Renal Physiology

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References:


Physiology Objectives

1. Describe the role of the kidneys in water balance.

2. Explain the functions and mechanism of action of antidiuretic hormone (ADH).

3. Explain, with the use of diagrams, why antidiuretic hormone (ADH) plays an important role in the production of either dilute or concentrated urine.

4. Describe the role of antidiuretic hormone (ADH) and urea in the generation of the medullary gradient.

Physiology Objectives

5. Describe the transport and permeability characteristics of the tubule including the distal nephron and collecting duct as they relate to the generation of the medullary osmolar gradient.

6. Describe the role of the vasa recta in maintaining an osmotic gradient i.e. the countercurrent exchanger mechanism.

7. Discuss the mechanisms involved in the reabsorption and secretion of electrolytes and water in the Loop of Henle, distal and collecting ducts i.e. the countercurrent multiplier system.
Today’s Topics

• Control of Body Fluid Osmolality and Volume
  – Control of Body Fluid Osmolality: Urine concentration and dilution
    • ADH
    • Thirst
    • Renal Mechanisms for Dilution and Concentration of Urine
  – Control of Extracellular Fluid Volume and Regulation of Renal NaCl excretion

Control of Body Fluid Osmolality & Volume

• The kidneys maintain the osmolality and volume of body fluids within a narrow range by regulating the:
  – excretion of water (urine concentration & dilution)
  – excretion of NaCl
Water Balance

• How much of the body is water anyway? %?
  – 60%

• How is water distributed in the body?
  – ICF 40%
  – ECF 20%
  – osmotic equilibrium

Table 34-1, Koeppen & Stanton, 2010
Water Balance

- water loss from sweating, defecation, and evaporation from the lungs and skin can vary with environmental conditions or during pathological conditions, but loss of water by these routes cannot be regulated

- BUT, renal excretion of water is tightly regulated to maintain whole-body water balance i.e. water intake = water loss

- the kidneys control water excretion independently of their ability to control the excretion of various other physiologically important substances such as Na+, K+, and urea

- this ability allows water balance to be achieved without upsetting the other homeostatic functions of the kidneys

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Water Balance

- intake > loss → positive water balance
- intake < loss → negative water balance

- ↑ intake or ↓ loss → kidneys lose water: ↑ volume of dilute urine i.e. urine that is hypo-osmotic with respect to plasma e.g. 50 mOsm/kg H2O; 18 L/day

- ↓ intake or ↑ loss → kidneys conserve water: ↓ volume of concentrated urine i.e. urine that is hyper-osmotic with respect to plasma e.g. 1200 mOsm/kg H2O; 0.5 L/day
Water Balance

- disorders in water balance are manifested by alterations in body fluid osmolality, which are usually measured by changes in plasma osmolality (Posm)

- the major determinant of plasma osmolality is Na+ (with its anions Cl- and HCO3-)

- so, disorders in water balance also result in alterations in plasma [Na+] e.g. SIADH → ↓ Posm & hyponatremia

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Regulation of Urine Concentration and Volume

- **Osmolality**
  - Number of solute particles in 1 kg of H₂O (mass)
  - Reflects ability to cause osmosis
  - Expressed in milliosmols (mOsm / kg H₂O)
  - The kidneys maintain osmolality of plasma at ~300 mOsm / kg H₂O, using countercurrent mechanisms

- **Osmolarity**
  - Number of solute particles in 1 L solvent (volume)
  - Reflects ability to cause osmosis
  - Expressed in milliosmols (mOsm / L)

Antidiuretic Hormone (ADH)

- small peptide: 9 aa
- synthesized in neuroendocrine cells in SON of the hypothalamus
- synthesized hormone packaged in granules that are transported down the axon of the cell and stored in nerve terminals located in the posterior pituitary

Figure 34-1, Koeppen & Stanton, 2010
Secretion of ADH

- Secretion of ADH by the posterior pituitary regulated by 2 primary physiological regulators:
  - osmotic
    - osmolality of the body fluids (the MOST important)
  - hemodynamic
    - volume & pressure of the vascular system

- Other factors that can alter ADH secretion include:
  - nausea (↑)
  - atrial natriuretic peptide (↓)
  - angiotensin II (↑)
  - drugs
    - nicotine ↑
    - ethanol ↓

Osmotic Control of ADH Secretion

- small changes in the osmolality of body fluids (1%) can alter secretion of ADH

- ↑ body fluid osmolality → osmoreceptors in anterior hypothalamus sense changes in body fluid osmolality (shrinking) → send signals to ADH-synthesizing/secreting cells located in the SON of the hypothalamus → ↑ synthesis & secretion of ADH

