Today we will focus on the regulation of the osmolality of the blood (and body fluids). Note that last time we discussed how ADH release is sensitive to changes in pOsm, and ADH can rapidly adjust water excretion to maintain a normal plasma osmolality. However, in doing so, ADH would also alter body fluid volume. [slide 1] Thus, there needs to be a mechanism to independently regulate excretion of osmoles, if body fluid volume were to be maintained. Note that total fluid volume is not as critical a parameter as osmolality (why?) and therefore does not need to be regulated as rapidly or sensitively. This is certainly reflected in the different sensitivities of ADH secretion for changes in volume and osmolality.

Interstitial fluid is ~300 mOsm/L (actually a little less, ~290). This is made up primarily of Na+ and the negatively-charged ions associated with it. Plasma Na+ is typically around 140-145 mOsm/L (or 140-145 mEq/L, since for a monovalent ion osm=Eq). Na+ and the associated anions account for greater than 90% of ECF osmolality.

The control of plasma osmolality (pOsm), which is then in equilibrium with interstitial fluid osmolality, is done by regulating how much water there is to dilute or concentrate the solutes. There are two major mechanisms to accomplish this: control of water loss (relative to solute) by the kidneys and control of water intake (thirst). Osmolality is regulated by altering water intake and excretion relative to the number of osmoles (which is primarily Na+). However the number of osmoles in the body is also a critical component of this regulation. And since Na+ is the major osmole, let’s consider the regulation of Na+ excretion.

Slide 2:
Na+ is freely filtered in the glomerulus and then reabsorbed by active transport in most segments of the tubule system. (Which segments don’t transport Na+?) As with water, ~2/3 of the Na+ is reabsorbed in the proximal tubule (indeed, it’s the Na+ that’s causing the reabsorption of water), and this is accomplished largely by primary active transport (i.e., the Na-K-ATPase) at the basolateral membrane and various processes on the apical membrane, including secondary active transport of other solutes (e.g., glucose, amino acids) [slide 4]. An additional 25-30% of the Na+ is reabsorbed in the ascending limb of the Loop of Henle (slide 5), and here the main transporter on the apical membrane is the Na-K-2Cl transporter. However, the regulated portion of reabsorption occurs distal to the loop of Henle, in the collecting duct. Before we talk about that, a few other comments on the non-regulated processes of Na+ reabsorption. [slides 6,7,8]

The control of Na+ reabsorption is primarily under the control of a single hormone, aldosterone. [slide 9] Aldosterone is a steroid hormone released from the adrenal cortex. Aldosterone acts on the cortical collecting ducts to promote Na+ reabsorption (active transport). In the absence of aldosterone, approximately 2% of the filtered load of Na+ is excreted in the urine. (This may not sound like a lot, but given that the filtered load of Na+ is ~25,000 millimoles/day, 2% represents a lot of Na+.) In contrast, in the presence of high concentrations of aldosterone, essentially all Na+ is reabsorbed. Therefore, ~98% of the filtered load of Na+ is reabsorbed in a non-regulated manner, whereas the excretion of ~2% of the filtered load is highly regulated.

How does aldosterone increase Na+ reabsorption? [slide 10] Aldosterone causes the synthesis of new Na+,K+-ATPase molecules that get inserted into the basolateral membrane in the cortical collecting ducts. In addition, aldosterone stimulates the insertion of Na channels into the luminal membrane. (It is interesting to note that aldosterone also has a similar effect in the intestines, which acts to promote Na+ absorption from the diet.) This action of aldosterone, like most actions of steroid hormones, is mediated via an action on the genome, to cause increased transcription, increased mRNA, and increased synthesis of these proteins involved in Na transport. Note that NaK-ATPase expression in the proximal tubule is not regulated by aldosterone.

[slides 11-15 provide some additional complexity to this, and add in some of the more rapid effects of aldosterone on regulation of these transporters.]
So, aldosterone controls the reabsorption of Na+. [slide 16] This leads to the question of what controls the release of aldosterone. The primary stimulus for aldosterone secretion is angiotensin acting on the aldosterone-releasing cells of the adrenal cortex. (K+ also acts directly to increase aldosterone release; we’ll come back to this.)

The renin-angiotensin system [slide 17]: Renin is released from the juxtaglomerular cells, which lie adjacent to the macula densa. Renin is an enzyme that, in blood, causes the synthesis of angiotensin 1 from angiotensinogen (also called renin substrate). Angiotensinogen, which is synthesized in the liver, is typically present in relatively high concentration, so the production of angiotensin 1 is dependent upon the amount of circulating renin. Angiotensin 1 is then converted to angiotensin II (the active hormone) by angiotensin converting enzyme, which is localized in pulmonary capillaries. (What is the significance of such localization?) Angiotensin II has a large number of actions in addition to stimulating aldosterone secretion, all of which act to maintain blood pressure and plasma volume and osmolality.

