

Pathophysiology Renal Anatomy and Function II

- I. Effects of blood volume on the filtration fraction (FF) {Altered Volume Effects in syllabus
 - A. Under normal conditions, ~20% of renal plasma flow becomes GFR → this is our FF
 - B. As long as one is euvolemic, the FF remains fairly constant
 - C. If some pathophysiologic disturbance that changes volume, we need to do something to keep GFR constant, kidney function constant, and get ourselves back to normal volume
 - D. If one becomes hypovolemic (e.g. bleeding, vomiting), the kidney needs to conserve salt and water in an effort to maintain blood pressure.
 1. Volume deficiency ⇒ have ↓ CO, ↓ renal blood flow (RBF)
 2. Kidney avidly conserves salt and water via the renal autoregulatory response
 3. Autoregulatory response involves:
 - a) vasodilation of the afferent arteriole
 - b) vasoconstriction of the efferent arteriole
 - c) this regulation of arteriolar tone maintains constant glomerular capillary hydrostatic pressure, which maintains normal GFR despite decreased renal blood flow
 - d) increase the filtration fraction above normal (i.e. more of the RBF becomes filtrate
 - e) the blood leaving the glomerulus has lower hydrostatic pressure (since there's a much bigger fraction of RBF that became filtrate) and has higher oncotic pressure (because more filtrate is removed and protein remains behind in the efferent arteriole)
 - 1) the efferent arterioles become the peritubular capillaries; thus the peritubular capillaries have an even greater than normal oncotic pressure → facilitates reabsorption (↓ hydrostatic pressure)
 - f) there are very large forces driving active reabsorption in the cortical peritubular capillaries
 - 1) get maximal reabsorption due to the low hydrostatic pressure and high oncotic pressure in the peritubular capillaries
 - g) these mechanisms help to preserve volume status and keep the person from going into shock while he's volume deficient
 4. Summary: person becomes hypovolemic → autoregulation occurs → FF is increased → the increased FF causes ↑ proximal nephron reabsorption → there's less delivery to the distal nephron, which is only capable of fine tuning and can avidly conserve salt and water when delivery is minimal
 - E. If one becomes hypervolemic, the opposite of the above would occur
 1. Renal perfusion pressure and renal plasma flow (RPF) are increased
 2. FF is reduced
 3. Proximal nephron reabsorption is decreased
 4. Fluid delivery to the distal nephron is increased
 - a) the distal nephron is not designed for bulk reabsorption, so the ↑ fluid delivery to the distal nephron won't cause ↑↑ reabsorption
- (Recall: the proximal tubule is built for bulk reabsorption; the distal tubule is built for fine tuning)**
5. Facilitates the removal of excess solute

Pathophysiology: Renal Anatomy and Function II

II. Renal tubular transport

A. In the previous lecture, we talked about how glomerular filtrate is produced, in this lecture we will discuss how the tubule handles it

1. The tubule must reabsorb 98-99% of the glomerular filtrate
2. 180 L are filtered, therefore roughly 178 L must be reabsorbed. Only 800-2000 mL of urine is produced per day.
3. Na^+ is the primary cation (osmole) of the extracellular fluid volume, therefore tubular reabsorption must focus on Na^+ .
4. The key factor in handling glomerular filtrate is the tubular epithelial cell

