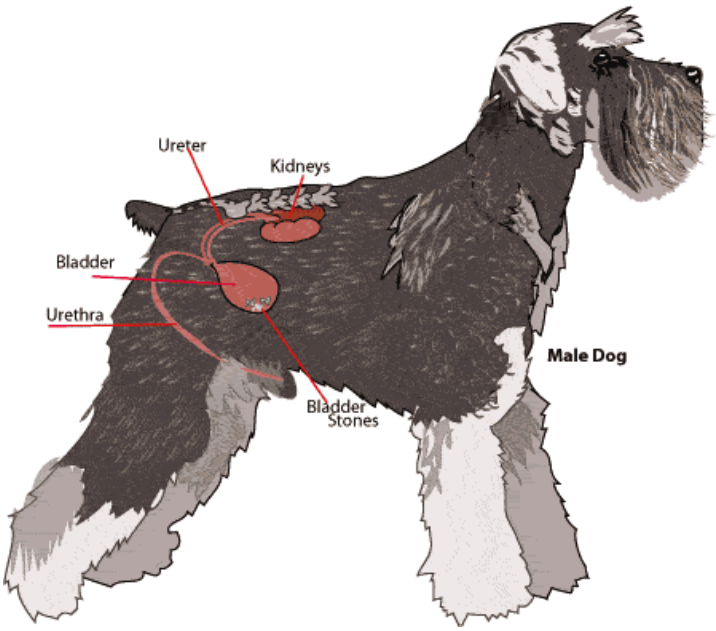
THE UNIVERSITY OF MELBOURNE
FACULTY OF VETERINARY & AGRICULTURAL SCIENCES

Structure and Function of the Kidney 3 Concentrating and Diluting Urine, + Role ADH

Veterinary Bioscience: Metabolism and Excretion



Source : whitneycatcare.com

A/Prof Wayne Kimpton
Room 186 Building 142
School of Veterinary Science
The University of Melbourne Victoria Australia 3010
Telephone: 83447347
Email: w.kimpton@unimelb.edu.au

CONCENTRATING AND DILUTING URINE

Learning objectives :

1. Describe the sequence of events and mechanisms involved needed for the kidney to produce either a dilute or concentrated urine.
2. Explain the role of the loop of Henle, countercurrent multiplication and the vasa recta in the production of dilute and concentrated urine
3. Discuss the role of ADH and urea in making concentrated urine

Blood and interstitial osmolality are normally 290-300mosmol/kg. In order to maintain these homeostatic levels the kidneys need to be able to excrete different amounts of water and solutes. The concentration of urine varies between 50 ~ 5000 mOsmol/L. depending upon the species examined and water balance in the body. The kidneys must be able to produce both hyperosmotic (concentrated) urine when water intake is low or when water loss increases and hypoosmotic (dilute urine) when water intake is high. The kidneys also need to remove 600mosm/day of waste products eg urea, creatinine etc which need to be dissolved in water so they have an obligatory water loss. The obligatory water loss in which solute can be dissolved = 600mOsmol/day divided by 1400Osmol/day (maximal urinary concentration in humans) ie 600/1400 = 0.44L/day.

The kidneys regulate water excretion separately from the excretion solutes (Na, K, H & urea). To make dilute urine the kidneys need to keep filtered water in urine and reabsorbed solutes. Whereas to concentrate urine the kidneys need to make hyperosmotic interstitial fluid in the medulla so water can osmotically diffuses out of the tubule into the blood vessels leaving solute behind in the tubular fluid.

Water reabsorption

In the glomerulus water is freely filtered into the Bowmans space and enters the PCT. Within the tubules water reabsorption id dependent upon the water permeability of the nephron segment involved and the osmotic gradient across the epithelial cell.

The proximal tubule is highly permeable to water and reabsorbs 65% of the filtrate (water). This movement of water first follows the transport of NaCl across the epithelial cell. While large amounts of H_2O and NaCl are reabsorbed at this site it does not contribute to making dilute or concentrated urine as equal quantities of NaCl and water are reabsorbed and the osmolality at end of PCT is still 300mosm/l. To make make concentrated or dilute urine, solute and H_2O must be separated .

Excretion of hypoosmotic urine require reabsorption of NaCl without allowing H_2O to follow.