- ADH is rapidly degraded in plasma, circulating levels can be reduced to zero within minutes after secretion is inhibited → ADH system can respond rapidly to fluctuations in body fluid osmolality
Osmotic Control of ADH Secretion

- steep slope indicates sensitivity of the system
- set point of the system is the plasma osmolality value at which ADH secretion begins to increase; set point varies among individuals and is genetically determined
- normal range set point: 275 to 290 mOsm/kg H2O
- physiological factors can also change the set point, e.g., changes in BVol & BP

Hemodynamic Control of ADH Secretion

- a decrease in blood volume or pressure also stimulates secretion of ADH
- ↓ BVol or BP → low-pressure (left atrium and large pulmonary vessels) and the high-pressure (aortic arch and carotid sinus) receptors → afferent fibers of the vagus & glossopharyngeal nerves to the brainstem (solitary tract nucleus of the medulla oblongata) → signals to the ADH-secreting cells of the SON of hypothalamus
Hemodynamic Control of ADH Secretion

- The sensitivity of the baroreceptor system is < that of the osmoreceptors: a 5% to 10% decrease in BVol or BP is required before ADH secretion ↑

- Substances alter the secretion of ADH through their effects on BP e.g. bradykinin & histamine, → ↓ BP → ↑ ADH secretion; NE → ↑ BP → ↓ ADH

Hemodynamic Control of ADH Secretion

- Alterations in BVol & BP also affect the response to changes in body fluid osmolality

- ↓ BVol or BP → the set point is shifted to lower osmolality values and the slope of the relationship is steeper e.g. in circulatory collapse, the kidneys will continue to conserve water, even though by doing so they ↓ the osmolality of body fluids
Actions of ADH on the Kidneys

1. Primary action of ADH on the kidneys is to increase the permeability of the collecting duct to water.

2. ADH increases the permeability of the medullary portion of the collecting duct to urea → an increase in reabsorption of urea and an increase in the osmolality of the medullary interstitial fluid.

3. ADH stimulates reabsorption of NaCl by the thick ascending limb of Henle’s loop, the distal tubule, and the collecting duct.

Figure 34-3, Koeppen & Stanton, 2010
Actions of ADH on the Kidneys

↑ permeability of the collecting duct to water

• ADH binds to V2 receptor on the basolateral membrane of the principal cell of late DT/CD

• receptor is coupled to adenylyl cyclase via a stimulatory G protein (Gs), → increases intracellular levels of cAMP

• ↑ intracellular cAMP activates protein kinase A (PKA) → insertion of vesicles containing aquaporin-2 (AQP2) water channels into the apical membrane of the cell + ↑ synthesis of more AQP2

Actions of ADH on the Kidneys

• with the removal of ADH, these water channels are reinternalized into the cell, and the apical membrane is once again impermeable to water

• this shuttling of water channels into and out of the apical membrane provides a rapid mechanism for controlling permeability of the membrane to water

• because the basolateral membrane is freely permeable to water as a result of the presence of AQP3 and AQP4 water channels, any water that enters the cell through apical membrane water channels exits across the basolateral membrane, thereby resulting in net absorption of water from the tubule lumen
Actions of ADH on the Kidneys

- in addition to the immediate effects of ADH, ADH also regulates the expression of AQP2 (and AQP3)

- when large volumes of water are ingested over an extended period (e.g., psychogenic polydipsia), expression of AQP2 and AQP3 in the collecting duct is reduced; when water ingestion is restricted in these individuals, they cannot maximally concentrate their urine

- conversely, in states of restricted water ingestion, expression of AQP2 and AQP3 in the collecting duct increases and thus facilitates the excretion of maximally concentrated urine

Actions of ADH on the Kidneys

- expression of AQP2 (and in some instances also AQP3) varies in pathological conditions associated with disturbances in urine concentration and dilution

- AQP2 expression is reduced in a number of conditions associated with impaired urine-concentrating ability

- by contrast, in conditions associated with water retention, such as congestive heart failure, hepatic cirrhosis, and pregnancy, AQP2 expression is increased
Actions of ADH on the Kidneys

↑ permeability of the terminal portion of the inner medullary collecting duct to urea

• apical membrane of medullary collecting duct cells contains two different urea transporters (UT-A1 & UT-A3)

• ADH, acting through the cAMP/PKA cascade, increases permeability of the apical membrane to urea (phosphorylation of UT-A1 and perhaps also UT-A3)

• ADH also increases the abundance of UT-A1 in states of chronic water restriction