B. Components of the renal tubular reabsorption mechanism

1. The epithelial cells lining the renal tubule are polarized: the membrane on the apical side (the side facing the tubular lumen) is different from the membrane on the basolateral side (the side facing the interstitium)
2. Apical membrane (on the lumen side of the renal tubule cell)
 - a) exposed to tubular fluid (urine space)
 - 1) the tubule must reabsorb 178L, so the apical membrane must be built for bulk reabsorption
 - b) has a very large surface area, due to villi and microvilli
 - 1) important for solute reabsorption
 - c) specific transport proteins and channels reabsorb solute into cell and towards interstitium
 - d) main job is to reabsorb Na^+
 - 1) to do this most efficiently, Na^+ reabsorption is coupled to virtually everything else
 - e) Na^+/K^+ ATPase absent
 - 1) this absence prevents Na^+ from being pumped back into lumen after you've reabsorbed it
 - f) has tight junctions (also utilized for reabsorption)
3. Basolateral membrane
 - a) exposed to interstitium
 - b) has different transport proteins to transport substances out of cells and into capillaries (LYN)
 - 1) main transport protein is Na^+/K^+ ATPase
 - c) Na^+/K^+ ATPase present
 - 1) key transporter on the basolateral membrane
 - 2) pumps Na^+ out of the cell and into the interstitium ($3 \text{ Na}^+ / 2 \text{ K}^+$ electrogenic)
 - i. want to get all of the Na^+ back into the blood stream
4. Solute is transported by one of two general pathways
 - a) Transcellular route
 - 1) Solute crosses the apical membrane and enters the epithelial cell, then exits through channels or transport proteins on the basolateral side to the interstitium and peritubular capillaries
 - b) Paracellular route
 - 1) Reabsorption that occurs across tight junctions

Pathophysiology: Renal Anatomy and Function II

- 2) Tight junctions tend to have the same permeability characteristics as their associated epithelial cell [see 5.d below]

5. Tight junctions

- a) bind epithelial cells together
- b) serve as a barrier between the different transport proteins on the apical and basolateral membranes
- c) can serve as a location for solute and water reabsorption.
 - 1) this is called paracellular reabsorption
- d) The transport properties of the tight junction depend on the nephron segment in which it resides.
 - 1) tight junction in proximal tubule = leaky = bulk absorption
 - i. low resistance, high capacitance to allow bulk movement
 - 2) tight junction in distal tubule = tight = fine tuning
 - ii. high resistance, low capacitance to create large gradients between urinary and blood sides

C. Mechanisms of transport in the tubules

1. Simple diffusion of non-charged substances such as urea or CO₂
 - a) no specific transport protein needed
2. Facilitated diffusion/carrier-mediated transport
 - a) uses carrier proteins to augment diffusion down a concentration gradient
 - b) e.g. glucose transport from the cell to the interstitium (across basolateral membrane)
 - 1) uses facilitated glucose carrier
3. Active transport
 - a) energy is required
 - b) oxygen is consumed
 - c) e.g. Na⁺/K⁺ ATPase, H⁺ ATPase, Ca²⁺ ATPase
 - d) Na⁺/K⁺ ATPase is the main O₂ consumer in the kidney
4. Cotransport (also known as coupled transport)
 - a) transport of one molecule is coupled to the active transport of Na⁺
 - b) e.g. chloride, glucose, amino acids, organic anions (formate, phosphate, urate), lactate [LYN], ketoanions
 - c) both molecules must be attached in order for cotransport to occur
 - d) exhibit saturation kinetics
 - e) are secondary active transport processes
 - f) are apical transport proteins
5. Exchangers (antiport, also known as counter transport)
 - a) Cl⁻/HCO₃⁻ exchanger, Na⁺/H⁺ antiporter
 - b) are usually apical
 - c) exhibit saturation kinetics
6. Channels
 - a) in apical and basolateral membrane
 - b) are selective for either ions (Na⁺, K⁺, or Cl⁻) or water
 - 1) especially important for water reabsorption, since water can't be reabsorbed via active transport

Pathophysiology: Renal Anatomy and Function II

- c) do not exhibit saturation kinetics → will transport as long as there are channels inserted and an electrochemical gradient for the given substance exists.

