

INTRODUCTION TO WATER EXCRETION

A. Role of the Kidney: to adjust urine formation rate and urine concentration to maintain

1. body fluid osmolar concentration
2. body fluid volume
3. intravascular volume

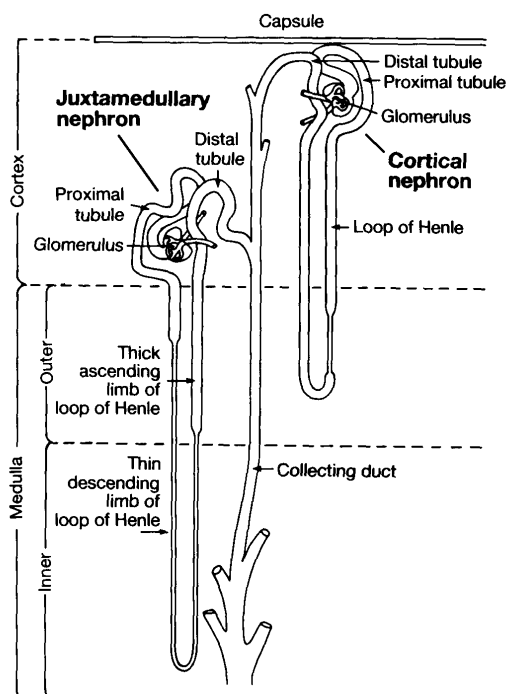
Note: the term "osmolar" refers to the total concentration of dissolved particles; the osmolar concentration determines the total osmotic pressure

B. Mechanism: the ability to adjust urine volume and concentration depends on establishing an appropriate osmotic environment in the renal medulla; this is accomplished by those nephrons whose loops of Henle dips deep into the medulla -- the juxtamedullary nephrons

Note: the fraction of total nephrons that are juxtamedullary governs the ability to survive in a water-deprived environment. Humans have about 20% juxtamedullary nephrons (and 80% cortical nephrons). Desert rats have almost 100% juxtamedullary nephrons.

C. Juxtamedullary Nephron Functional Anatomy

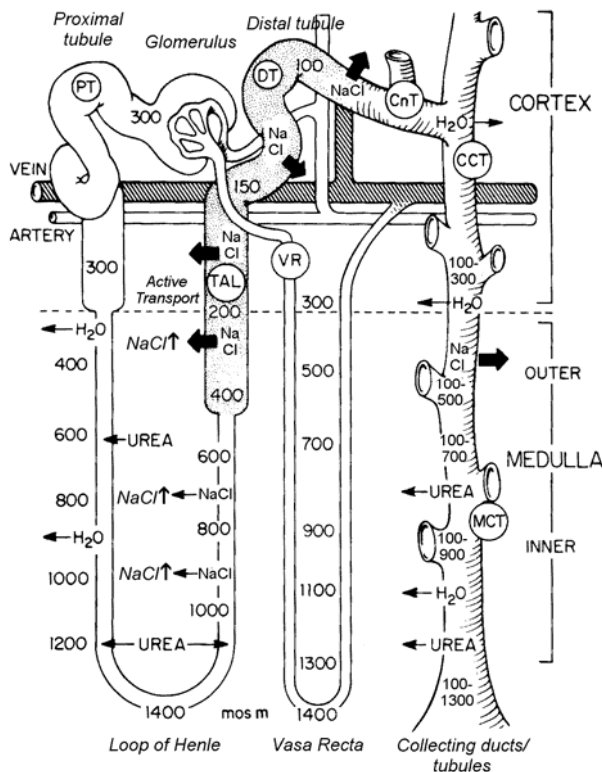
1. descending thin limb
2. "hairpin" loop
3. ascending thin limb
4. ascending thick limb and initial segment of the distal tubule
5. parallel capillaries and venules (vasa recta)



LOOP OF HENLE FUNCTION

A. Countercurrent Multiplication

1. The ascending thick limb of the Loop of Henle has an active transport pump that reabsorbs Na^+ and Cl^- ; however, it is impermeable to water. This results in an increased osmolality in the renal medulla interstitial fluid
2. The high accumulation of Na^+ and Cl^- in the renal medulla interstitial fluid causes exchange of water and dissolved particles between the interstitium and the descending and ascending thin limbs, leading to trapping of most of the sodium and chloride in the medulla. As a result, interstitial fluid throughout the whole medulla becomes hyperosmotic and the fluid leaving the ascending thick limb and entering the distal tubule is hyposmotic.
3. Because this process occurs as the fluid is flowing along the loop of Henle and exchange takes place between the interstitium and fluid streams moving in opposite directions (descending and ascending) and because osmolality increases progressively with depth in the medulla, the mechanism is termed countercurrent multiplication.
4. The interstitial osmolality is further increased by the accumulation of urea (explained later).