• in contrast, with water loading (i.e., suppressed ADH levels), UT-A1 abundance in the collecting duct is reduced

Actions of ADH on the Kidneys

• increasing the osmolality of the interstitial fluid of the renal medulla also increases the permeability of the collecting duct to urea

• this effect is mediated by the phospholipase C pathway and involves phosphorylation by protein kinase C

• this effect is separate and additive to that of ADH
Actions of ADH on the Kidneys

- reabsorption of NaCl by the thick ascending limb of Henle's loop and by the DT and cortical segment of the collecting duct

- increase in Na+ reabsorption is associated with increased abundance of key Na+ transporters:
  - $\text{Na}^+\text{-K}^+\text{-Cl}^-$ symporter - thickALoH
  - $\text{Na}^+\text{-Cl}^-$ symporter - DT
  - epithelial Na+ channel (ENaC) - DT/CD

- stimulation of NaCl transport by the thickALoH may help maintain the hyperosmotic medullary interstitium that is necessary for the absorption of water from the medullary portion of the collecting duct

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Thirst

- changes in plasma osmolality & BVol or BP also → alterations in the perception of thirst

- ↑ body fluid osmolality or ↓ blood volume or pressure → perception of thirst (hypertonicity more potent)
  - ↑ plasma osmolality of only 2% - 3% produces a strong desire to drink, whereas a larger ↓ blood volume & pressure (10% - 15%) is required to produce the same response (compare with ADH)

Thirst

- similar to the plasma osmolality threshold for triggering ADH, there is a genetically determined threshold for triggering the sensation of thirst

- BUT, the thirst threshold is higher than the threshold for ADH secretion; threshold for ADH secretion ~ 285 mOsm/kg H2O, vs the thirst threshold ~ 295 mOsm/kg H2O → thirst is stimulated at a body fluid osmolality at which secretion of ADH is already maximal
Thirst

- neural centers involved in regulating water intake (the thirst center) are located in the same region of the hypothalamus involved in regulating ADH secretion

- pathways involved in the thirst response to ↓ BVol or BP believed to be the same as those involved in the volume and pressure related regulation of ADH secretion (see Hemodynamic Control of ADH)

- Angiotensin II, acting on cells of the thirst center (subfornical organ), also evokes the sensation of thirst (Ag II levels ↑ when BVol & BP are ↓, so this effect of Ag II contributes to the homeostatic response that restores and maintains body fluids at their normal volume

Thirst

- ADH and thirst systems work in concert to maintain water balance

- ↑ plasma osmolality evokes drinking and, via ADH action on the kidneys, the conservation of water

- ↓ plasma osmolality → thirst is suppressed, and in the absence of ADH, renal water excretion is enhanced
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Renal Mechanisms for Dilution & Concentration of Urine

• the ability of the kidneys to excrete hypoosmotic or hyperosmotic with respect to body fluids requires that solute be separated from water at some point along the nephron

• the thick ascending limb of the loop of Henle, is the major site where solute and water are separated
  – excretion of both dilute & concentrated urine requires normal function of the loop of Henle
Renal Mechanisms for Dilution & Concentration of Urine

• for excretion of hypoosmotic urine the nephron must reabsorb solute from the tubular fluid and not allow reabsorption of water to also occur
  
  – reabsorption of solute without concomitant water reabsorption occurs in the ascending limb of Henle's loop, and (in the absence of ADH), the distal tubule & collecting duct → dilute urine

Renal Mechanisms for Dilution & Concentration of Urine

• for excretion of hyperosmotic urine the nephron must remove water from the tubular fluid without solute
  
  – for this to occur, the kidney must generate a hyperosmotic compartment that then reabsorbs water osmotically from the tubular fluid. (since water movement is passive and driven by an osmotic gradient)

  – the hyperosmotic compartment in the kidney is the interstitium of the renal medulla

  – Henle's loop, in particular, the thick ascending limb, is critical for generating the hyperosmotic medullary interstitium

  – this hyperosmotic compartment drives reabsorption of water from the collecting duct → concentrated urine
Countercurrent Mechanism

• so, how does Henle’s loop, in particular, the thick ascending limb generate the hyperosmotic medullary interstitium?

