

RENAL LECTURE 3
Regulation of Extracellular Fluid Volume

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Learning Objectives

- Contrast the function of the juxtamedullary and cortical nephrons.
- Explain the change in permeability along the renal tubule to ions and water.
- Explain the importance of the osmotic gradient in the medulla of the kidney.
- Draw the RAAS pathway. Identify which components of the renal tubule are involved in RAAS and the conditions that activate this pathway.
- Explain the function of aldosterone, antidiuretic hormone (ADH) and atrial natriuretic factor (ANF) in regulating ECF volume and osmolarity in day to day conditions and under conditions of expanded volume and contracted volume. Locate where in the renal tubule these hormones act.
- Define diuresis and explain the different causes of diuresis.

FLUID & ELECTROLYTE BALANCE

Over the course of a day, we ingest about 2 liters of food and drink that contains varying amounts of ions and solutes. To maintain mass balance, what comes in and is not used must be excreted. Two of the major functions of the renal system are to maintain fluid volumes of the body by regulating Na+ and to maintain the osmolarity of the body by regulating water. Adjustments made by the kidney are slow (over hours) because they are mediated by hormones.

MEDULLARY GRADIENT

The kidney can conserve water but cannot replenish lost water. Of the water lost by the body due to evaporation of sweat, breathing, and metabolism, only water which is excreted by the kidney can be regulated. When water is conserved, the urine becomes concentrated up to 1200 mOsM (blood is 300 mOsM).

Conservation of water is regulated by the peptide hormone, vasopressin (antidiuretic hormone, ADH), which is secreted by the posterior pituitary. When the body needs to eliminate excess water, copious amounts of dilute urine are made with an osmolarity as low as 50 mOsM. This is called **diuresis**. Drugs that cause diuresis are called **diuretics**.

The kidneys control the concentration of urine by varying the reabsorption of water in the distal regions of the renal tubule. Here water moves across the tubular epithelial cells by **osmosis**. Recall that osmosis will not take place unless a concentration gradient for water exists. Within the kidney medulla, there exists a standing osmotic gradient (due to Na+ and urea) within the interstitial space (ISF) of 300-1200 mOsM. This gradient is established and maintained by nephrons, called the juxtamedullary nephrons which are located near the cortex-medulla boundary. The renal tubule of these nephrons, unlike the cortical nephrons, extend deep within the medulla. Both the loop of Henle and urea transporters located in the collecting ducts (CD) of the juxtamedullary nephrons contribute to the osmotic gradient within the medulla.

How does this work? In the medulla, the epithelial cells lining the renal tubule have selective permeability to water and ions (Fig 1). In the **descending loop of Henle, the epithelial cells are impermeable to Na+ but permeable to water**. This means that as the filtrate flows through the

descending thin loop of Henle, it becomes progressively more hyperosmotic. Ultimately, at the bottom of the loop deep in the medulla, the loop filtrate reaches 1200 mOsM.

In contrast, in the **thick ascending loop of Henle (TAL)**, the epithelial cells **are permeable to ions and impermeable to water.** Here Na+, K+, and Cl- are reabsorbed (Na-K-2Cl, 2nd active transport) from the renal tubule, but water from the tubule cannot follow (Fig 1) due to the absence of aquaporin in the luminal surface of the epithelial cells. Because the epithelial cells of the TAL are **NOT** permeable to water, the tubular filtrate becomes **hyposmotic (100mOsM) as it flows towards the cortex-medullary boundary.** This filtrate will be dilute urine, if water is not reabsorbed in either the distal convoluted tubule (DCT) and collecting duct (CD).

To prevent "washing out" of the standing osmotic gradient in the medulla, the blood in the capillary flows opposite to the flow of filtrate in the tubule (i.e., counter- current manner) (Fig 1).