Excretion of hyperosmotic urine requires removing H_2O from solute and requires a hyperosmotic interstitium (vertical osmotic gradient in medullary interstitium) to osmotically remove H_2O from tubular fluid.

Countercurrent multipler system and the loop of Henle .

The juxtaglomerular nephrons with the loop of Henle (LOH) going deep into the medulla creates a concentration gradient in the medullary interstitium by the use of a countercurrent multiplier system. This ultimately allows the nephron to absorb more water and concentrate the urine.

Loop of Henle has a U shape structure made up of a descending loop of Henle, a thin ascending loop of Henle and the thick ascending loop of Henle. Each segment functions differently and handles solute and water differently.

Thick ascending loop of Henle.

Two important features .

1. Impermeable to water. Tight junctions stop movement of water in or out.

2. Uses Na+/K+ pumps and ATP on basolateral side to establish an electrochemical gradient and ultimately stimulates luminal Na2ClK symporter to move K+ Na+ and Cl- out of the tubular fluid into the cell and eventually increase Na+ and Cl- ion concentration in the interstitium of the medulla. Can pump up to 200mOsm/Kg H_2O difference. This makes the medulla interstitium hypertonic while making the fluid as it reaches the distal tubule very dilute (100 mOsmol /L).

Descending loop of Henle.

- Tubular fluid entering from PCT is 300mOsm/l
- Permeable to water (allow the passive movement of water across the epithelial cell) but is impermeable to ions
- At the top of the descending loop of Henle the filtrate (tubular fluid) is isotonic (300mOsm/l) with the interstitium.
- As it descends deeper into the medulla water is gradually removed from the loop because the interstitium surrounding the loop has a high salt concentration put there by reabsorption by thick LOH. With water leaving the descending LOH the NaCl becomes more concentrated in the tubular fluid as it moves towards the bottom of the loop.

Thin ascending limb of Henle

- Impermeable to water but permeable to ions .
- As the LOH goes back up the Na and Cl ions that are high in concentration inside and now move out of the tubular fluid down their concentration gradient into the interstitium making the tubular fluid more dilute (loses Na+) but interstitium more concentrated (gains Na+).
- The countercurrent multiplier system sets up vertical osmotic gradient.
- The resulting increase in interstitial osmolarity by Na+ being reabsorbed from ascending limb is balanced by diffusion of water (osmosis) out of the descending limb. The osmotic gradient established by active ion transport is said to have been "multiplied" because of "countercurrent" flow, i.e., flow in opposing directions through the ascending and descending limbs of the loop. As fluid flows down the collecting duct, it passes through medullary interstitial fluid of increasing osmolarity. Tip of the LOH has an osmolarity of 1200 mOsm/Kg H_2O . This increased osmolarity in interstitium allows more water to be absorbed from the LOH and from the collecting duct.
- Produces a vertical osmotic gradient cortex isotonic (300 mosm/L) and the medulla very hypertonic (1200 mosm/L).
- The hair pin loop allows the ascending and descending loops to be brought together to form countercurrent multiplier system whereby the Na that is pumped out of the ascending tubule by active transport facilitates the movement of water (via osmosis) from descending LOH
- New fluid is pushed into top of LOH from PCT (300mosmol/L) into the tubule which pushes the now concentrated fluid at bottom of descending LOH and tip of loop around into thin region . (see figure 1).

Antidiuretic hormone (ADH)

Antidiuretic hormone (ADH) acts upon the collecting ducts (principal cells) inserting aquaporin (AQP) water channels. H_2O from the dilute tubular fluid can then passively diffuses out of the collecting ducts into the interstitium (high osmolarity due to counter current multiplication) producing concentrated urine. In contrast when ADH concentration is absent or low, water is retained and a large volume of hypoosmsotic urine is produced.

Recent evidence suggest that the osmotic gradient is modulated by ADH. ADH is thought to directly enhance the NaK ATPase of the thick ascending LOH . This pronmotes increased solute

transport into the interstitium. ADH is also reported to increase Na channels in collecting duct thus increasing the reabsorption of Na into interstitium which also increases water reabsorption.

