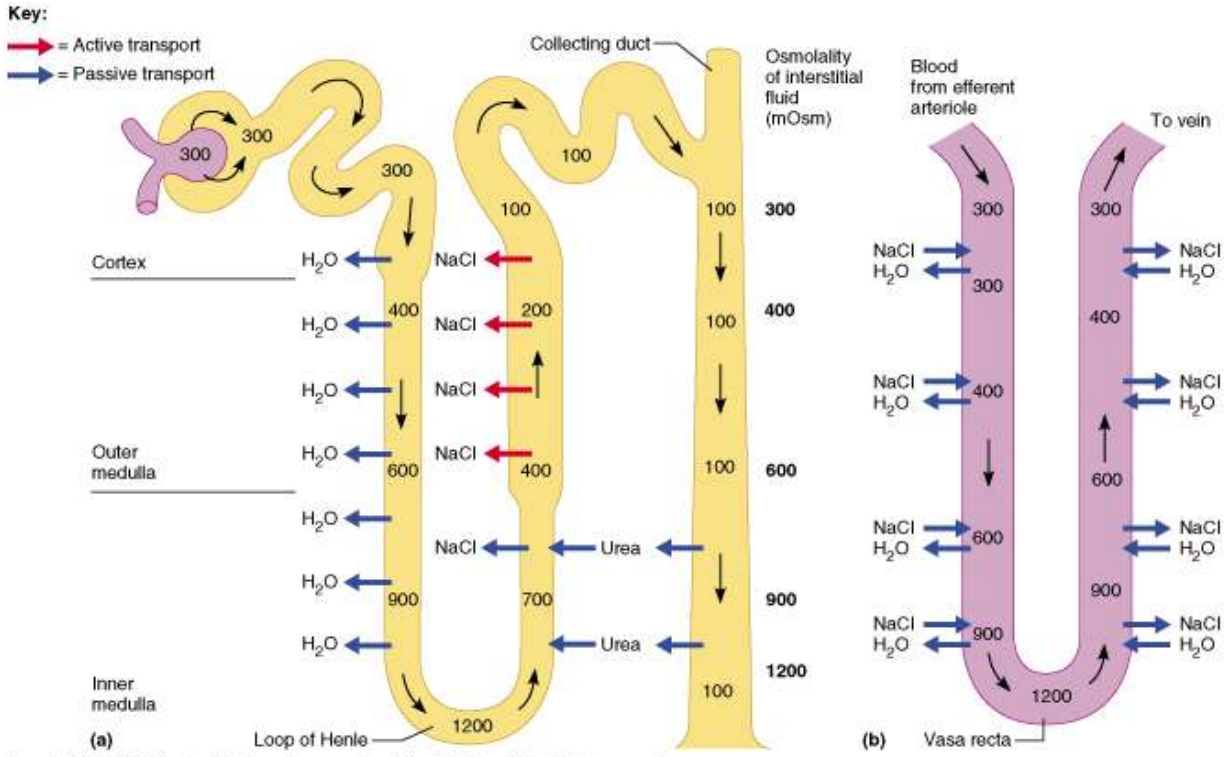
COUNTERCURRENT SYSTEM and the LOOP OF HENLE

1. The Loop of Henle establishes medullary hyperosmolarity



The **ascending limb** of the loop of Henle transports **solutes (NaCl) out of the tubule lumen** with **little or no water**, generating an **hyperosmotic medullary interstitium** and delivering an **hyposmotic tubule fluid** to the distal tubule. This is called the "**single effect".**

The osmolarity of the interstitium **rises progressively from cortex to medulla and papilla** through multiplication of the "single effect" by **countercurrent flow** in the branches of the loop: The single effect in fluid processed by loop segments located near the tip of the papilla occurs in fluid already subject to the single effect when the fluid was in loop segments located closer to the cortex.

Countercurrent exchange of solutes between ascending and descending **vasa recta** (the renal medullary capillaries) minimizes solute washout from the medullary interstitium.

2. The countercurrent system permits forming a concentrated urine

In the presence of **ADH**, which increases water permeability, the **hyposmotic fluid** that enters the **distal tubule (DT**) from the thick ascending limb (TAL) looses most of its water by osmotic equilibration with the surrounding cortical interstitium along the CNT and cortical collecting

duct (CCD). It also continues loosing NaCl through reabsorptive transport along DT, CNT and CCD, until the tubule fluid becomes isoosmotic with plasma, by the end of the CCD.

The relatively small amount of isoosmotic fluid that flows into the medullary collecting ducts losses progressively more and more water to the hyperosmotic medullary and papillary interstitia and is finally excreted as hyperosmotic, highly concentrated urine.

3. The countercurrent system permits forming a dilute urine

In the absence of ADH, the hyposmotic fluid that enters the DT from the loop of Henle, continues to be diluted by transport of NaCl via NaCl (thiazide sensitive) **cotransporters** into DT cells and via **Na channels** (amiloride sensitive) along the CD. Water reabsorption is limited so that the tubule fluid becomes more and more dilute along DT, CNT and collecting ducts (CCD, OMCD and IMCD), until it is excreted as a large volume of hyposmotic urine.

4. Mechanism of hyperosmotic reabsorption in the TAL

There is **apical Na-K-2Cl reabsorptive** cotransport with K recycling through **apical K-channels**, and **basolateral transport of Na via the Na-K-ATPase** and of Cl via Cl- channels, in the water impermeable epithelium of the TAL.

A lumen positive electrical potential difference is generated by the luminal Na-K-2Cl cotransporter operating in parallel with channels that allow K to recycle into the lumen. The lumen positive potential drives passive paracellular reabsorption of more Na+ and of other cations (Mg++, Ca++)

The higher the delivery of Cl (Km=50 mM), the higher the activity of the luminal Na-K-2Cl cotransporters and the higher the rate of hyperosmotic Na reabsorption at the TAL.

5. Mechanism for hyperosmotic reabsorption in the tAL (thin ascending limb)

Water abstraction along the early part of the thin descending limb (tDL) is driven by the high osmolarity (at least half due to urea) present in the medullary interstitium. In the deep nephrons, water reabsorption increases the tubule fluid osmolarity (up to 1200 mOsm/L) and the Na concentration (up to 300 mEq/L) by the bend of the loop.

Along the water impermeable tAL, Na diffuses from the tubule lumen into the medullary interstitium driven by its concentration gradient and some urea enters from the interstitium into the lumen; the osmolarity decreases as the fluid ascends along the tAL.

Operation of this passive mechanisms of Na reabsorption along the tAL is critically dependent on efficient **medullary recirculation of urea** from IMCD to interstitium, to tAL.

5. Other functions of the Loop of Henle

Bicarbonate reabsorption through Na-H exchange

Reabsorption of cations such as Ca2+ and Mg2+

Generation of cortical to medullary gradients of gaseous NH_3 and O_2 and of medullary to cortical gradients of CO_2 and lactic acid

Production of Tamm-Horsfall mucoprotein (casts)

Cells survive in the hyperosmotic medullary environment through slow accumulation of osmolytes (75 mM sorbitol and 25 mM glycerophosphocholine (GPC) by synthesis, and 25 mM betaine and 10 mM inositol by Na+ driven cotransport), which can be rapidly released from the cells through channels that open when the osmolarity decreases.