Renal Pharmacology

3rd Year Pharmacology and Toxicology- Biomedical Sciences
School of Health Sciences UNZA

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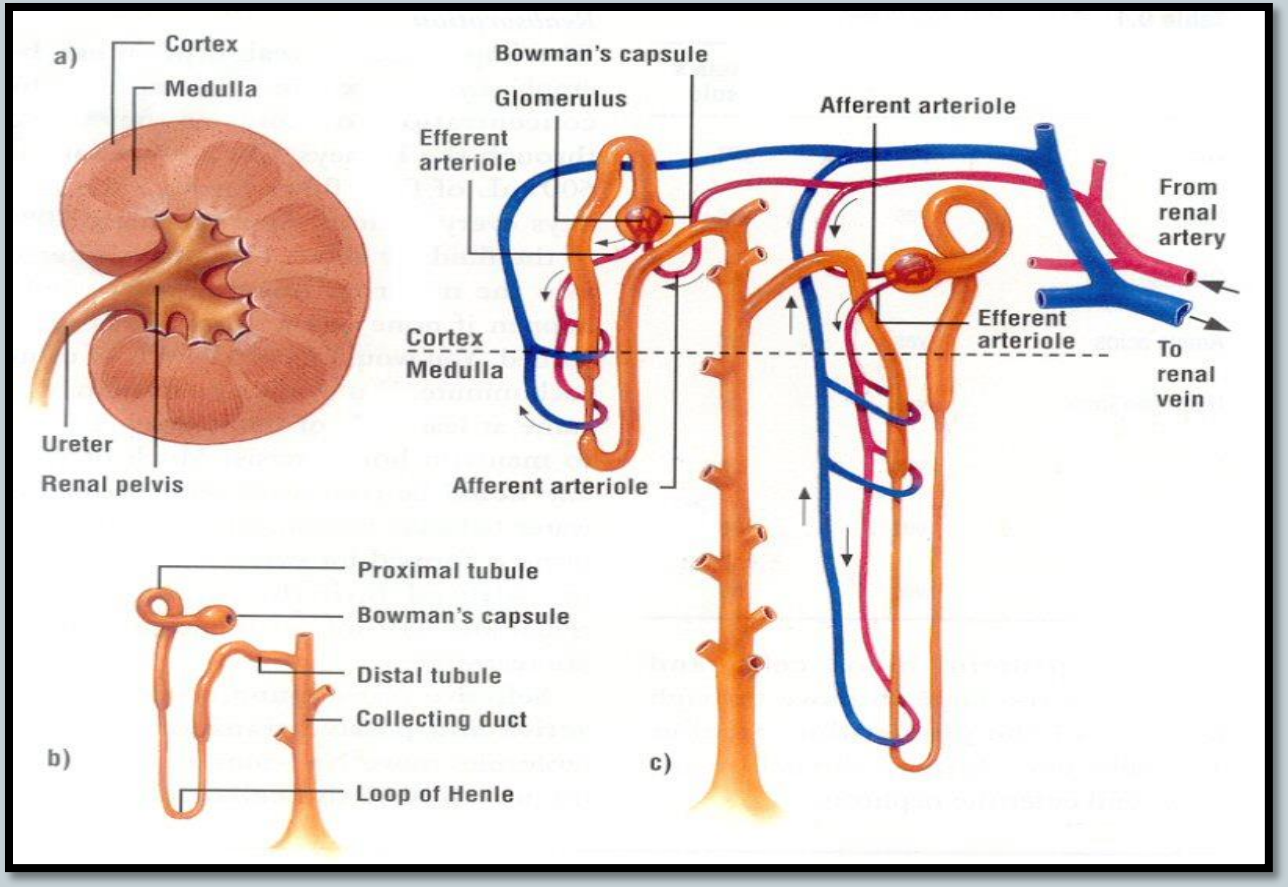

a)
Cortex
Medulla
Ureter
Renal pelvis
Bowman's capsule
Glomerulus
Afferent arteriole
Efferent arteriole
From renal artery
Efferent arteriole
Cortex
Medulla
To renal vein
Afferent arteriole
Proximal tubule
Bowman's capsule
Distal tubule
Collecting duct
Loop of Henle
b)
c)

