The Countercurrent Multiplier System

After studying this lecture, you should be able to . . .

1. Describe active transport and osmosis in the loop of Henle and explain how these processes produce a countercurrent multiplier system.
2. Explain how the vasa recta function in countercurrent exchange.
3. Predict the role of urea in water osmosis.
4. Describe the role of antidiuretic hormone (ADH) in regulating the final urine volume.

Water cannot be actively transported across the tubule wall, and osmosis of water cannot occur if the tubular fluid and surrounding interstitial fluid are isotonic to each other. In order for water to be reabsorbed by osmosis, the surrounding interstitial fluid must be hypertonic.

The osmotic pressure of the interstitial fluid in the renal medulla is, in fact, raised to over four times that of plasma by the juxtamedullary nephrons. This permits interaction between the descending and ascending limbs. Since the ascending limb is the active partner in this interaction, its properties will be described before those of the descending limb.

Ascending Limb of the Loop of Henle

Salt (NaCl) is actively extruded from the ascending limb into the surrounding interstitial fluid. This is not accomplished, however, by the same process that occurs in the proximal tubule. Instead, Na+ diffuses from the filtrate into the cells of the thick portion of the ascending limb, accompanied by the secondary active transport of K+ and Cl−. This occurs in a ratio of 1 Na+ to 1 K+ to 2 Cl−.
The Na+ is then actively transported across the basolateral membrane to the interstitial fluid by the Na+/K+ pumps. Cl− follows the Na+ passively because of electrical attraction, and K+ passively diffuses back into the filtrate.

The ascending limb is structurally divisible into two regions: a thin segment, nearest the tip of the loop, and a thick segment of varying lengths, which carries the filtrate outward into the cortex and into the distal convoluted tubule. It is currently believed that only the cells of the thick segments of the ascending limb are capable of actively transporting NaCl from the filtrate into the surrounding interstitial fluid.

The salt (NaCl) is extruded into the surrounding fluid. Unlike the epithelial walls of the proximal tubule, however, the walls of the ascending limb of the loop of Henle are not permeable to water. The tubular fluid thus becomes increasingly dilute as it ascends toward the cortex, whereas the interstitial fluid around the loops of Henle in the medulla becomes increasingly more concentrated. By means of these processes, the tubular fluid that enters...
the distal tubule in the cortex is made hypotonic (with a concentration of about 100 mOsm), whereas the interstitial fluid in the medulla is made hypertonic.

**Descending Limb of the Loop of Henle**
The deeper regions of the medulla, around the tips of the loops of juxtamedullary nephrons, reach a concentration of 1,200 to 1,400 mOsm. In order to reach this high a concentration, the salt pumped out of the ascending limb must accumulate in the interstitial fluid of the medulla. This occurs because of the properties of the descending limb, and because blood vessels around the loop do not carry back all of the extruded salt to the general circulation. The capillaries in the medulla are uniquely arranged to trap NaCl in the interstitial fluid. The descending limb does not actively transport salt, and indeed is believed to be impermeable to the passive diffusion of salt. It is, however, permeable to water. Since the surrounding interstitial fluid is hypertonic to the filtrate in the descending limb, water is drawn out of the descending limb by osmosis and enters blood capillaries. The concentration of tubular fluid is thus increased, and its volume is decreased, as it descends toward the tips of the loops.

**Countercurrent Multiplication**
Countercurrent flow (flow in opposite directions) in the ascending and descending limbs and the close proximity of the two limbs allow for interaction between them. Since the concentration of the tubular fluid in the descending limb reflects the concentration of surrounding interstitial fluid, and since the concentration of this fluid is raised by the active extrusion of salt from the ascending limb, a positive feedback mechanism (one increase the
other also increase) is created. The more salt the ascending limb extrudes, the more concentrated will be the fluid that is delivered to it from the descending limb. This positive feedback mechanism multiplies the concentration of interstitial fluid and descending limb fluid, and is thus called the countercurrent multiplier system. The countercurrent multiplier system recirculates salt and thus traps some of the salt that enters the loop of Henle in the interstitial fluid of the renal medulla. This system results in a gradually increasing concentration of renal interstitial fluid from the cortex to the inner medulla; the osmolality of interstitial fluid increases from 300 mOsm (isotonic) in the cortex to between 1,200 and 1,400 mOsm in the deepest part of the medulla. This hypertonicity is required for water reabsorption.