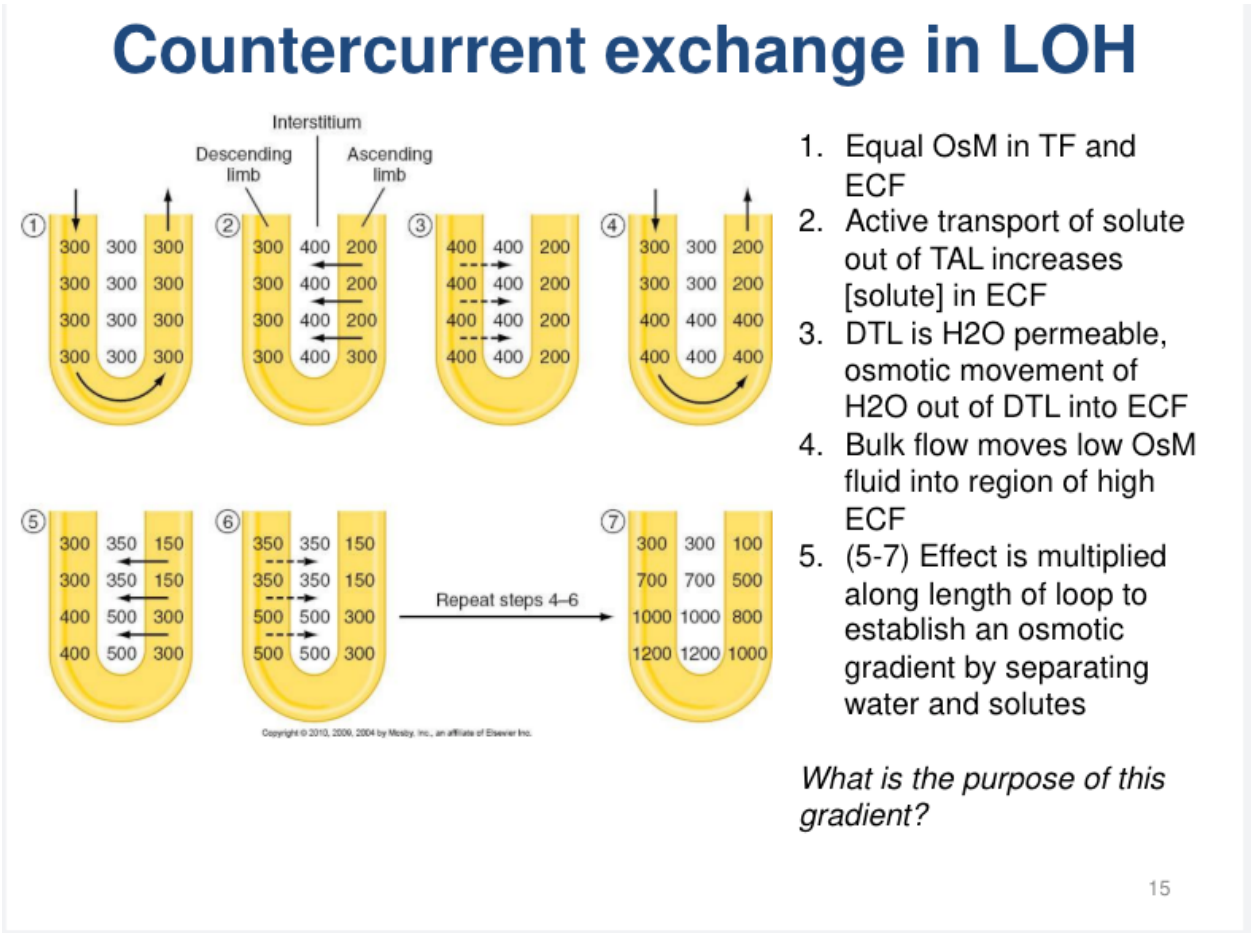


Fig Adapted from Sherwood Human Physiology 2016

Antidiuretic hormone (ADH) (other name **vasopressin)**
Peptide hormone released by the posterior pituitary. ADH acts via a G-protein linked receptor V2) on principal cells within the collecting ducts. This stimulates the production of cAMP second messenger which results in the insertion into the luminal membrane AQP2 (aquaporin 2).

Control of ADH secretion

Hypothalamic neurons with axons terminating in the posterior pituitary produce ADH. Triggers for release are increased osmolarity and decreased blood volume.

1. Osmoreceptors
    a. A change in osmolarity within interstitium of hypothalamus (as a consequence of changes in osmolality in the the body is detected by osmoreceptors and this stimulates ADH sectetion
2. Baroreceptor control of secretion
    a. Decreased extracellular volume is detected by baroreceptors in the cardiovascular system which signals the hypothalamus to secrete ADH whereas increased cardiovascular pressures decrease the secretion of ADH.