III. Structure and function of the nephron

A. Proximal nephron (everything up to the macula densa)

1. Components

- a. Proximal convoluted tubule—entirely within cortex, where there's enormous blood flow (thus kidney can easily reabsorb mass quantities back to blood volume)
- b. Proximal straight tubule— primarily within the cortex (descends to the corticomedullary junction, where we have the loop of Henle)
- c. Loop of Henle
 - 1) Thin descending limb
 - 2) Thin ascending limb
 - 3) Thick ascending limb: medullary and cortical portions
 - a) 85% of nephrons have a short loop of Henle
 - i. don't have much medullary thick ascending limb
 - b) 15% have a juxtaglomerular loop of Henle
 - i. have more medullary thick ascending limb
 - ii. these nephrons are more important than short nephrons for total amount of salt reabsorption and for urinary concentration (H₂O reabsorption).
- d. macula densa
 - 1) the end of the cortical thick ascending limb
 - 2) the sensor that allows the tubule to tell the glomerulus what to do (tubuloglomerular feedback [TGF])
 - i. purpose of TGF is to get bulk reabsorption done in the proximal tubule and to keep fine tuning in the distal nephron tubule
 - 3) senses the quantity of the filtrate delivered to the distal nephron, and is part of the juxtaglomerular (JG) apparatus

2. Function

- a. bulk reabsorption
- b. 90% of the total filtrate is reabsorbed by the proximal nephron

B. Distal nephron

1. Components

- a. Distal convoluted tubule
- b. Short connecting segment
- c. Collecting duct
 - 1) Cortical—lots of blood flow in cortex, and capillaries to reabsorb the solute/water
 - 2) Medullary—fine tuning occurs here

2. Function

- a. Reabsorbs only 10% of total filtrate
- b. Fine tuning function

Pathophysiology: Renal Anatomy and Function II

- C. Proximal tubule (proximal straight and convoluted tubules)
1. Reabsorption characteristics
 - a. Reabsorption of 55% of the total salt and water (per Rose and Rennke)
 - b. Reabsorption of 90% of the total filtered $\text{Na}^+\text{HCO}_3^-$, (80-90%) HCO_3^- acids, and organic anions by coupling to Na^+ reabsorption
 - d. Major site of phosphate and urate reabsorption
 - e. Occurs isoosmotically: when filtrate leaves the proximal tubule, has same osmolality as it did when it entered the nephron, but now it has different constituents
 - f. 100% of glucose, amino acids
 2. Secretory pathways
 - a. Organic anion and cations, such as PAH and many drugs (medicines)
 3. NH_3 production
 - a. Important downstream for acid excretion as NH_4^+
 - 1) ammonia is produced through glutamine metabolism
 - b. Contributes to acidification of the urine
 4. Glomerulotubular balance (GTB)
 - a. another mechanism by which kidney tries to limit what reaches the distal nephron, so it doesn't get overwhelmed with more than it can transport via fine tuning homeostasis
 - b. property of proximal tubule only
 - c. during euvolemic conditions, the proximal tubule typically absorbs about 55% of the filtered load of salt and water, even if GFR changes
 - 1) if \uparrow GFR, the absolute amount absorbed goes up, but the percentage absorbed stays the same
 - d. if GFR changes, fractional reabsorption remains constant (assuming euvoolemia), although absolute amount filtered and reabsorbed varies
 - e. if GTB did not occur, when \uparrow GFR, too much solute would be delivered to the distal nephron, and would lead to volume depletion
 - f. GTB occurs in euvolemic conditions \rightarrow the percent reabsorbed can be altered in the presence of hypervolemia (in which case, would reabsorb a greater percentage) and hypovolemia (reabsorb a lesser percentage)
 5. Mechanisms of proximal tubule reabsorption
 - a. Na^+/K^+ ATPase on basolateral membrane
 - 1) the key player in proximal tubule reabsorption
 - 2) the main energy and oxygen consumer in the kidney
 - 3) pumps 3 Na^+ ions out and 2 K^+ ions in to the tubular epithelial cell
 - 4) produces a negative charge (thus is electrogenic) and a low Na^+ concentration inside the cell
 - a) produces a very large electrochemical gradient for Na^+ to move into the cell— Na^+ is then pumped out across the basolateral membrane by the Na^+/K^+ ATPase
 - 5) Use huge electrochemical gradient for Na^+ to come back into the cell from tubular fluid to move other substances out of cell