The functions of the renal system are:

- *The elimination of waste products.*
- *The regulation of body homeostasis, regulating extracellular fluid volume, and electrolyte balance.*
- *The synthesis of hormones that affect metabolism. For example, 25-hydroxy-vitamin D3 is metabolized to the active form, 1,25-dihydroxy-vitamin D3.*

The functions of the renal system are:

- *kidneys are equipped with a variety of detoxification mechanisms and have considerable functional reserve and regenerative capacities.*
- *Nonetheless, the nature and severity of the toxic insult may be such that these detoxification and compensatory mechanisms are overwhelmed, and kidney injury ensues.*
- *The outcome of renal failure can be profound; permanent renal damage may result, requiring chronic dialysis treatment or kidney transplantation*

Kidney- many different functions

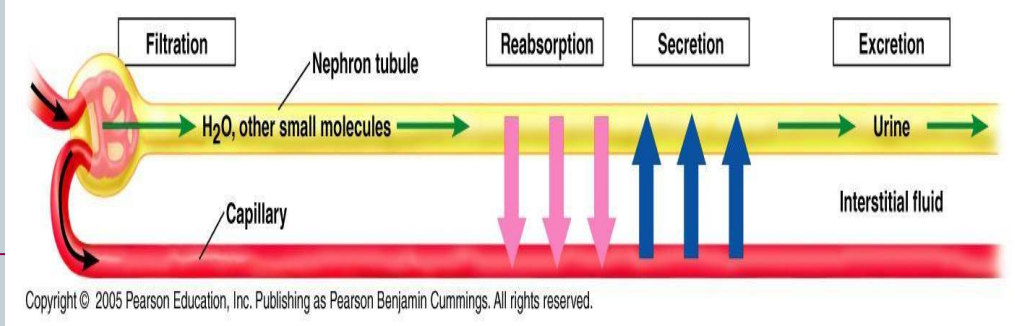
- Regulation of blood
  → ionic composition
  → pH
  → volume
  → blood pressure
  → osmolarity
  → glucose and nutrients

- Excretion of waste and foreign substances

- Hormone production (calcitriol, renin, prostaglandins, erythropoietin)

Urine production

- GOAL: to maintain homeostasis by regulating the volume and composition of blood.
- Involves excretion of solutes, especially waste products:
  - → **Ammonia and urea**: breakdown of amino acids (most abundant).
  - → **Creatinine:** breakdown of creatinine phosphate, important role in muscle contraction.
  - → **Uric acid:** recycling of nitrogenous bases from RNA molecules.
- Removal associated with unavoidable water loss (thus important to concentrate urine) and also to reabsorb useful organic substrates.
- Accomplished by **filtration, reabsorption**, **secretion and excretion**.
- Rate of urinary excretion: glomerular filtration + secretion - reabsorption



