PHYSIOLOGY

- SHEET NO. 8 - Urine Concentration and Dilution
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Urine Concentration and Dilution

Healthy kidneys have the capability to vary the relative proportions of solutes and water in the urine in response to various challenges. When there is excess water in the body and body fluid osmolarity is reduced, the kidneys can excrete urine with an osmolarity as low as 50-70 mOsm/L. Conversely, when there is a deficit of water in the body and extracellular fluid osmolarity is high, the kidneys can excrete highly concentrated urine with an osmolarity of 1200 to 1400 mOsm/L. Equally important, the kidneys can excrete a large volume of dilute urine or a small volume of concentrated urine without major changes in rates of excretion of solutes such as sodium.

Regarding urine dilution and concentration, normally we have a balance between:

- water reabsorption/ water execration.
- Solute reabsorption/solutes execration.
- a hormonal system, mainly ADH.

Any condition in our body results in a reduction of fluid volumes such as fasting, or physical activity accompanied with water loss by expiration or sweating this will lead to:

- Activate thirst sensation so, more water intake.
- Reduce the amount of water loss by reducing the volume of urine (concentrating the urine), which reduces the need to drink a huge amount of water to correct the water loss.

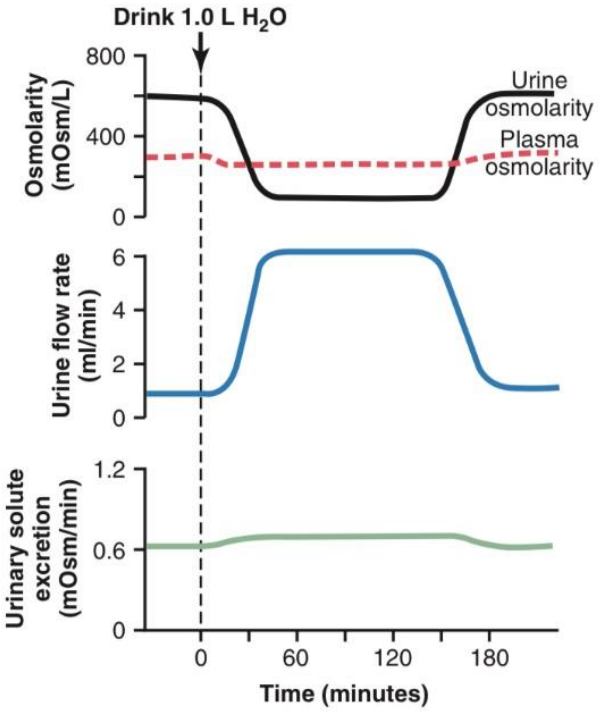
This will happen by ADH -Thirst Osmoreceptor System which will sense even the minimal change in the plasma osmolarity and activate the thirst center in the brain and stimulate ADH release to maintain a normal volume of fluid in the body and normal Osmolarity of ECF (mainly sodium).

Mechanism:

Shortage of body water → increase extracellular osmolarity (mainly sodium, chloride, and bicarbonate) → Osmoreceptor → stimulates ADH release → increases H2O reabsorption, and stimulates thirst (intake of water)
So, the main player is the **Antidiuretic hormone (ADH).**
ADH release→ insertion of aquaporin channels in the late distal and collecting tubule → more permeable to water → increase water reabsorption **without affecting solutes excretion.**
Note: to estimate ECF osmolarity = osmolarity of sodium *2.1

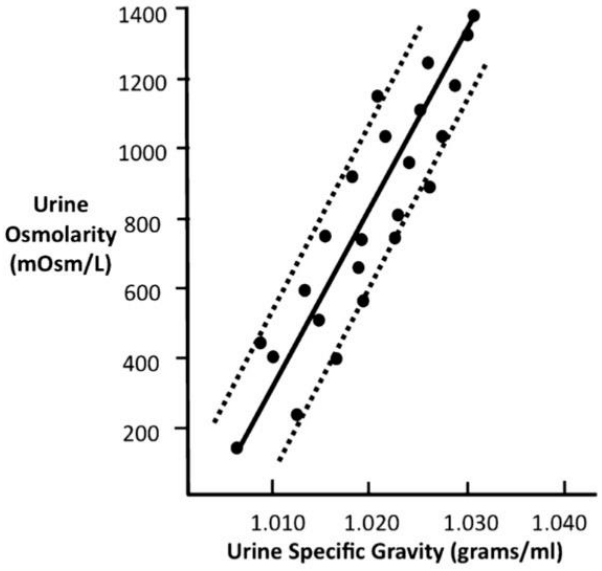
An experiment of ingestion of 1 liter of water and tracing the osmolarity (black) mOsm/L, plasma osmolarity(red) mOsm/L, urine flow rate (blue) ml/min, urinary solute excretion (green) mOsm/min over a period of time:

- In the first graph, after 30-45min from ingestion, urine concentration (urine osmolarity) drops, at the same time in the second graph urine flow rate increase 6 times the original flow rate.
- In the last graph, urinary solute excretion doesn't change.
- After 160 min, the urine osmolarity, and urine flow rate back to normal.
- So, increasing the water intake will **inhibit ADH** which will affect only water excretion and doesn't affect urinary solute excretion.



Before we dig deeper into the kidney mechanisms in concentrating and diluting urine let's understand the term **specific gravity.**

- **specific gravity** is the weight of the urine compared with the weight of water, so the difference in weight is because of the **solutes**. In other words, **specific gravity** is a measure of the weight of solutes in a given volume of urine and is therefore determined by the **number and size** of the solute molecules. In contrast, **osmolarity** is determined only by the **number** of solute molecules in a given volume.
- Normal specific gravity: (1.002-1.028) g/ml
- The diagram illustrates the relationship between **urine osmolarity(mOsm/L)** and **specific gravity(g/ml)**:
- In a healthy kidney, urine specific gravity increases linearly with increasing urine osmolarity, it's mainly related to the normal solutes present in the urine (Na, Cl, urea….).

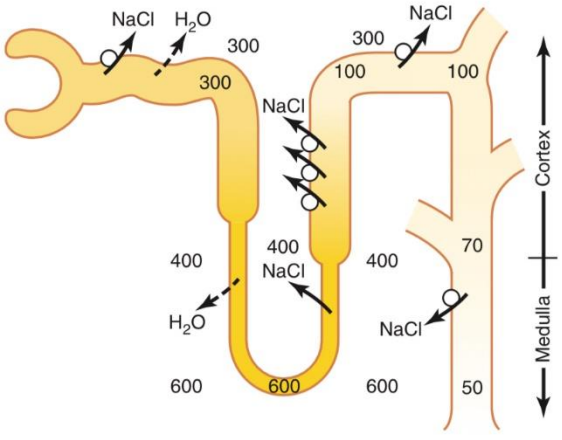


- In a diseased kidney, when there are significant amounts of large molecules in the urine, such as glucose, protein, antibiotics, or radiocontrast media, this will **shift the curve to the right**, so higher specific gravity.
- normally, specific gravity Increases by .001g/ml for every 40mOsm/L increase in the urine concentration.
- The more concentrated the urine, the higher the urine specific gravity and the opposite not always true, sometimes we have high specific gravity because of the presence of glucose and protein which is abnormal.

Formation of a dilute urine

When there is a large excess of water in the body the kidney will continue electrolyte reabsorption and decrease water reabsorption. This happened in the **absence of ADH.** So, getting rid of the excess amount of water without affecting the execration of the solutes.

1. Filtered fluid from the glomerulus flows to the bowman's capsule. Tubular osmolarity = plasma osmolarity =300mOsm/L.
2. Tubular fluid flows to the Proximal Tubule; reabsorption of **solutes and water** happened, so the ratio between tubular osmolarity and plasma osmolarity =1.
3. Thin descending Henle; which is permeable to water (passive and depends on the interstitial osmolarity to achieve the equilibrium). As we go down from the cortex to the medulla, interstitial osmolarity increases from 300 to 400 to 600, so Tubular osmolarity will increase too (equilibrium).
4. Thin Ascending Henle; Impermeable to water, permeable to solutes mainly NaCl (passive and depend on the interstitial osmolarity to achieve the equilibrium). As we go up from medulla to cortex, interstitial osmolarity decrease from 600 to 400 to 200 so, Tubular osmolarity will decrease too **(Start dilution)**.
5. Thick Ascending Henle; Impermeable to water, **Active** reabsorb of solutes mainly NaCl. So, extensive solutes reabsorption actively regardless of the gradient until the Tubular osmolarity reaches 100mOsm/L which is **very diluted.**
6. Early distal; Impermeable to water, continuous reabsorption of the solutes actively.