**Vasa Recta**

In order for the countercurrent multiplier system to be effective, most of the salt that is extruded from the ascending limbs must remain in the interstitial fluid of the medulla, while most of the water that leaves the descending limbs must be removed by the blood. This is accomplished by the vasa recta—long, thin walled vessels that parallel the loops of Henle of the juxtamedullary nephrons. The descending vasa recta have characteristics of both capillaries and arterioles. These vessels have urea transporters (for facilitative diffusion) and aquaporin proteins, which function as water channels through the membrane. The ascending vasa recta are capillaries with a fenestrated endothelium. The wide gaps between endothelial cells in such capillaries permit rapid rates of diffusion. The vasa recta maintain the hypertonicity of the renal medulla by means of a mechanism known as countercurrent exchange.
Salt and other dissolved solutes (primarily urea, described in the next section) that are present at high concentrations in the interstitial fluid diffuse into the descending vasa recta. However, these same solutes then passively diffuse out of the ascending vasa recta and back into the interstitial fluid to complete the countercurrent exchange (came out and the re-enter). They do this because, at each level of the medulla, the concentration of solutes is higher in the ascending vessels than in the interstitial fluid and higher in the interstitial fluid than in the descending vessels. Solutes are thus recirculated and trapped within the medulla.

**Effects of Urea**

Countercurrent multiplication of the NaCl concentration is the mechanism that contributes most to the hypertonicity of the interstitial fluid in the medulla. However, urea is a waste product of amino acid metabolism. Human body forms 25-30 gm/day and the normal level in blood is around 25 mg/dl. It contributes significantly to the total osmolality of the interstitial fluid.

Osmolality of the fluid depends on the number of the solute dissolved in that fluid and since urea contains large number of solute it will highly increase the osmolality.

The ascending limb of the loop of Henle and the terminal portion of the collecting duct in the inner medulla are permeable to urea. Indeed, the region of the collecting duct in the inner medulla has specific urea transporters that permit a very high rate of diffusion into the
surrounding interstitial fluid. Urea can thus diffuse out of this portion of the collecting duct and into the ascending limb. In this way, a certain amount of urea is recycled through these two segments of the nephron. The urea is thereby trapped in the interstitial fluid where it can contribute significantly to the high osmolality of the medulla. This relates to the ability to produce concentrated urine.

Urea is reabsorbed passively at the collecting ducts. The factors that affect the excretion are

1. Plasma urea level, and
2. GFR

On low GFR, fluid remains for a long time in the tubules allowing much absorption and little excretion, while high at GFR almost all the urea is excreted.

When the plasma level of urea increased for any reason there would be fluid retention and oedema.

**Renal Water Regulation**

Water excretion is the difference between the volume of water filtered (the GFR) and the volume reabsorbed.

Regulation of extracellular fluid osmolarity and sodium concentration are closely linked because sodium is the most abundant ion in the extracellular compartment. Plasma sodium concentration is normally regulated within close limits of 140 to 145 mEq/L, with an average concentration of about 142 mEq/L. Osmolarity averages about 300 mOsm/L and seldom changes more than ±2 to 3 per cent. These variables must be precisely controlled because they determine the distribution of fluid between the intracellular and extracellular compartments.

Vasopressin or anti-diuretic hormone ADH is produced by a discrete group of hypothalamic neurons whose axons terminate in the posterior pituitary, from which vasopressin is released into the blood. The most important of the inputs to these neurons are from **baroreceptors** and **osmoreceptors**.

**Osmoreceptor-ADH Feedback System**
When osmolarity (plasma sodium concentration) increases above normal because of water deficit, for example, this feedback system operates as follows:

An increase in extracellular fluid osmolarity (which in practical terms means an increase in plasma sodium concentration) causes the special nerve cells called osmoreceptor cells, located in the anterior hypothalamus near the supraoptic nuclei, to shrink.

Shrinkage of the osmoreceptor cells causes them to fire, sending nerve signals to additional nerve cells in the supraoptic nuclei, which then relay these signals down the stalk of the pituitary gland to the posterior pituitary.

These action potentials conducted to the posterior pituitary stimulate the release of ADH, which is stored in secretory granules (or vesicles) in the nerve endings.

ADH enters the blood stream and is transported to the kidneys, where it increases the water permeability of the late distal tubules, cortical collecting tubules, and medullary collecting ducts.

The increased water permeability in the distal nephron segments causes increased water reabsorption and excretion of a small volume of concentrated urine.

Thus, water is conserved in the body while sodium and other solutes continue to be excreted in the urine. This causes dilution of the solutes in the extracellular fluid, thereby correcting the initial excessively concentrated extracellular fluid.
The opposite sequence of events occurs when the extracellular fluid becomes too dilute (hypo-osmotic). For example, with excess water ingestion and a decrease in extracellular fluid osmolarity, less ADH is formed, the renal tubules decrease their permeability for water, less water is reabsorbed, and a large volume of dilute urine is formed. This in turn concentrates the body fluids and returns plasma osmolarity toward normal.