Pathophysiology: Renal Anatomy and Function II

into interstitium via several Na^+ cotransporters and the Na^+ channel

- a) Na^+ /glucose transporter
 - b) Na^+ /amino acid transporter
 - c) Na^+ /phosphate cotransporter
 - d) Na^+ /urate cotransporter
 - e) Na^+ /organic anion cotransporter (lactate, ketoanions)
 - f) These cotransporters won't work unless have both Na^+ and the other molecule attached
 - g) These cotransporters display saturation kinetics, so they can be overwhelmed when excess solute is present
 - i. e.g. diabetes: if glucose exceeds a certain amount (~180 mg/dL), transport protein has absorbed all it can → filtered load exceeds the transport maximum, and start excreting glucose (glycosuria).
 - ii. High blood sugar prevents complete reabsorption of glucose, causing increased glucose delivery to the distal nephron → impairs salt and water handling → acts as an osmotic diuretic. Uncontrolled diabetes is the most common cause of osmotic diuresis.
[LYN] FYI: a glucose titration curve is on p. 164 of the Physiology grid book.
 - iii. Kidney would act same way with any substance that is reabsorbed via cotransport with Na^+
 - h) Na^+ channels—if channel open, Na^+ can enter, and then be pumped out by Na^+/K^+ ATPase
- b. Reabsorption of $\text{Na}^+\text{HCO}_3^-$
- 1) Proximal tubule reabsorbs 90% of filtered bicarbonate
 - 2) Energy for this reabsorption is from Na^+/K^+ ATPase
 - a) creates electrochemical gradient
 - 3) Inside the cell there is carbonic anhydrase → breaks down carbonic acid into H^+ and HCO_3^- .
 - 4) The Na^+/H^+ antiporter then transports H^+ out of the cell (into the lumen) and Na^+ into the cell.
 - 5) The H^+ can recombine with HCO_3^- in the tubular fluid, because there is much carbonic anhydrase on the apical membrane microvilli
 - 6) The carbonic acid formed produces water and CO_2 , which are freely reabsorbed into the epithelial cell by simple diffusion.
 - 7) The CO_2 forms HCO_3^- in the cell and then leaves the cell by a transporter in the basolateral membrane that takes 3 HCO_3^- with one Na^+ . (Electrogenic, leaves interstitium with more negative charges → driving Na^+ reabsorption across tight junction)
 - a) This movement of Na^+ into the interstitium/peritubular capillary creates an electrochemical driving force for Na^+ reabsorption across the tight junctions (i.e. is electrogenic)

Pathophysiology: Renal Anatomy and Function II

Recall that proximal tubule tight junctions are designed for bulk reabsorption (high capacitance—can reabsorb 55% of the total salt and water in the proximal tubule), but cannot promote steep gradients between tubular and interstitial spaces (therefore, they are low resistance).

- b) This movement of Na^+ into the interstitium/peritubular capillary also creates an osmotic gradient that leads to water reabsorption
 - i. Even water reabsorption is linked to Na^+ transport
- c) Net effect: reabsorb lots of Na^+ and HCO_3^-