7. Late distal and collecting tube; its Permeability to water variable and **depends on ADH**, and here we have high water volume, **ADH is absent**. So, it's Impermeable to water but the reabsorption of the solutes will continue actively, so more urine dilution until tubular osmolarity reaches 50mOsm/L with a **huge volume of urine.**

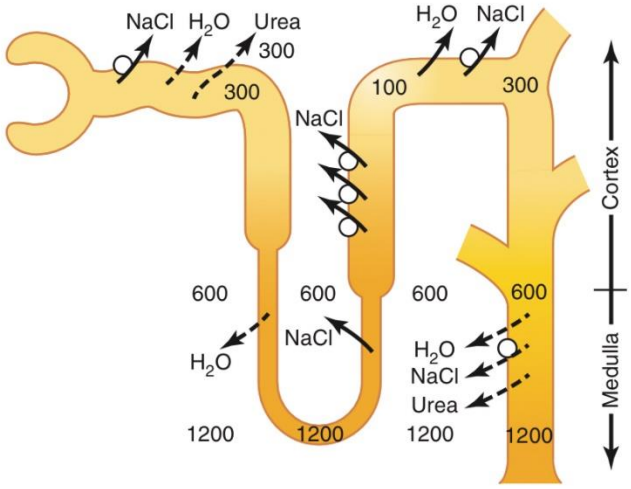
So, Decreased ADH release and reduced water permeability in distal and collecting tubules = a large volume of diluted urine.

Formation of a Concentrated urine

When there is a deficit of the water in the body either because of low intake or high loss (Sweating, high expiration rate, Diarrhea, hemorrhage), the kidney will continue electrolyte reabsorption and Increase water reabsorption. This happened in the **presence of ADH.** So, conserve the amount of the water without affecting the solutes execration.

Remember: The kidneys contain two types of nephrons, superficial cortical nephrons (75-85%) and juxtamedullary nephrons (15-25%). These names refer to the location of the glomerular capsule, which is either in the outer cortex of the kidney or near the corticomedullary border, each with a different structure and function. The loops of Henle of the juxtamedullary nephrons penetrate deeply within the inner medulla which means **high interstitial osmolarity,** could reach 1200mOsm/L. Although both cortical and juxtamedullary nephrons regulate the concentrations of solutes and water in the blood, **countercurrent multiplication in the loops of Henle of juxtamedullary nephrons** is largely responsible for developing the osmotic gradients that are needed to concentrate urine.

1. Thin descending Henle; passive water reabsorption to reach equilibrium, TO=IO=1200mOsm/L.
2. Thin Ascending Henle; passive solutes reabsorption to reach equilibrium, **dilution** in the tubular fluid, TO=IO=600 mOsm/L.
3. Thick Ascending Henle; reabsorption of solutes actively, more dilution in the tubular fluid, TO=100 mOsm/L.
4. Late distal and **cortical** collecting tube; its Permeability to water variable and **depends on ADH**, and here we have low water volume, so **stimulation of ADH release** thus increases aquaporin insertion which increases water permeability in late distal and **cortical** collecting tubules, so concentrating the urine.



5. In the medullary collecting tubules; ADH increases **urea transporter insertion**, so reabsorption to urea down their gradient, which will increase the urea concentration in the interstitium, thus increasing the interstitial osmolarity and increasing the kidney's ability to concentrate urine.

So, the urea concentration increases as we go deep into the medulla because of the direct effect of ADH on the urea transporter and increases water reabsorption in the cortical portion.