- PT = Proximal Tubule
- TAL = Thick Ascending Limb
- DT = Distal Tubule
- CnT = Connecting tubule
- CCT = Cortical Collecting Tubule (collecting duct)
- MCT = Medullary Collecting Tubule (collecting duct)
- VR = Vasa Recta

Note: Numbers represent total osmolal concentration in mOsm/kg

LOOP OF HENLE (continued)

C. Consequences of Countercurrent Multiplication

1. Water is reabsorbed from the loop of Henle at the rate of about 6 ml/min (8 L/day); this represents 20% of the water entering the loop of Henle
2. About two-thirds of the Na^+ and Cl^- entering the loop of Henle are reabsorbed
3. The fluid leaving the loop of Henle has an osmolality of 100 mOsm/kg (one-third that of blood plasma)
4. The osmotic concentration in the depth of the medulla can become as high as 1200-1400 mOsm/kg (about half from NaCl and half from urea)

D. Role of Urea

1. Urea trapping
 - a. medullary collecting duct: Some (but not all) of the urea in the collecting duct fluid is reabsorbed by passive diffusion into the interstitial fluid.
 - b. loop of Henle: The high interstitial concentration of urea causes some of the interstitial urea to enter the lumen of the loop. This urea is carried to the medullary collecting duct, where it again diffuses into the interstitial fluid. This process results in a high concentration of urea in the medulla
2. The urea that is not trapped is excreted in the urine

DISTAL TUBULE AND COLLECTING DUCTS

A. Sequence in the Distal Tubule and Collecting Ducts

1. Hypo-osmotic fluid (100 mOsm/kg) enters the latter distal tubule at a rate of about 20-25 ml/min
2. As the fluid passes through the renal medulla in the collecting ducts, a large osmotic gradient exists between the tubular and interstitial fluids favoring water reabsorption
3. Rate of water reabsorption depends on the water permeability of the distal tubule and collecting ducts
4. Water permeability is controlled by antidiuretic hormone

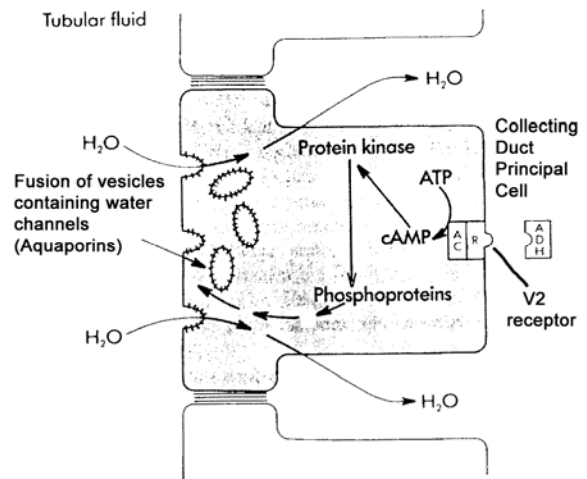
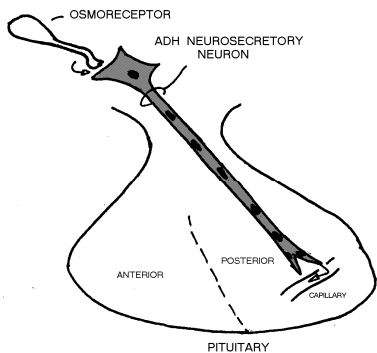
ANTIDIURETIC HORMONE

A. Terminology

1. Official name: Vasopressin (because it raises blood pressure when present at high concentrations; in the physiological range of concentrations, its main action is on water permeability)
2. Abbreviated ADH (**Anti**Diuretic **H**ormone)

B. Synthesis and Release

1. Synthesized by specialized neurons in the hypothalamus (neurosecretory cells)
2. Migrate by axonal transport to nerve endings in the posterior pituitary (neurohypophysis) via the hypothalamo-hypophyseal tract
3. Stored in the posterior pituitary
4. Released into the posterior pituitary capillaries when the neurosecretory cells discharge (action potentials)



C. Transport and Action

1. Transported to all parts of the body by the circulation, but major action is in the kidney
2. Collecting duct action: binds to collecting duct ADH receptors causing an increase in water permeability by inducing water channels (aquaporins) stored in intracellular vesicles to fuse with the luminal membrane (major effect)