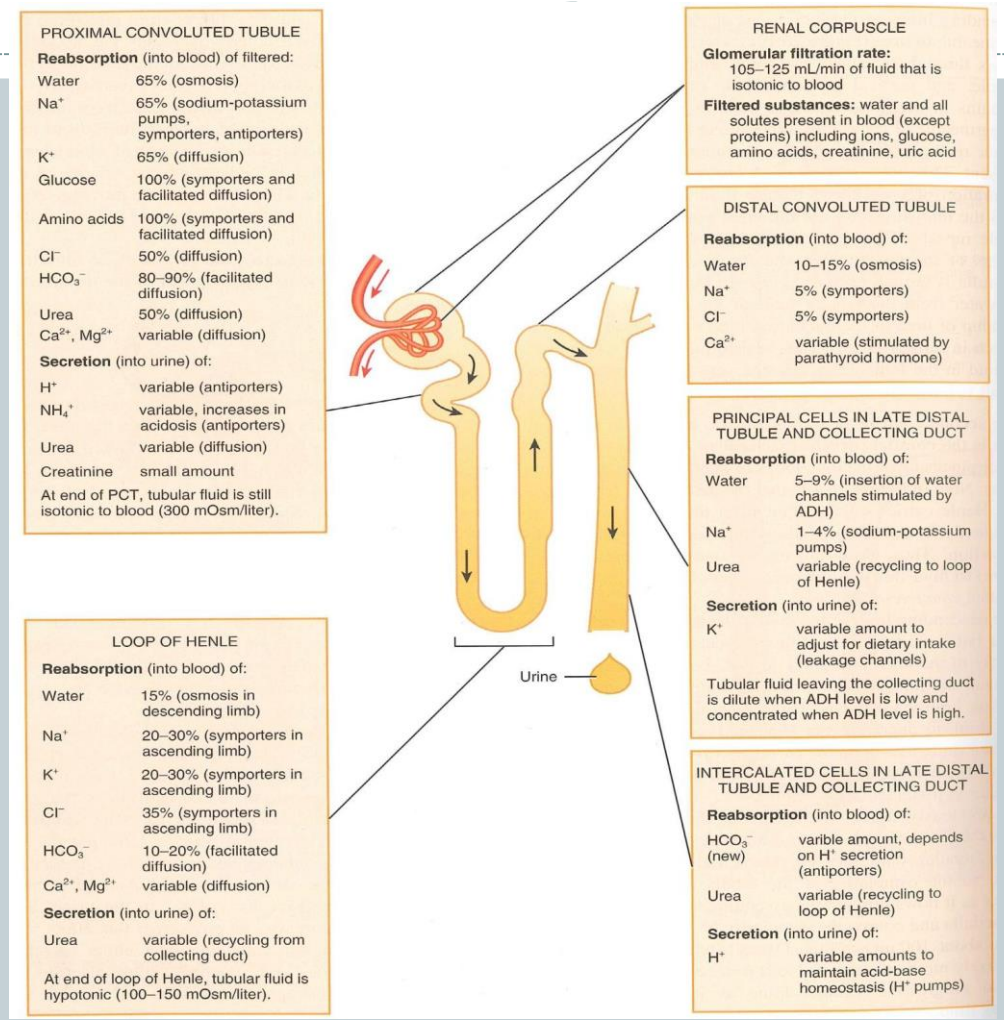
Differences

Component	Urine	Plasma
Ions (mEq/l)		
Sodium	147.5	138.4
Potassium	47.5	4.4
Chloride	153.3	106
Bicarbonate	1.9	27
Metabolites and nutrients (mg/dl)		
Glucose	0.009	90
Lipids	0.002	600
Amino acids	0.188	4.2
Proteins	0.000	7.5 g/dl
Nitrogenous wastes (mg/dl)		
Urea	1800	10-20
Creatinine	150	1.-1.5
Ammonia	60	<0.1
Uric acid	40	3

Glomerular filtration rate (GFR)

- Amount of filtrate formed in all renal corpuscles of both kidneys each minute = GFR
- Average GFR 125 ml/min in males, 105 ml/min females
- Relatively constant to maintain homeostasis of body fluids
- Directly related to pressures that determine NFP, example severe blood loss
  - → Reduced arterial blood pressure => decreased GBHP (45 mm Hg)
  - → Filtration ceases since opposing pressure add up to 45 mm Hg
- Not affected by raise in systematic blood pressure, GFR nearly constant at arterial blood pressure 80-180 mm Hg

- **THREE** mechanisms control GFR
  - → Auto-regulation
  - → Neural regulation
  - → Hormonal regulation