Obligatory Urine Volume

- The **minimum urine volume** in which the excreted solute can be dissolved and excreted
- Depend on the ability of the kidney to concentrate urine.
- Maximal urine concentration = 1200 - 1400 mOsm / L (specific gravity ~ 1.030)
- Minimal urine concentration = 50 - 70 mOsm / L (specific gravity ~ 1.003)
- Normal Plasma osmolarity = 280-300 mOsm/L
- So, the Kidney able to concentrate the urine 4-6 times as the osmolarity of the plasma.

Example1: in a normal kidney, If the max. urine osmolarity is 1200 mOsm/L, and 600 mOsm of solute must be excreted each day to maintain electrolyte balance, the obligatory urine volume is:

$$\frac{600\ \text{mOsm/d}}{1200\ \text{mOsm/L}} = 0.5\ \text{L/day}$$

- In renal disease, the obligatory urine volume may be increased due to impaired urine concentrating ability.

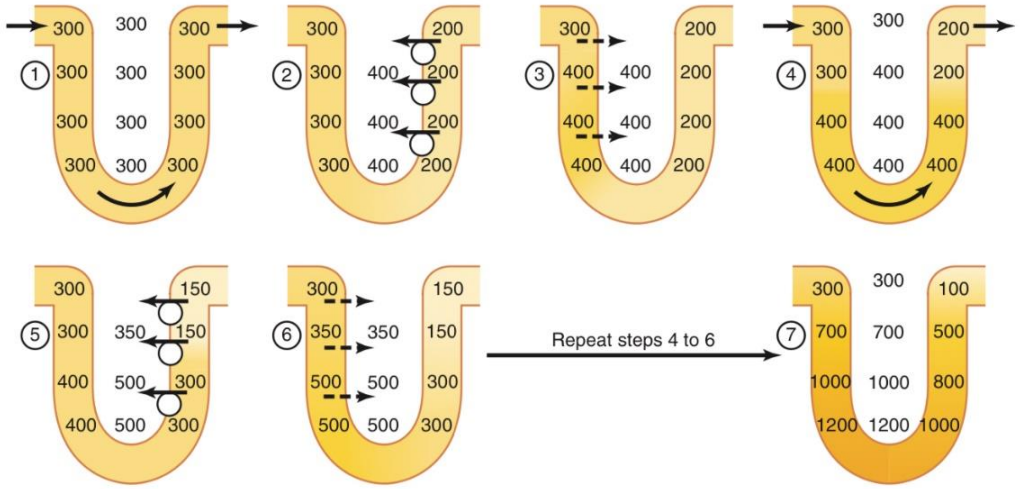
Example2: If the max. urine osmolarity = 300 mOsm/L, and 600 mOsm of solute must be excreted each day to maintain electrolyte balance, the obligatory urine volume is?

$$\frac{600\ \text{mOsm/d}}{300\ \text{mOsm/L}} = 2.0\ \text{L/day}$$

Factors That Contribute to Build-up of Solute in Renal Medulla:

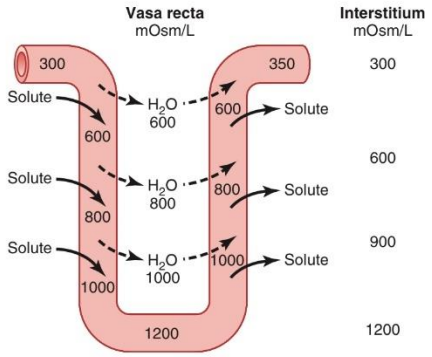
1. Juxtamedullary nephrons through **Countercurrent Multiplier**. As we increase the renal medulla solutes the interstitial osmolarity will increase, thus the capability of the kidney to concentrate urine increases.
2. Active transport of Na+, Cl-, K+, and other ions from the thick ascending loop of Henle into the medullary interstitium.
3. Active transport of ions from medullary collecting ducts into the interstitium
4. Passive diffusion of urea from medullary collecting ducts into the interstitium
5. Diffusion of only small amounts of water into the medullary interstitium

In the experiment to understand the Countercurrent multiplier system in the loop of Henle, follow the numbers:



1. assume that the loop of Henle is filled with fluid with a concentration of 300mOsm/L, the same as that leaving the proximal tubule, the interstitial fluid concentration also 300mOsm/L, so we have equilibrium (zero point). Remember, we don't have zero points in our bodies but it's an experimental assumption.
2. the active ion pump of the thick ascending limb on the loop of Henle reduces the concentration inside the tubule to 200mOsm/L and raises the interstitial concentration to 400mOsm/L; this pump establishes a 200-mOsm/L concentration gradient between the tubular fluid and the interstitial fluid. The limit to the gradient is about 200mOsm/L because paracellular diffusion (leaking) of ions back into the tubule eventually counterbalances the transport of ions out of the lumen when the 200mOsm/L concentration gradient is achieved.
3. the descending limb of the loop of Henle is permeable to water so, tubular fluid in the descending limb and the interstitial fluid quickly reach an osmotic equilibrium of 400mOsm/L.
4. the additional flow of fluid into the loop of Henle from the proximal tubule causes the hyperosmotic fluid previously formed in the descending limb to flow into the ascending limb.
5. Once this fluid is in the ascending limb, additional ions are pumped into the interstitium, with water remaining in the tubular fluid, until a 200mOsm/L osmotic gradient is established, with the interstitial fluid osmolarity rising to 500mOsm/L.
6. These steps are repeated over and over, with the net effect of adding more and more solutes to the medulla; with sufficient time, this process gradually traps solutes in the medulla and multiplies the concentration gradient established by the active pumping of ions out of the thick ascending loop of Henle, eventually raising the interstitial fluid osmolarity to 1200.

This Countercurrent multiplier system in the loop of Henle is accompanied by **Vasa recta**; a unique U-shaped medullary peritubular capillary system that parallels the loop of Henle with High permeability to water and solutes thus, an exchange between water and solutes will happen with no change in the net interstitial osmolarity (in descending solutes gets in and water gets out, in ascending solutes gets out and water gets in). this will not build up a gradient, but it will prevent the washout of the solutes in the matrix to preserve the hyperosmolarity of the Renal Medulla.



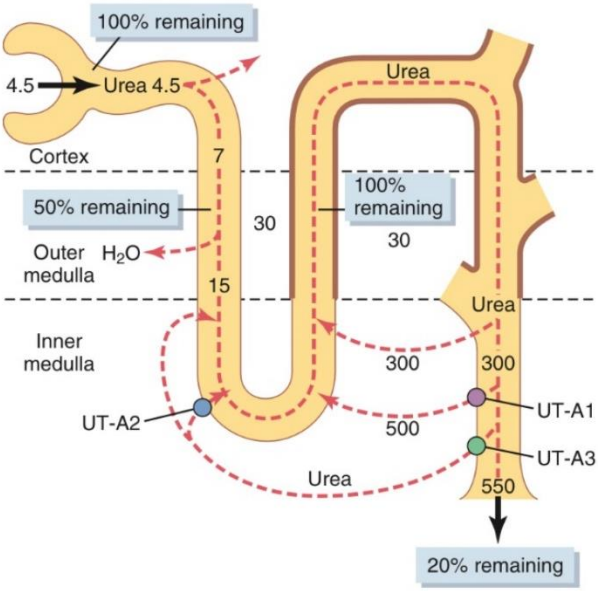
Vasa recta blood flow is low (only 1-2 % of total renal blood flow)

Net Effects of Countercurrent Multiplier:

1. More solute than water is added to the renal medulla. i.e solutes are "trapped" in the renal medulla.
2. Fluid in the ascending loop is diluted.
3. Most of the water reabsorption occurs in the cortex (i.e. in the proximal tubule and in the distal convoluted tubule) rather than in the medulla.
4. Horizontal gradient of solute concentration established by the active pumping of NaCl is "multiplied" by the countercurrent flow of fluid.