Countercurrent exchange by Vasa Recta
The vasa recta is important for Hairpin loops in the vasa recta act as countercurrent exchangers to protect the medullary interstitial concentration gradient created by the loop of Henle. This hairpin loop structure minimises losses of solute or water from the interstitium by diffusion,

As blood flows down the vasa recta Na+ and Cl- diffuse into the vasa recta from the interstitium and water diffuses out of the vasa recta into the interstitium. After the bend in the hairpin loop is reached, blood flows up the ascending portion and water diffuses back into the vasa recta and Na+ and Cl- diffuse back out of the vasa recta, with vasa recta plasma osmolarity almost returned to normal.

Medullary washout

Blood flow through the medulla is normally "sluggish" to permit adequate diffusion of water in and solutes out of vasa recta. With increased blood flow inappropriate exchange of solutes between ascending and descending limbs of the vasa recta may occur which can causr a medullary 'washout' reducing the medullary osmotic gradient and making it harder to concentrate urine.

Role of urea recycling

Fifty percent of Urea is passively reabsorbed in the proximal tubule. As water is removed along the nephron urea concentration rises. In the inner medullary collecting tubules urea is passively reabsorbed by an ADH dependent urea transporter (UT-A1). Not all Urea is reabsorbed some is still secreted as a waste product but the urea that is reabsorbed is moved into the medullary interstitium and re-enters the loop of Henle by passive diffusion. . This recycling of urea can accounts for up to 50% of the medullary interstitial osmolarity. By contributing to the medullary interstitial concentration the urea draws out more water and further concentrates the urine. As urea cycles in this way, termed "Urea Recycling", the medullary concentration gradient increases in size.

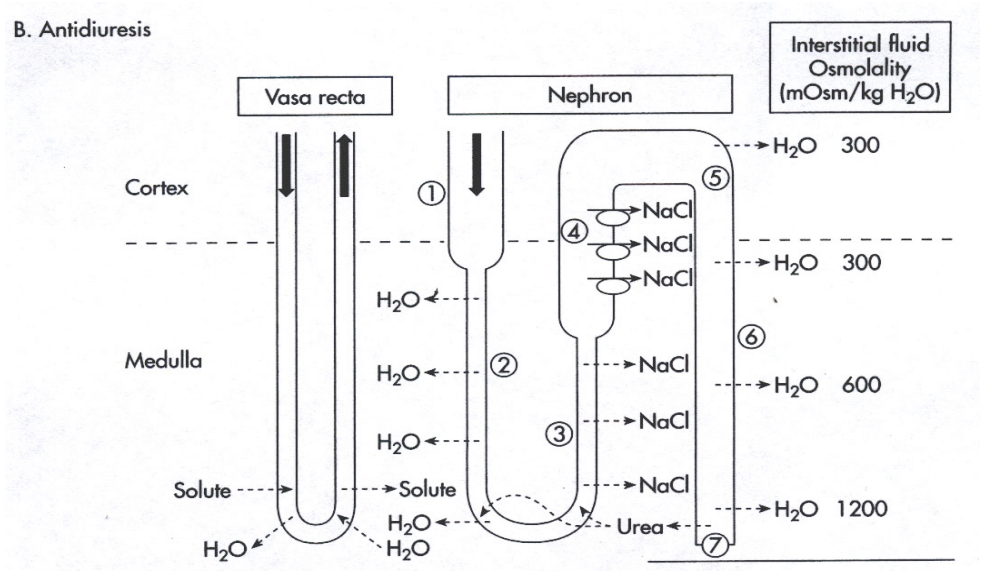


Fig 1 Summary of key steps in concentrating urine. Koeppen, B.M. and Stanton, B.A. (2012)

References

1. Renal Physiology. Koeppen, B.M. and Stanton, B.A. (2018) 9th Edition, The C.V. Mosby Company.
2. Cunningham's Textbook of Veterinary Physiology, Klein (2019) 6th Edition, Saunders Co.
3. Berne and Levy Physiology B. Koeppen B Stanton 7th Edition 2017.
4. Medical Physiology. Boron, W.F. & Boulpaep, E.L. (2016) Saunders.
5. Clinical Physiology of Acid Base And Electrolyte Disorders. Rose, B. (2001) Elseiver