PROXIMAL CONVOLUTED TUBULE
Reabsorption (into blood) of filtered:
Water 65% (osmosis)
Na+ 65% (sodium-potassium pumps, symporters, antiporters)
K+ 65% (diffusion)
Glucose 100% (symporters and facilitated diffusion)
Amino acids 100% (symporters and facilitated diffusion)
Cl− 50% (diffusion)
HCO3− 80–90% (facilitated diffusion)
Urea 50% (diffusion)
Ca2+, Mg2+ variable (diffusion)
Secretion (into urine) of:
H+ variable (antiporters)
NH4+ variable, increases in acidosis (antiporters)
Urea variable (diffusion)
Creatinine small amount
At end of PCT, tubular fluid is still isotonic to blood (300 mOsm/liter).
LOOP OF HENLE
Reabsorption (into blood) of:
Water 15% (osmosis in descending limb)
Na+ 20–30% (symporters in ascending limb)
K+ 20–30% (symporters in ascending limb)
Cl− 35% (symporters in ascending limb)
HCO3− 10–20% (facilitated diffusion)
Ca2+, Mg2+ variable (diffusion)
Secretion (into urine) of:
Urea variable (recycling from collecting duct)
At end of loop of Henle, tubular fluid is hypotonic (100–150 mOsm/liter).
Urine
RENAL CORPUSCLE
Glomerular filtration rate: 105–125 mL/min of fluid that is isotonic to blood
Filtered substances: water and all solutes present in blood (except proteins) including ions, glucose, amino acids, creatinine, uric acid
DISTAL CONVOLUTED TUBULE
Reabsorption (into blood) of:
Water 10–15% (osmosis)
Na+ 5% (symporters)
Cl− 5% (symporters)
Ca2+ variable (stimulated by parathyroid hormone)
PRINCIPAL CELLS IN LATE DISTAL TUBULE AND COLLECTING DUCT
Reabsorption (into blood) of:
Water 5–9% (insertion of water channels stimulated by ADH)
Na+ 1–4% (sodium-potassium pumps)
Urea variable (recycling to loop of Henle)
Secretion (into urine) of:
K+ variable amount to adjust for dietary intake (leakage channels)
Tubular fluid leaving the collecting duct is dilute when ADH level is low and concentrated when ADH level is high.
INTERCALATED CELLS IN LATE DISTAL TUBULE AND COLLECTING DUCT
Reabsorption (into blood) of:
HCO3− (new) varible amount, depends on H+ secretion (antiporters)
Urea variable (recycling to loop of Henle)
Secretion (into urine) of:
H+ variable amounts to maintain acid-base homeostasis (H+ pumps)

DIURETICS: DEFINITION,

- Diuretics as “water pills”
- promote excretion of urine
- Increases the excretion of water from body
- cause a net loss of Na+ and water in urine
- Ion transport inhibitors that decrease the reabsorption of Na+ at different sites in the nephron

NORMAL REGULATION OF FLUID AND ELECTROLYTES BY THE KIDNEYS

- Approximately 16-20% of the blood plasma entering the kidneys is filtered from the glomerular capillaries into Bowman's capsule.
- These include glucose, sodium bicarbonate, amino acids, and other organic solutes, plus electrolytes, such as Na +, K +, and CI-.
- The kidney regulates the ionic composition and volume of urine by reabsorption or secretion of ions and/or water at five functional zones along the nephron,
  - Proximal convoluted tubule,
  - Descending loop of Henle,
  - Ascending loop of Henle,
  - Distal convoluted tubule,
  - Collecting duct