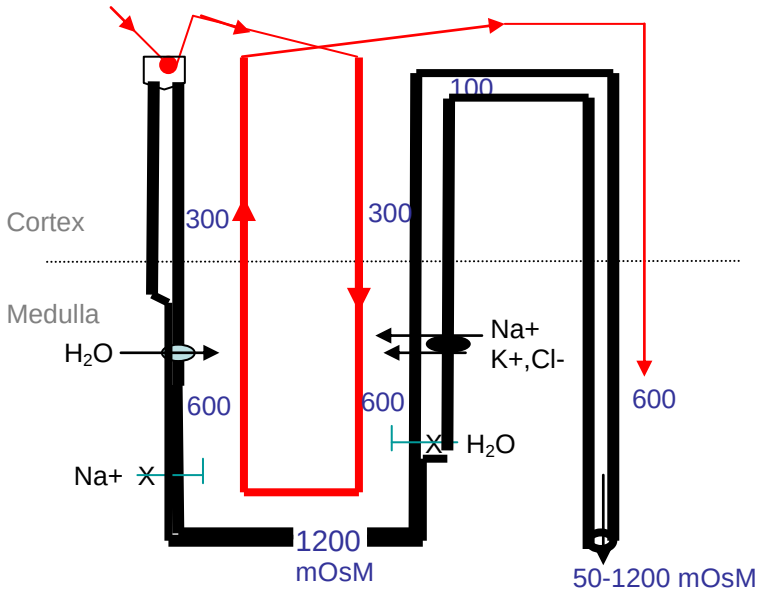

Figure 1. Schematic of the renal tubule shows the medullary gradient (300-1200 mOsM) versus the isosmotic state of the cortex (300mOsM). As water leaves the descending loop of Henle, it is removed by the capillary (red line). Flow within the capillary is opposite to that in the tubule (counter current). Note that the capillary "gains" Na+ on its downward path (right side of its loop) and "gains" water (left side of the loop) as it returns to the cortex.

HORMONES & URINE CONCENTRATION

In the DCT and CD, the osmolarity and ionic content of the urine can be altered. This is regulated by two hormones: antidiuretic (DH, vasopressin) and aldosterone.

Antidiuretic hormone (ADH) acts on the CD epithelial cells in the kidney medulla to increase their permeability to water. Recall that ADH is secreted by the posterior pituitary in response to either increased plasma osmolarity or a large decrease in plasma volume. Within the CD, activation of the ADH receptor results in the insertion of aquaporin 2 channels into the luminal plasma membrane. In the presence of the aquaporin 2 channels, water moves from the filtrate (urine) to the blood. The end result is more a concentrated urine and increased blood pressure**. In the absence of ADH, this tubule is impermeable to water and 18 L/day of urine is excreted (Table 1)**.

Vasopressin also increases **facilitated transport of urea** across the CD epithelial cells. Urea, a byproduct of protein metabolism, must be excreted by the kidney but it is also used to generate in

part the osmotic gradient in the inner medulla. Urea transporters are located in the CD and within cells lining the thin loop of Henle and the medullary capillaries, as well as in red blood cells. These transporters enable rapid equilibration of urea preventing cell shrinkage in the inner (deep) medulla.

TABLE 1. Changes in osmolarity and volume of filtrate per day

Location	Volume (L/day)	mOsM
Bowman's capsule	**180**	**300**
End PCT	**54**	**300**
End Loop of Henle	**18**	**100**
End CD (final urine)	**1.5**	**50-1200**

Aldosterone regulates the movement of water and Na+ across the CD epithelial cells**.**
The adrenal gland secretes aldosterone in response to either elevated plasma K+ or angiotensin II (see below). Aldosterone increases the expression of the Na+ and K+ channels on the luminal surface of the CD epithelial cells and the number of Na+-K+ ATPases in the basal surface of these cells. Consequently, Na+ is reabsorbed from the filtrate and K+ is secreted into the renal tubule from the blood. Because water follows Na+, aldosterone concentrates urine, increases the volume of the blood and increases blood pressure. Note that aldosterone is not secreted when plasma Na+ concentration is high.

Renin- Angiotensin II- Aldosterone System (RAAS) is a **third** pathway that can alter the volume of the urine and blood pressure. This pathway works as follows. Each nephron has an osmo- and mechano-sensor, the **macula densa,** which signals to the **juxtaglomerular (JG) cells (smooth muscle) of the afferent arteriole to regulate glomerular filtration rate (GFR).** When the flow of the filtrate is low in the TAL, the macula densa triggers the JG cells to secrete **renin** into the blood. Renin, an enzyme, activates a cascade of signals in the blood to generate angiotensin II, a potent vasoconstrictor (Fig 2). Angiotensin II, in turn, increases the secretion of **aldosterone** from the adrenal gland and **vasopressin (ADH)** from the posterior pituitary.

The RAAS pathway is **NOT** activated and aldosterone is **NOT** secreted when the osmolarity of the filtrate is high or when the volume of filtrate is high (Fig 3).

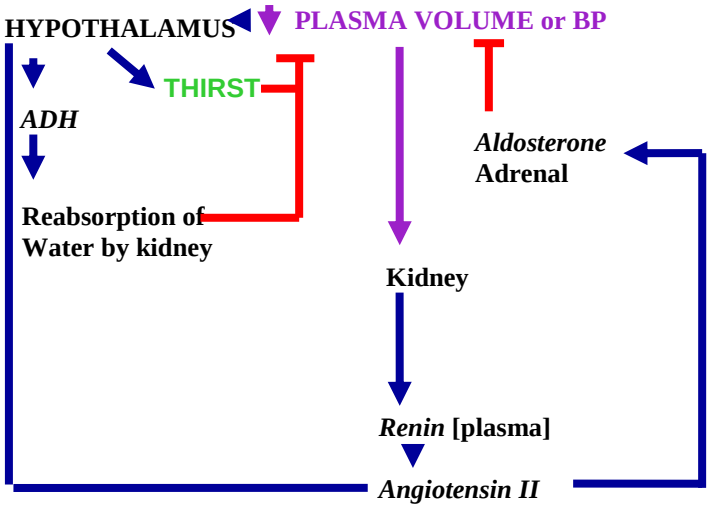

Figure 2. RAAS includes secretion of Renin, Aldosterone and ADH.