• by countercurrent mechanisms:
  – occurs when fluid flows in opposite directions in two adjacent segments of the same tube
    • filtrate flow in the loop of Henle (countercurrent multiplier)
    • blood flow in the vasa recta (countercurrent exchanger)

• role of countercurrent mechanisms:
  – establish and maintain an osmotic gradient (300 mOsm to 1200 mOsm/Kg H₂O) from renal cortex through the medulla
  – allow the kidneys to vary urine concentration

Osmotic gradient in the renal medulla

Figure 25.15; Marieb & Hoehn, 2010
Countercurrent Multiplier: LoH

- **Descending limb**
  - Freely permeable to H₂O, which passes out of the filtrate into the hyperosmotic medullary interstitial fluid (due to presence of NaCl & urea)
  - Filtrate osmolality increases to ~1200 mOsm/Kg H₂O

- **Ascending limb**
  - Impermeable to H₂O
  - Selectively permeable to solutes
    - Na⁺ and Cl⁻ are passively reabsorbed in the thin segment, actively reabsorbed in the thick segment
  - Filtrate osmolality decreases to 100 mOsm/Kg H₂O

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(a) Countercurrent multiplier. The long loops of Henle of the juxtamedullary nephrons create the medullary osmotic gradient.
Countercurrent Multiplier: LoH

- “Single effect” of countercurrent multiplication process
  - the separation of H$_2$O & solute in ascending LoH

- solute removed from tubular fluid in ascending limb (which becomes more dilute) accumulates in surrounding interstitial fluid → ↑ osmolality of medullary interstitium

- descending limb highly permeable to water, the increased osmolarity of medullary interstitium causes water to be reabsorbed (which concentrates the tubular fluid in this segment)

- countercurrent flow within the ascending & descending limbs of LoH “multiplies” the osmotic gradient between tubule fluid in the descending & ascending limb of LoH → increasing osmotic gradient is generated throughout the interstitium

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**Countercurrent Multiplier: LoH**

![Diagram showing countercurrent multiplier effect in LoH](image)

Koeppen and Stanton: Renal & Uroradiology, 5th Edition. Copyright © 2010 by Mosby, an imprint of Elsevier, Inc. All rights reserved.

Figure 34-5, Koeppen & Stanton, 2010
Urea Recycling

- generated by liver: by product of protein metabolism
- enters tubular fluid by glomerular filtration
- permeability of most nephron segments to urea = low, except for high permeability to urea in medullary collecting duct, that is further increased by ADH
- as fluid moves along the nephron and water is reabsorbed in the collecting duct, the urea concentration in tubular fluid increases
- when this urea-rich tubular fluid reaches the medullary collecting duct, where permeability to urea is not only high but also increased by ADH, urea diffuses down its concentration gradient into medullary interstitial fluid, where it accumulates
- when ADH levels are elevated, the urea within the lumen of the collecting duct and the interstitium equilibrates $\Rightarrow$ [urea] in urine $=$ [urea] in medullary interstitium at papilla $\sim 600$ mOsm/ Kg H$_2$O

Urea Recycling

- some of the urea within the interstitium enters the descending thin limb of the loop of Henle via the UT-A2 urea transporter
- this urea is then trapped in the nephron until it again reaches the medullary collecting duct, where it can reenter the medullary interstitium
- so, urea recycles from the interstitium to the nephron and back into the interstitium
- this process of recycling facilitates the accumulation of urea in the medullary interstitium
- consequently, during antidiuresis, the concentration of urea can reach 600 mOsm/ Kg H$_2$O, which is approximately half of the total medullary interstitial concentration
- because reabsorption of water from the collecting duct is driven by the osmotic gradient established in the medullary interstitium, urine can never be more concentrated than that of the interstitial fluid in the papilla
- therefore, any condition that reduces medullary interstitial osmolality impairs the ability of the kidneys to maximally concentrate urine
Urea Recycling

- Urea within the medullary interstitium contributes to the total osmolality of the urine.
- BUT, because the inner medullary collecting duct is highly permeable to urea, especially in the presence of ADH, urea cannot drive water reabsorption across this nephron segment.
- Instead, the urea in tubular fluid and the medullary interstitium equilibrates, and a small volume of urine with a high concentration of urea is excreted.
  - Allows the kidneys to excrete the daily urea load in a relatively small volume of urine.
  - If urine with a high concentration of urea could not be excreted, the need to excrete the daily urea load would obligate the excretion of a much larger volume of urine.
- The medullary interstitial NaCl concentration that is responsible for reabsorbing water from the medullary collecting duct → concentrating the nonurea solutes (e.g., NH4+ salts, K+ salts, creatinine) in urine.

Countercurrent Exchanger: Vasa Recta

The vasa recta preserve the medullary gradient while removing reabsorbed water and solutes.