five functional zones and the Drugs

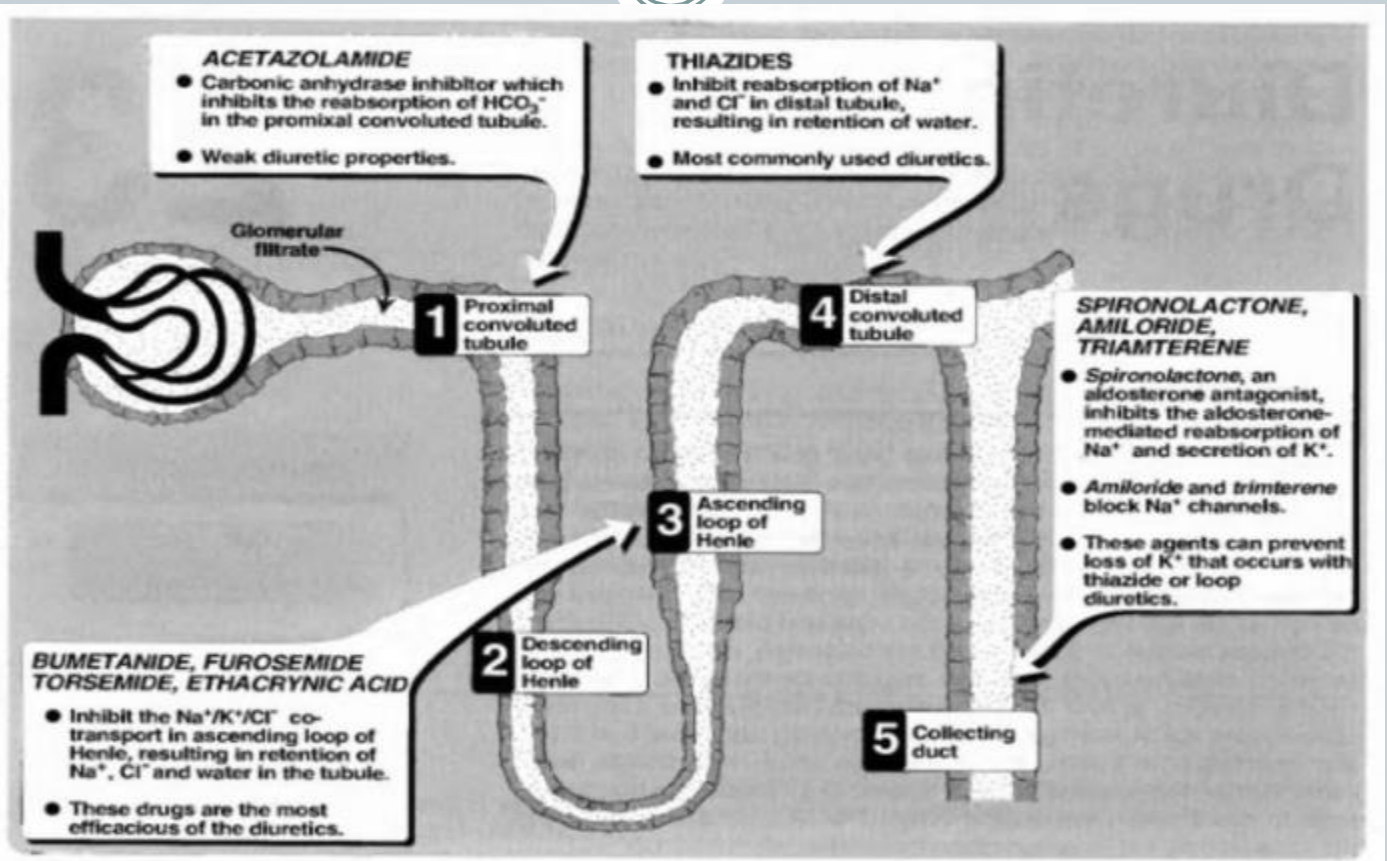