Urea Recirculation

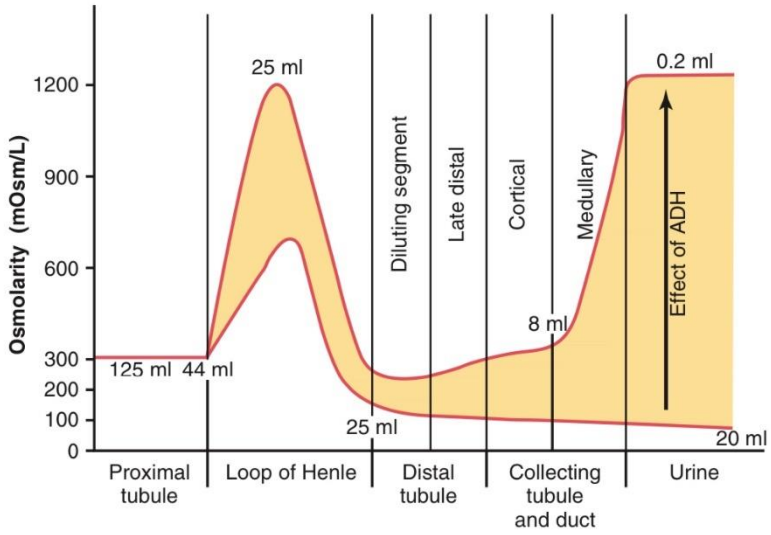
- Urea is passively reabsorbed in the proximal tubule (~ 50% of the filtered load is reabsorbed).
- In the presence of ADH, water is reabsorbed in distal and collecting tubules, concentrating urea in these parts of the nephron.
- The inner medullary collecting tubule is highly permeable to urea, which diffuses into the medullary interstitium.
- ADH increases urea permeability of medullary collecting tubule by activating urea transporters (UT-1)
- some of the urea which reabsorbed in the medullary collecting duct into interstitial fluid will be secreted into the medullary portion of Henle.



- then will undergo recirculation with the reabsorption.
- So, 20% of urea is execrated, but more urea will circulate to establish high interstitial concentration.
- This recycling process aims to keep the medullary interstitium concentrated and prevent the washout of the urea to increase the kidney's ability to concentrate urine.
- Problems in urea ingestion, malnutrition of urea and reduction in proteins and protein breakdown, will lead to low urea concentration in the body → low urea in the interstitium, kidney capacity to concentrate urine decrease.

Summary of water reabsorption and osmolarity in different parts of the tubule:

- Proximal Tubule: 65 % reabsorption, isosmotic
- Desc. loop: 15 % reabsorption, osmolarity increases
- Asc. loop: 0 % reabsorption, osmolarity decreases
- Early distal: 0 % reabsorption, osmolarity decreases
- Late distal and coll. tubules: ADH dependent water reabsorption and tubular osmolarity
- Medullary coll. ducts: ADH dependent water reabsorption and tubular osmolarity



"Free" Water Clearance (CH2O)

Rate of solute-free water excretion, where high Clearance indicates diluted urine and low Clearance indicates concentrated urine.

Urine flow rate clearance of osmoles = Free water clearance

$$CH2O = V - \frac{Uosm\ x\ V}{Posm}$$

where: Uosm = urine osmolarity
V = urine flow rate
P = plasma osmolarity

If: Uosm < Posm, CH2O = positive → dilution

If: Uosm > Posm, CH2O = negative → concentration

Question: Given the following data, calculate "free water" clearance:

urine flow rate = 6.0 ml/min
urine osmolarity = 150 mOsm /L
plasma osmolarity = 300 mOsm / L

Is free water clearance in this example positive or negative?

Answer:

$$CH2O = V - \frac{\text{Uosm x V}}{\text{Posm}}$$

$$= 6.0 - \frac{(\ 150 \text{ x } 6\ )}{300}$$

= 6.0 - 3.0

= + 3.0 ml / min (positive)

Disorders of Urine Concentrating Ability:

1. Failure to produce ADH: "Central" diabetes insipidus.
2. Failure to respond to ADH: "nephrogenic" diabetes insipidus, could happen because:

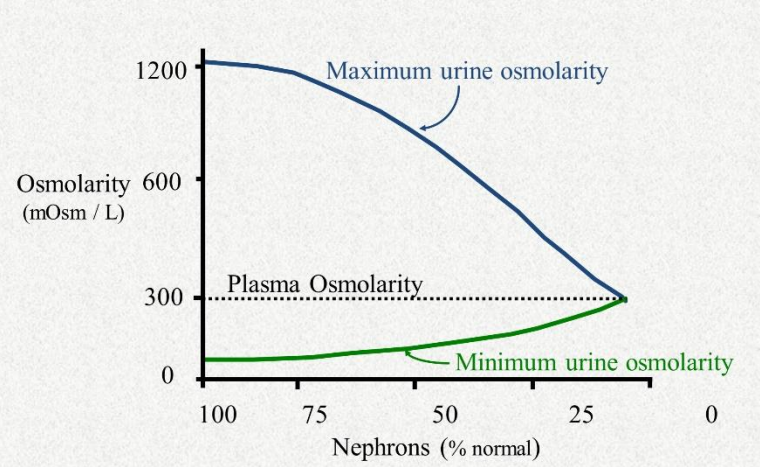
- impaired loop NaCl reabsorption (because of the use of loop diuretics).
- drug-induced renal damage: (lithium, analgesics).
- malnutrition (decreased urea concentration).
- some kidney diseases such as; pyelonephritis, hydronephrosis, and chronic renal failure.

Isosthenuria

When there is a condition where the body can't increase the concentration of urine above the normal osmolarity or decrease the concentration of urine below the normal osmolarity this is called **Isosthenuria.** Isosthenuria can be accompanied by nephrons loss in conditions such as Chronic Renal Failure.

Damage in the nephron's structure → decrease in the proportion of normal functioning nephrons → Chronic Renal Failure → inability to concentrate or dilute the urine → Isosthenuria.

In this diagram:



- illustrate the relation between the proportion of the normal nephrons in the kidney %(x-axis) and the osmolarity mOsm/L (y-axis).
- Normal plasma osmolarity 300 mOsm/L.
- As we go to the right on the x-axis, decrease the proportion of the normal nephrons due to chronic renal failure.
- As the proportion of the normal nephrons decreases, the minimum, and maximum urine osmolarity decrease too.
- When the nephrons are 100% normal, the kidney can dilute urine as low as 50 mOsm/L, and concentrate urine as high as 1200 mOsm/L.
- When 50% damaged (50% normal), the minimum and maximum urine osmolarity become closer to the plasma osmolarity → Isosthenuria.

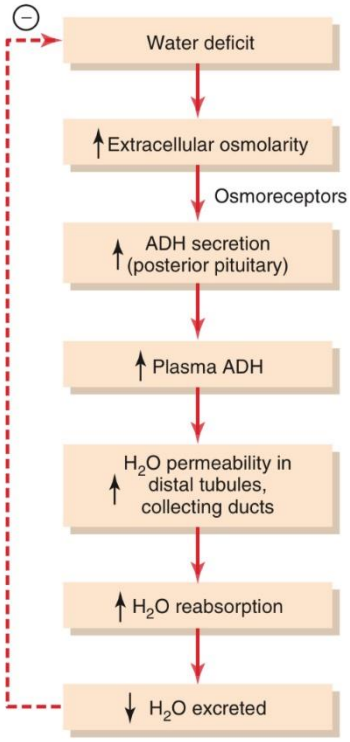
		NORMAL	CHRONIC RENAL FAILURE 75 % LOSS OF NEPHRONS
1	Number of nephrons	2,000,000	500,000
2	Total GFR (ml/min)	125	40
3	GFR per nephron (nl/min)	62.5	80
4	Total Urine flow rate (ml/min)	1.5	1.5
5	Volume excreted per nephron (nl/min)	0.75	3.0

Regarding the table:

1. The normal number of nephrons in a single kidney is 2,000,000. And 500,000 in a kidney with 75% damage.
2. Normal GFR =125 ml/min. in CRF, total GFR will diminished = 40 ml/min.
3. GFR per nephron = 2,000,000/125 = 62.5, but in CRF = 500,000/40 = 80 which is higher than the normal (compensatory mechanism to the reduction in nephrons number).
4. The total Urine flow rate doesn't change.
5. Volume excreted per single nephron will be higher more than three times in CRF.