Figure 25.16b; Marieb & Hoehn, 2010
Countercurrent Exchanger: Vasa Recta

- The vasa recta
  - capillary networks that supply blood to the medulla
  - highly permeable to solute and water (water via AQP1)
  - similar to the loop of Henle, the vasa recta form a parallel set of hairpin loops within the medulla
  - bring nutrients and oxygen to the medullary nephron segments (nutritive function)
  - remove the excess water and solute that is continuously being added to the medullary interstitium by these nephron segments → maintain the medullary interstitial gradient

Countercurrent Exchanger: Vasa Recta

- The vasa recta
- ability to maintain the medullary interstitial gradient is flow dependent
- ↑ vasa recta blood flow dissipates the medullary gradient (i.e., washout of osmoles from the medullary interstitium)
- ↓ vasa recta blood flow decreases $O_2$ delivery to the nephron segments within the medulla → ↓ transport of salt and other solutes (which require $O_2$ & ATP) → ↓ ability to maintain medullary interstitial osmotic gradient
Formation of Dilute Urine

- filtrate is diluted in the ascending loop of Henle
- in the absence of ADH, dilute filtrate continues into the renal pelvis as dilute urine
- $\text{Na}^+ \text{ & other ions may be selectively removed in the DT & CD decreasing osmolality to as low as } 50 \text{ mOsm \& low concentration of NaCl \& urea; volume of urine excreted can be as much as } 18 \text{ L/day}$
- when dilute urine is produced over long periods, the osmolality of the medullary interstitium declines
- this reduced osmolality is almost entirely caused by a decrease in the concentration of urea
- this decrease reflects washout by the vasa recta and diffusion of urea from the interstitium into the tubular fluid

Figure 25.17a; Marieb & Hoehn, 2010
Formation of Concentrated Urine

- depends on the medullary osmotic gradient and ADH
- ADH stimulates reabsorption of NaCl by the thick ascending limb of Henle’s loop
  - this is thought to maintain the medullary interstitial gradient at a time when water is being added to this compartment from the medullary collecting duct, which would tend to dissipate the gradient

Formation of Concentrated Urine

- reabsorption of NaCl by the ascending limb of the loop of Henle → fluid reaching the CD is hypoosmotic with respect to the surrounding interstitial fluid → osmotic gradient across the CD
- ADH → ↑ the permeability of the last half of the DT & CD to water, water → diffuses out of the tubule lumen, and tubule fluid osmolality increases → beginning the process of urine concentration
- the osmolality of the interstitial fluid in the medulla progressively increases from the junction between the renal cortex & medulla → osmotic gradient between tubule fluid and interstitial fluid along the entire medullary collecting duct
- ADH → ↑ the permeability of the medullary collecting duct to water → the osmolality of tubule fluid increases as water is reabsorbed
Formation of Concentrated Urine

- initial portions of the CD (cortical and outer medullary) are impermeable to urea, so it remains in the tubular fluid, and its concentration increases

- BUT medullary collecting duct significantly permeable to urea, even in the absence of ADH

- recall that by the time the tubular fluid reached the medullary collecting duct, the concentration of urea in the tubular fluid has been ↑ by reabsorption of water from DT/CD in the cortex and outer medulla, (which is impermeable to urea) so the concentration of urea in tubular fluid > its concentration in interstitial fluid, and some urea diffuses out of the tubule lumen into the medullary interstitium

- ADH → ↑ permeability of the last portion of the medullary collecting duct (inner medullary CD) to urea → ↑ accumulation of urea in the medullary interstitium

Formation of Concentrated Urine

- the maximal osmolality that the fluid in the medullary collecting duct can attain is equal to that of the surrounding interstitial fluid

- the major components of the tubular fluid within the medullary collecting ducts are substances that have either escaped reabsorption or have been secreted into the tubular fluid: urea is the most abundant

- the urine produced when ADH levels are elevated has an osmolality of 1200 mOsm/Kg H2O and contains high concentrations of urea and other nonreabsorbed solutes

- urea in tubular fluid equilibrates with urea in the medullary interstitial fluid → its concentration in urine is similar to that in the interstitium

- urine volume under this condition can be as low as 0.5 L/day
Formation of Concentrated Urine

Figure 25.17b; Marieb & Hoehn, 2010

Reabsorption of water in DT/CD depends on ADH

- reabsorption of water by the PT (67% of the filtered amount) & the thin descending limb of the loop of Henle (15% of the filtered amount) is essentially the same regardless of whether the urine is dilute or concentrated
- therefore a relatively constant volume of water is delivered to the DT and CD each day
- the plasma ADH concentration regulates how much of this water is then reabsorbed (8% to 17% of the filtered amount), with water excretion ranging from less than 1% to 10% of the filtered water