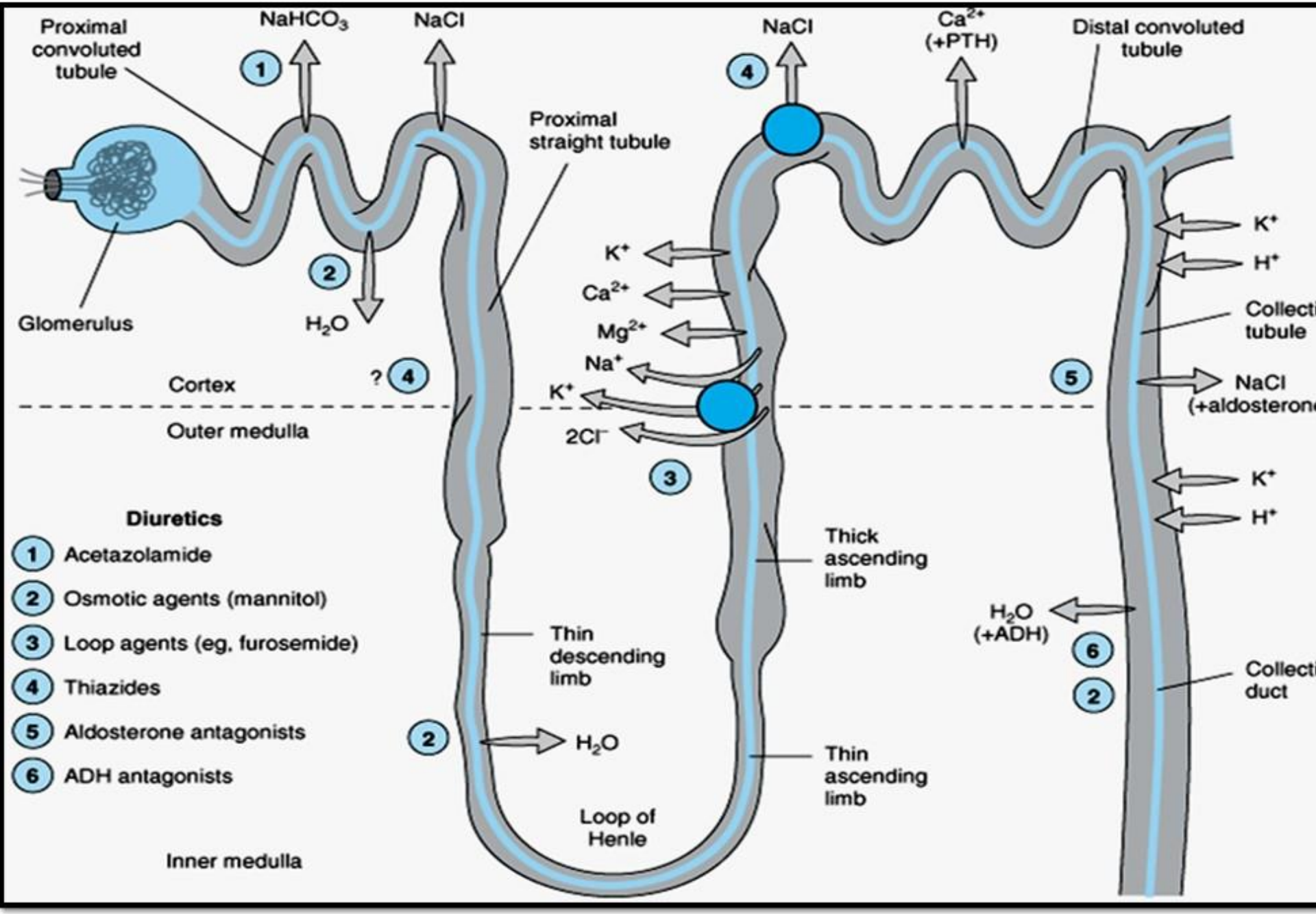
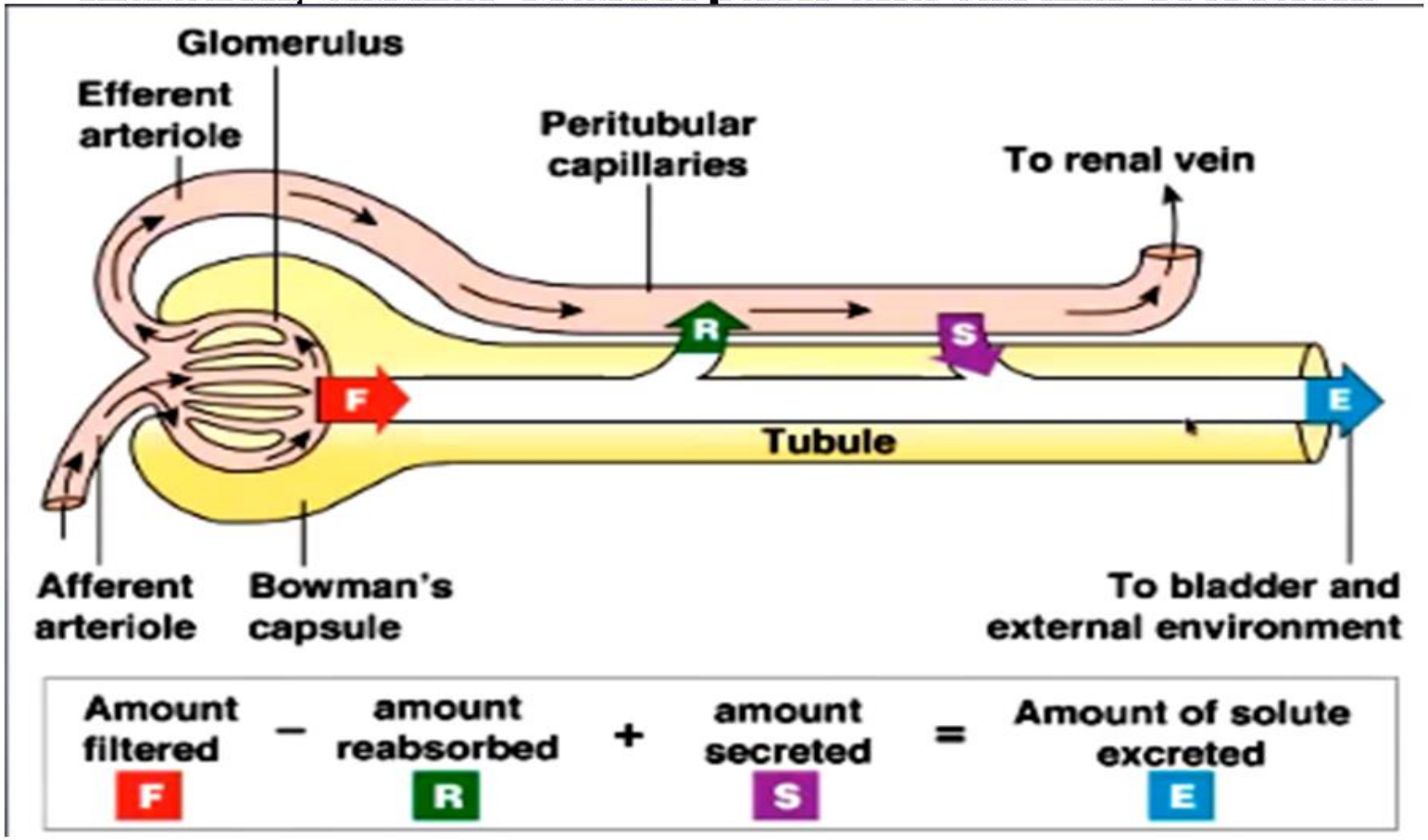