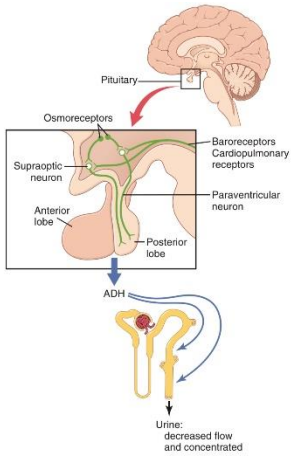
Control of Extracellular Osmolarity and Osmoreceptor ADH feedback mechanism

As we said before, extracellular osmolarity is achieved by ADH -Thirst Osmoreceptor System.



So, increased extracellular osmolarity (NaCl) will stimulate Osmoreceptor in the hypothalamus (osmoreceptor cells will shrink and get stimulated), which produce signals that:

1. induce ADH secretion from the posterior pituitary, ADH will increase in the plasma, which increases H2O reabsorption from late distal and collecting tubules, so water execration will reduce (that is why it's called anti-diuretic), and this will reduce the water defect (negative feedback).
2. stimulates the thirst center that present in the brain with ADH receptor, thus stimulating intake of water, end up by adjusting extracellular osmolarity.

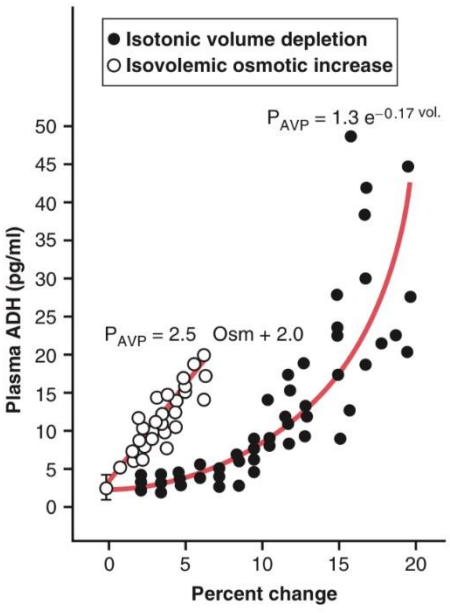


ADH

- synthesis in the magnocellular neurons of the hypothalamus.
- Released by the posterior pituitary.
- action on the kidneys.

The effect of increased plasma osmolarity or decreased blood volume.

- The graph illustrates the relation between plasma ADH pg/ml on the y-axis and the percent of the volume change (black dots) and osmolarity (white dots) on the x-axis.
- As we go to the right on the x-axis:
- volume → decrease without changing the osmolarity.
- osmolarity→ increase without changing the volume.
- At low percent change, less than 5%, the osmolarity will significantly increase plasma ADH, and this is much more than the effect of volume depletion.
- So, at a low percent change, the osmolarity increase is a stronger stimulus than the volume depletion.
- After more than 10% percent change, volume depletion becomes a stronger stimulus than osmolarity.



ADH Secretion:

Stimuli for ADH Secretion

1. Increased osmolarity
2. Decreased blood volume (cardiopulmonary reflexes)
3. Decreased blood pressure (arterial baroreceptors)
4. Other stimuli:
   - input from the cerebral cortex (e.g., fear)
   - angiotensin II
   - nausea
   - nicotine
   - morphine

Factors That Decrease ADH Secretion

1. Decreased osmolarity
2. Increased blood volume (cardiopulmonary reflexes)
3. Increased blood pressure (arterial baroreceptors)
4. Other factors:
   - Alcohol
   - clonidine (antihypertensive drug)
   - haloperidol (antipsychotics, used to treat Tourette's syndrome)

Thirst:

Stimuli for Thirst

1. Increased osmolarity
2. Decreased blood volume(cardiopulmonary reflexes)
3. Decreased blood pressure(arterial baroreceptors)
4. Increased angiotensin II
5. Other stimuli:
   - dryness of mouth

Factors That Decrease Thirst

1. Decreased osmolarity
2. Increased blood volume (cardiopulmonary reflexes)
3. Increased blood pressure(arterial baroreceptors)
4. Decreased angiotensin II
5. Other stimuli:
   - Gastric distention

Sorry for errors, if there was

Good luck ♥