So, angiotensin II has a bunch of actions, which prompts the question of what initiates this. What is the stimulus for renin secretion. [slide 18] There are 3 primary stimuli for rennin release: sympathetic innervation of the juxtaglomerular cells (beta-adrenergic receptor stimulated renin secretion), the macula densa, and intrarenal baroreceptors (the JG cells themselves are stretch-sensitive; less stretch, which reflects lower renal perfusion pressure, stimulates renin secretion)

![Diagram](image_url)
One more thing about the renin-angiotensin system while we are talking about it: in recent years the whole system has gotten way more complex (slide 19). Now in addition to the classic angiotensin system, there is ACE2 generating Ang1-7; there is a receptor for renin itself, and more.... [The only point I want to make here is that this is an active area of research, with new twists and turns.]

In addition to aldosterone, other hormones influence Na+ reabsorption. [slide 20] Angiotensin II appears to act directly on the proximal tubule to promote Na+ reabsorption, as does sympathetic innervation of the kidney. Atrial natriuretic hormone, released from the right atrium in response to stretch promotes Na+ excretion. Atrial natriuretic hormone decreases Na reabsorption, and also increases GFR (which promotes Na excretion). [An aside: Recent data also indicate that oxytocin, released from the posterior pituitary in response to increased osmolality, is also natriuretic (at least in some species) Though oxytocin may also increase renin section (at least in some species) so the effects of oxytocin might be quite complicated.]

Also, sympathetic innervation of proximal tubule promotes Na reabsorption. Note that we have mentioned 3 things that sympathetic innervation of the kidneys influence: renin secretion, Na reabsorption, and renal blood flow [slide 21]. These 3 effects of sympathetic input to the kidney are differentially sensitive to renal nerve activity and are mediated by different types of adrenergic receptors.

Brief comment on salt appetite and contribution of salt intake to sodium balance. (slide 22)

Brief comment on salt, blood pressure, and a brief comment on dietary salt and dietary salt recommendations. (slides 23, 24, 25)

Slide 26: a nice flow chart for you to work through.
What about K+? K+ does not contribute substantially to osmolality; its extracellular fluid concentration is quite low (~4.2 mEq/L). However, the extracellular fluid level of K+ must be maintained within narrow limits for normal function of cells [slide 27], especially excitable cells. K+ is freely filtered in the glomerulus and largely reabsorbed. [slide 28, 29] Regulation occurs by secretion at the level of the cortical collecting ducts. This regulation is primarily by aldosterone. Remember that one stimulus for aldosterone release is a direct action of increased extracellular K+ level on the aldosterone-releasing cells. Aldosterone increases Na/K-ATPase in the collecting ducts, which would promote K+ secretion. [slide 30]

Slides 31, 32, 33 (from textbook), making points regarding the relationship between aldosterone and K+ homeostasis.

Note: the same hormone controls Na+ reabsorption and K+ secretion. Thus, one would tend to change at the expense of the other. However, see slides 34 and 35.

A comment on Ca++ homeostasis and the central role that parathyroid hormone plays in this; simple negative feedback reflex control relating Ca++ and parathyroid hormone: slides 36, 37

### Diuretic Drugs

Several classes of drugs serve as clinically-useful diuretics. [slide 38]

| Table 31-1: Classes of Diuretics, Their Mechanisms of Action, and Tubular Sites of Action |
|---------------------------------|---------------------------------|---------------------------------|
| **Class of Diuretic**           | **Mechanism of Action**         | **Tubular Site of Action**     |
| Osmotic diuretics               | Inhibit water and solute reabsorption by increasing osmolarity of tubular fluid | Mainly proximal tubules       |
| Loop diuretics                  | Inhibit Na-K-Cl co-transport in luminal membrane                          | Thick ascending loop of Henle  |
| Thiazide diuretics              | Inhibit Na-Cl co-transport in luminal membrane                          | Early distal tubules          |
| Carbonic anhydrase inhibitors   | Inhibit H* secretion and HCO3^- reabsorption, which reduces Na* reabsorption | Proximal tubules              |
| Competitive inhibitors of aldosterone | Inhibit action of aldosterone on tubular receptor, decrease Na* reabsorption, and decrease K* secretion | Collecting tubules            |
| Sodium channel blockers         | Block entry of Na^+ into Na^+ channels of luminal membrane, decrease Na^+ reabsorption, and decrease K^+ secretion | Collecting tubules            |

Is coffee a diuretic? [slides 39]
The role of the kidney in long-term pH regulation. In the collecting tubule H⁺ reabsorption or secretion (and the opposite with bicarbonate) is altered in response to plasma H⁺ (slides 44-45). Given the high concentration of bicarbonate in the plasma, the filtered load of bicarbonate is large and the vast majority is “reabsorbed” in the proximal tubule. The word reabsorbed was placed in quotations, because as illustrated in slides 46 and 46 it is not the actual bicarbonate molecules in the tubule fluid that are transported into the peritubular capillaries.

Recently renal nerve denervation has received considerable attention as a treatment for hypertension [slides 48 -54]. Does it work? Yes, no, yes... Why?

Renal Dialysis  [slides 55-56]