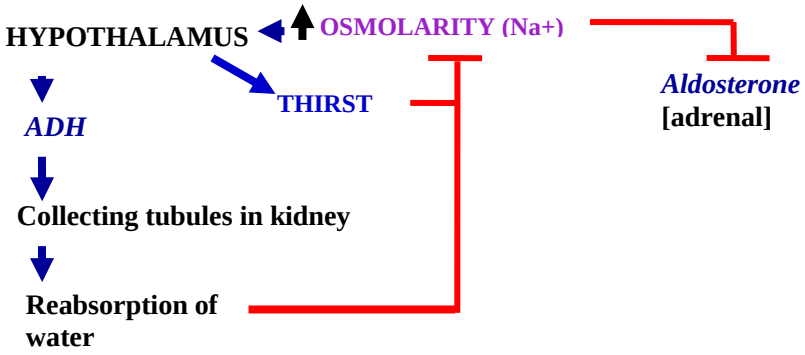

Figure 3. Increased plasma osmolarity increases secretion of ADH but not aldosterone.

CHANGES IN BODY FLUID COMPARTMENTS

Water can be lost from the body by diarrhea, vomiting, and excessive sweating. If sufficient, this can lead to volume contraction and alter the size of the major fluid compartments of the body (ECF and ICF). Fluid loss can include:

1. Loss of isosmotic fluid (i.e., volume depletion) from the ECF which leads to a decrease in blood pressure and the disruption of O_2 and nutrient delivery to tissues.

2. Loss of hypoosmotic water from the ECF which leads to an increase in the omolarity of the ECF and a decrease in ICF volume (i.e., cells shrink).

In contrast, when an excess of fluid is ingested, then the ECF volume expands. In this condition blood volume is increased. If this increase in blood volume is sufficiently large, it can stretch the cardiac muscle cells of the atria. Stretching of the atrial muscle cells releases a hormone called **atrial natriuretic factor (ANF).** ANF relaxes the juxtaglomerular (JG) cells of the afferent arteriole and thereby increases GFR and urine output. ANF also inhibits the reabsorption of Na+ by the renal tubule epithelial cells and thereby increases the loss of water and sodium from the body.

DIURESIS & DIURETICS

Increased urine excretion above 1mL/min is called **diuresis**. There are several causes including the following:

Water diuresis occurs when the osmolarity of the plasma is decreased. This condition inhibits secretion of antidiuretic hormone (ADH).

Osmotic diuresis occurs when an osmotically active substance (such as glucose) is present within the renal tubule.

Diuretics are drugs that increase loss of body water primarily by inhibiting Na+ reabsorption by the renal tubule. Diuretics act at different segments of the renal tubule (Table 2).

Table 2. Diuretics and their sites of action within the kidney.

Type	*Site of action (inhibition of)*	*Increased loss of*
caffeine	DCT Na+ channel	Na+, K+, water
Loop diuretic	TAL Na-K-2Cl symporter	Na+, K+, water
thiazides	DCT Na-Cl symporter	Na+, K+, water
K+ sparing	DCT, CD Na channels or Aldosterone receptor	Na+, water

KEY CONCEPTS

1. The kidneys' primary functions are to maintain fluid volumes of the body by regulating salt balance and to maintain the osmolarity of the body by regulating water balance.
2. Reabsorption and secretion of water and solutes is governed by concentration gradients and secondary active transport.
3. Healthy people use hormones to regulate osmolarity (ADH), to regulate K+ (aldosterone), and to regulate fluid volume (ADH, aldosterone, or ANF).
4. Diuresis is the excess loss of body water as urine. Diuresis may be caused by excess total body water, presence of osmotically active solutes within the renal tubules, and drugs (diuretics) which inhibit the reabsorption of Na+ across the tubular epithelium.

PROBLEM

Complete Table 3, indicating gain, loss or unchanged (=).

TABLE 3. Effects of various conditions on body fluid compartments

Condition	Total Body Water	ECF volume	ICF volume	ECF osmolarity	Serum Na
IV isotonic NaCl	increase			=	=
Diarrhea (isotonic loss)	decrease				=
Excessive NaCl intake but no fluid	=				increase
Excessive sweating (hypotonic loss)	decrease				increase

ANSWERS

TABLE 3. Effects of various conditions on body fluid compartments

Condition	Total Body Water	ECF volume	ICF volume	ECF osmolarity	Serum [Na]
IV isotonic NaCl	increase	**increase**	**=**	**=**	=
Diarrhea (isotonic loss)	decrease	**decrease**	**=**	**=**	=
Excessive NaCl intake but no fluid intake	=	**increase**	**decrease**	**increase**	increase
Excessive sweating (hypotonic loss)	decrease	**decrease**	**decrease**	**increase**	increase