D. Loop of Henle

1. Reabsorption in the thin descending limb and thin ascending limb is predominantly passive
 - a. these segments have different channels, so have different transport properties
2. Thin descending limb
 - a. Very permeable to water due to abundant water channels (CHIP proteins)
 - 1) Main job of this segment is passive reabsorption of water
 - b. Low Na^+ permeability (because few Na^+ channels)
 - c. Recall that the fluid leaving the proximal nephron is isotonic to plasma, so it has the same osmolality as plasma. The thin descending limb enters the medulla, which has a progressively increasing osmotic pressure in the interstitium. This high medullary osmolality (high in urea and salt) produces a large gradient for the movement of water from the lumen to the interstitium. Thus we passively reabsorb water across the cell through the water channels.
 - d. This water reabsorption increases the tubular fluid Na^+ concentration.
 - e. Tubular Na^+ concentration exceeds that of the interstitium
 - f. Urea is reabsorbed along with water passively. The handling of urea always parallels the handling of water.
 - 1) However, since the high medullary osmolality is ~50% due to salt and ~50% due to urea, the urea flows back in to the tubular fluid, since it doesn't have a concentration gradient keeping it in to the interstitium
 - g. At the hairpin loop, the types of channels/transport proteins changes
3. Thin ascending limb
 - a. Water channels are absent
 - b. Na^+ channels are present
 - c. NaCl is very permeable
 - d. Since tubular Na^+ concentration exceeds that of the interstitium, salt is passively reabsorbed
4. Thick ascending limb
 - a. The first part is medullary and the distal part is cortical
 - b. Juxtamedullary nephrons have much longer medullary segments than do cortical nephrons and therefore have more NaCl reabsorptive capacity.
 - c. 35% of total NaCl reabsorption occurs in the two segments of the thick ascending limb (Note: 35% per Rose and Rennke)
 - d. Water impermeable. Every part of the nephron distal to the hairpin loop is impermeable to water.

Pathophysiology: Renal Anatomy and Function II

- e. Active NaCl transport occurs, producing increasingly dilute tubular fluid, and is responsible for making the medullary interstitium hypertonic (increasing NaCl content in interstitium).
 - f. Main job of this segment is to reabsorb salt without water and put the salt back into interstitium to get hypertonic medulla
 - g. Can't get hypertonic medulla without expending energy—this segment uses Na^+/K^+ ATPase
 - h. The proper functioning of the thick ascending limb is essential for producing dilute or concentrated urine.
 - i. A major site for Mg^{2+} and Ca^{2+} reabsorption along with some NH_4^+ reabsorption
 - j. Mechanisms of reabsorption
 - 1) Na^+/K^+ ATPase on the basolateral membrane pumps Na^+ out of the epithelial cell
 - 2) $\text{Na}^+/\text{K}^+/2\text{Cl}^-$ transporter on the apical membrane pumps one Na^+ , one K^+ , and 2 Cl^- from the lumen into the tubular epithelial cell
 - 3) The Cl^- then exits the basolateral side through Cl^- channels
 - 4) Since 2 Cl^- were transported for each Na^+ , there is a passive driving force to reabsorb an additional Na^+ across the tight junction, thus limiting the amount of active transport
 - 5) The K^+ is recycled back into the tubular fluid by K^+ channels. This makes the tubular fluid more positive and creates a driving force for other positively charged ions (Mg^{2+} and Ca^{2+}) to leave the tubular fluid
 - 6) The net result is the driving of Na^+ , Cl^- , Mg^{2+} , and Ca^{2+} across the tight junction
 - 7) Loop diuretics (furosemide) inhibit the $\text{Na}^+/\text{K}^+/2\text{Cl}^-$ transporter resulting in inhibition of NaCl reabsorption. This results in natriuresis and diuresis as well as reduced Mg^{2+} and Ca^{2+} reabsorption.
5. Macula densa (at end of cortical thick ascending limb)
- a. The site of tubuloglomerular feedback
6. 90% of salt has been reabsorbed by the time the tubular fluid reaches the end of the proximal nephron
7. Reabsorption in this segment is load dependent (more delivery, more reabsorption)
- E. Distal convoluted tubule
1. 5-8% of NaCl reabsorption
 2. Water and urea impermeable
 3. This segment is critical in maintaining maximal urine dilution
 4. Major site of Ca^{2+} reabsorption that is stimulated by PTH
 5. Mechanisms of transport
 - a. Na^+/K^+ ATPase on basolateral membrane
 - b. Electroneutral Na^+/Cl^- cotransporter
 - 1) Located on the apical membrane
 - 2) The Cl^- exits through channels

Pathophysiology: Renal Anatomy and Function II

- 3) The Na^+ is pumped out (via Na^+/K^+ ATPase)
- 4) Thiazide diuretics inhibit the Na^+/Cl^- cotransporter. They are less potent than loop diuretics; however, they do impair maximal urine dilution and increase Ca^{2+} reabsorption.
- c. Ca^{2+} binding proteins involved in Ca^{2+} entry
 - 1) Ca^{2+} exits cell actively or via $\text{Na}^+/\text{Ca}^{2+}$ antiporter