Note: The effect on water permeability is graded -- the higher the ADH concentration, the more receptor sites occupied, and the greater the water permeability (up to the maximum effect)

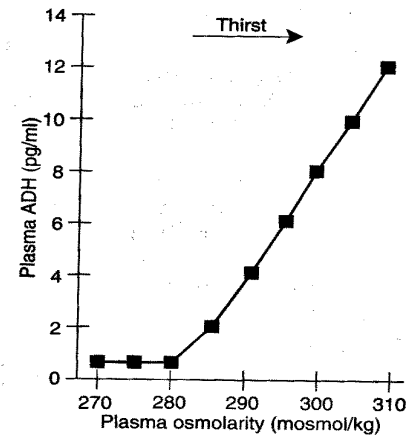
3. ADH has rapid action and rapid turnover (10-20 minutes)

ANTIDIURETIC HORMONE (continued)

D. Control of ADH Release: Controlled by influences which excite (causing release) or inhibit excitation of the ADH neurosecretory cells, among which are the following:

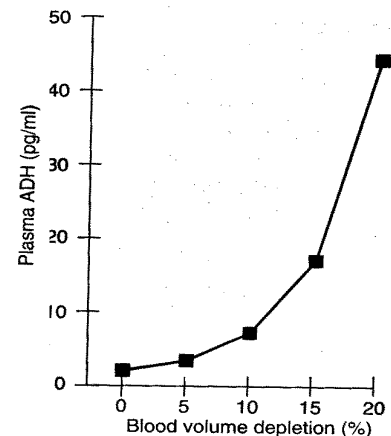
1. Hypothalamic osmoreceptors (major influence)

- specialized sensory cells in the hypothalamus generate APs proportional to interstitial fluid (and blood plasma) osmotic activity (and are silent when osmotic activity is low)
- make excitatory synapses with ADH neurosecretory cells
- result: Plasma Osmolality $\uparrow \Rightarrow$ ADH \uparrow
- very sensitive; small increase in osmolality is sufficient to significantly increase ADH secretion rate
- this form a negative feedback loop stabilizing plasma osmolality (very important to prevent cell damage)



2. Blood volume

- mediated by stretch-sensitive atrial cells (low pressure baroreceptors or vascular volume receptors)
- blood volume $\downarrow \Rightarrow$ ADH \uparrow
- less sensitive (high threshold): 5-10% decrease in blood volume required for significant ADH increase
- potent: once threshold is passed (e.g. serious dehydration), cause large increase in ADH
- this acts to preserve body fluid volume in hypovolemic stress



3. Systemic arterial blood pressure

- mediated by baroreceptors in the carotid sinus and aortic arch (same baroreceptors involved in blood pressure regulation)
- blood pressure $\downarrow \Rightarrow$ ADH \uparrow
- less sensitive (high threshold): 10% decrease in blood pressure required for significant ADH increase
- very potent: once threshold is passed (e.g. major hemorrhage), can cause large increase in ADH (emergency response)
- this acts to preserve blood volume in cases circulatory fluid loss

4. Other influences

- inhibit ADH release: cold, ethanol, opiates
- increase ADH release: stress, nausea, hypoxia, nicotine, pain, morphine
- diurnal variation: ADH secretion generally increases at night during sleep

PATHOPHYSIOLOGY

ANURIA

Low glomerular filtration pressure	Shock	Reduced systemic arterial pressure
Reduced number of functioning nephrons (Note: Creatinine clearance is an index of the number of functioning nephrons)	Renal degenerative disease	Reduced area available

POLYURIA

Inability of pituitary to secrete ADH	Diabetes insipidus (pituitary)	Reduced H ₂ O reabsorption in distal tubule and col. ducts
Inability of the distal tubule to respond to ADH	Diabetes insipidus (nephrogenic)	Reduced H ₂ O reabsorption in distal tubule and col. ducts

Note: Diabetes insipidus (any cause) is termed a water diuresis (excretion of a large volume of dilute urine)

Lack of diurnal reduction of ADH release	Nocturnal enuresis (bed wetting) Nocturnal frequency	Rapid filling of the bladder
Excess filtered load of osmotically active particles high blood glucose	Diabetes mellitus	Reduced osmotic gradient for water reabsorption
Reduced tubular reabsorption of Na ⁺	Most clinical diuretics	Reduced osmotic gradient for water reabsorption

Note: the last two result in an osmotic diuresis (excretion of a large volume of concentrated or iso-osmotic urine)