Cardiovascular Reflex Stimulation of ADH Release by Decreased Arterial Pressure and/or Decreased Blood Volume

ADH release is also controlled by cardiovascular reflexes that respond to decreases in blood pressure and/or blood volume, including (1) the arterial baroreceptor reflexes and (2) the cardiopulmonary reflexes.

These reflex pathways originate in high-pressure regions of the circulation, such as the aortic arch and carotid sinus, and in the low-pressure regions, especially in the cardiac atria. Afferent stimuli are carried by the vagus and glossopharyngeal nerves with synapses in the nuclei of the tractussolitarius. Projections from these nuclei relay signals to the hypothalamic nuclei that control ADH synthesis and secretion.

Thus, in addition to increased osmolarity, two other stimuli increase ADH secretion: (1) decreased arterial pressure and (2) decreased blood volume. Whenever blood pressure and blood volume are reduced, such as occurs during hemorrhage, increased ADH
secretion causes increased fluid reabsorption by the kidneys, helping to restore blood pressure and blood volume toward normal.

**Other Stimuli for ADH Secretion**

Nausea is a potent stimulus for ADH release, which may increase to as much as 100 times normal after vomiting. Also, drugs such as nicotine and morphine stimulate ADH release, whereas some drugs, such as alcohol, inhibit ADH release. The marked diuresis that occurs after ingestion of alcohol is due in part to inhibition of ADH release.

**ADH Synthesis in Supraoptic and Paraventricular Nuclei of the Hypothalamus and ADH Release from the Posterior Pituitary**

Once ADH is synthesized, it is transported down the axons of the neurons to their tips, terminating in the posterior pituitary gland. When the supraoptic and paraventricular nuclei are stimulated by increased osmolarity or other factors, nerve impulses pass down these nerve endings, changing their membrane permeability and increasing calcium entry. ADH stored in the secretory granules (also called vesicles) of the nerve endings is released in response to increased calcium entry. The released ADH is then carried away in the capillary blood of the posterior pituitary into the systemic circulation.

Secretion of ADH in response to an osmotic stimulus is rapid; so that plasma ADH levels can increase sevenfold within minutes, thereby providing a rapid means for altering renal excretion of water.

**Thirst and salt appetite:**

Deficits of salt and water must eventually be compensated for by ingestion of these substances, because the kidneys cannot create new sodium ions or water, they can only minimize their excretion until ingestion replaces the losses.

The subjective feeling of thirst, which leads us to obtain and ingest water, is stimulated both by a lower extracellular volume and a higher plasma osmolarity, the latter being the single most important stimulus under normal physiological conditions.

Note that these are precisely the same two changes that stimulate vasopressin production and the osmoreceptors and baroreceptors that control vasopressin secretion.
are identical to those for thirst. The brain centers that receive input from these receptors and mediate thirst are located in the hypothalamus, very close to those areas that produce vasopressin.

Another influencing factor is angiotensin II, which stimulates thirst by a direct effect on the brain. Thus, the renin-angiotensin system helps regulate not only sodium balance but water balance as well and constitutes one of the pathways by which thirst is stimulated when extracellular volume is decreased.

There are still other pathways controlling thirst. For example, dryness of the mouth and throat causes profound thirst, which is relieved by merely moistening them.

The analog of thirst for sodium, salt appetite, is an important part of sodium homeostasis in most mammals.

Salt appetite consists of two components: “pleasure” appetite and “regulatory” appetite; that is, animals “like” salt and eat it whenever they can, regardless of whether they are salt-deficient, and, in addition, their drive to obtain salt is markedly increased in the presence of bodily salt deficiency. Human beings certainly have a strong hedonistic appetite for salt, as manifested by almost universally large intakes of salt whenever it is cheap and readily available (for example, the average American consumes 10–15 g/day despite the fact that human beings can survive quite normally on less than 0.5 g/day).

**Diabetes insipidus:**
A disease associated with the inadequate secretion or action of ADH. When the secretion of ADH is adequate, but a genetic defect in the ADH receptors or the aquaporin channels renders the kidneys incapable of responding to ADH, the condition is called nephrogenetic diabetes insipidus. Without proper ADH secretion or action, the collecting ducts are not very permeable to water, and so a large volume (5 to 10 L per day) of dilute urine is produced.

The dehydration that results causes intense thirst, but a person with this condition has difficulty drinking enough to compensate for the large volumes of water lost in the urine. In this case the specific gravity and the osmolarity of the urine are very low.