F. Collecting duct

1. Only 1-2% of net NaCl reabsorption
2. Responsible for all of the fine tuning
3. Final urinary composition is determined by collecting duct
 - a. Urine osmolality can range from 50-1,200 mOsm
 - b. Urine Na^+ can be lowered to less than 1 mEq/L or increased to greater than 100 mEq/L to remove excess Na^+ . (remember that plasma $[\text{Na}^+]=140\text{mEq/L}$)
 - c. Urine pH can be lowered to 4.5. Since blood pH is 7.4, there can be nearly a 1000:1 gradient (i.e. urine is 1000 fold more acidic than plasma).
 - d. The final urinary K^+ concentration is determined by K^+ secretion in the cortical collecting duct. Can actively secrete K^+ in the collecting duct.
 - e. Urinary urea is a function of urine flow rate and the presence of vasopressin (ADH).
4. Collecting duct tight junctions are low capacitance and high resistance to maintain steep gradients.
5. Cortical collecting duct
 - a. Very hypotonic fluid reaches the cortical collecting duct
 - b. Na^+ concentration is too low for coupled transporters to effectively transport Na^+ ; therefore, channels play an important role in the collecting duct.
 - 1) Channels are regulated by aldosterone
 - 2) Na^+ channels are present in the apical membrane
 - c. The primary site of action of aldosterone
 - 1) Aldosterone is the primary hormone involved in Na^+ conservation
 - 2) Produced mostly in response to angiotensin II
 - 3) Aldosterone binds a cytoplasmic receptor which is transported to the nucleus
 - a) upregulates Na^+ and K^+ channels in the apical membrane
 - i. \uparrow the number of channels
 - ii. \uparrow likelihood that these channels will be in the “open” position, which is required for transport
 - b) upregulates Na^+/K^+ ATPase
 - 4) Negatively charged lumen (produced by active Na^+ reabsorption) and high intracellular K^+ provide the driving force for K^+ secretion
 - a) this is the main site for K^+ secretion
 - 5) Diuretics such as amiloride and triamterene work by blocking the Na^+ channel. Spironolactone is a competitive inhibitor of aldosterone. Enters cell from basolateral (blood side/interstitium) membrane. All are weak diuretics, since only 1-2% of Na^+ is

Pathophysiology: Renal Anatomy and Function II

reabsorbed in the collecting duct. (Diuretics inhibit NaCl transport, so are really natriuretics.)

- a) By inhibiting the Na^+ reabsorption, K^+ secretion is inhibited, therefore, these diuretics are known as K^+ sparing diuretics.
- 6) All other diuretics increase Na^+ delivery to the cortical collecting duct. Increased Na^+ delivery is associated with increased K^+ secretion, therefore these drugs are kaliuretic.
- d. Also responsive to vasopressin (ADH)
 - 1) if water restricted:
 - a) posterior pituitary releases ADH
 - b) ADH binds to V_2 receptors on cortical collecting duct
 - c) Activates adenylate cyclase and cAMP
 - d) leads to insertion of preformed water channels from subcellular level
 - e) the great bulk of water reabsorption in response to ADH occurs in the collecting duct, not in the medulla
 - e. Two cell types
 - 1) Principal cells—are involved in the above processes
 - 2) Intercalated cells—are involved in acid/base balance. It is the primary site of active H^+ transport into the urine by the H^+ ATPase in the apical membrane. Aldosterone stimulates H^+ ATPase activity.
6. Medullary collecting duct (outer and inner portions)
 - a. Not responsive to aldosterone
 - b. Responsiveness to vasopressin (ADH)
 - c. Site of action of atrial natriuretic peptide (ANP) through activation of cyclic GMP
7. Effect of ADH on the collecting duct
 - a. ADH is released from the posterior pituitary in response to water restriction and increased plasma osmolality
 - b. ADH binds to the basolateral membrane and activates the adenylate cyclase, increasing intracellular cAMP. This activates a cascade that results in the insertion of preformed water channels into the apical membrane, which is otherwise impermeable to water.
 - c. Most water reabsorption occurs in the cortical collecting duct.
 - 1) This reabsorption is driven by the large gradient between the tubular fluid (around 50mOsm) and the cortical interstitium (around 300 mOsm)
 - 2) When ADH is maximal, 2/3 of water delivered to the cortical collecting duct is reabsorbed.
 - 3) Since 90% of the renal blood flow is in the cortex, this allows water to be easily returned to the systemic circulation.
 - 4) This also limits the amount of water that enters the renal medulla that needs to maintain a high interstitial osmolality in order to form concentrated urine.

Pathophysiology: Renal Anatomy and Function II

- d. In the medullary collecting duct, water channels are also inserted allowing urine to be concentrated to 1,200 mOsm. The osmolality of the medullary interstitium is \uparrow to 1,200 mOsm (~50% is NaCl and ~50% is urea). The urine can't be more concentrated than the medullary interstitium.
- e. Distal to the thin descending limb of the loop of Henle, the epithelial cells are impermeable to urea unless vasopressin is present, and then it is only permeable in the inner medullary collecting duct, due to urea channels. This concentrates urea in the inner medulla.
- f. After the hairpin loop, the tubule is very impermeable to water and urea, so $[\text{urea}]_{\text{collecting duct}}$ keeps increasing. Once filtrate reaches medullary collecting duct, urea channels are inserted in the apical membrane, and get urea reabsorbed in the inner medulla. (Recall, once again, that the hypertonicity of the medullary interstitium is ~50% due to NaCl and ~50% due to urea.)
- g. ADH leads to insertion of the urea channels in inner medullary collecting duct (similar to N_2O channels), therefore increasing urea reabsorption when urine is concentrated via ADH (ie:urine clearance)

H. Summary of homeostatic mechanisms

1. Bulk reabsorption occurs in the proximal nephron
2. Fine tuning of tubular fluid composition occurs in the distal nephron
3. Solute excretion influences water excretion
4. Regulatory mechanisms
 - a. Glomerulotubular feedback is a process that occurs in the proximal tubule
 - 1) 55% of filtered load of salt and water absorbed here
 - 2) A high-protein meal increases GFR by 15-20% and this increases the filtered load. Therefore the proximal tubule must work harder to prevent increased distal delivery. It functions in a load dependent manner, so that it keep reabsorbing around 55%, although the absolute amount reabsorbed would increase.
 - b. Tubuloglomerular feedback: The macula dense regulates its own glomerulus to keep delivery to the distal nephron normal and constant
 - c. Autoregulation of arteriolar resistance of afferent and efferent arterioles to maintain a normal GFR
 - d. In pathophysiologic volume depletion, blood can be shunted away from the cortical nephrons to juxtamedullary nephrons, which have a greater capacity for salt and water reabsorption
 - e. In severe shock, the sympathetic nervous system shunts blood away from the kidney by vasoconstriction to divert blood to the brain and heart

I. Angiotensin II

1. Potent vasoconstrictor (especially in efferent arteriole)
2. Supports blood pressure in shock
3. Directly stimulates proximal tubule Na^+ reabsorption
4. Stimulates aldosterone secretion

Pathophysiology: Renal Anatomy and Function II

5. Augments sympathetic nervous system stimulation
 6. May augment vasopressin secretion
- J. Atrial natriuretic peptide (ANP)
1. Hormone made primarily by the cardiac atria in response to expanded volume and stretch
 2. Binds to receptors in the medullary collecting duct
 3. Inhibits Na⁺ channels in the medullary collecting duct and decreases the number in the open position
 4. Not a potent diuretic because of the limited amount of Na⁺ reabsorption that occurs in the medullary collecting duct.
 5. Activates cyclic GMP