Figure 23.2
Major locations of ion and water exchange in the nephron, showing sites of action of the diuretic drugs.

Electrolyte Transport and Site of Action of Diuretics



The excretion by kidney is dependent on: glomerular filtration, tubular reabsorption and tubular secretion.



Amount filtered	–	amount reabsorbed	+	amount secreted	=	Amount of solute excreted
F		R		S		E

Proximal convoluted tubule

- Almost all of the glucose, bicarbonate, amino acids, and other metabolites are reabsorbed.
- Approximately two thirds of the Na + is also reabsorbed in the proximal tubule; chloride and water follow passively to maintain electrical and osmolar equality.
- The proximal tubule is the site of the organic acid and base secretory systems
- The secretory system secretes a variety of organic acids (such as uric acid, some antibiotics, diuretics) from the blood- stream into the proximal tubule's lumen.
- Most diuretic drugs are delivered to the tubular fluid via this system.

Descending and Ascending loop of Henle

- Isotonic filtrate enters the descending limb and passes into the medulla of the kidney.
- Osmolarity increases along the descending portion because of the countercurrent mechanism.
- This results in a tubular fluid with a three-fold increase in salt concentration.
- Impermeable to water.
- Active reabsorption of Na +, K + and CI- is mediated by a Na+/K+/2CI - cotransporter.
- Mg ++ and ca ++ enter the interstitial fluid via the paracellular pathway.
- A diluting region of the nephron.
- Approximately 25-30% of the tubular sodium chloride returns to the interstitial fluid, thus helping to maintain the fluid's high osmolarity.

Distal convoluted tubule

- impermeable to water.
- About 10% of the filtered sodium chloride is reabsorbed via a Na+/CI - transporter, which is sensitive to thiazide diuretics

Collecting tubule and duct

- Responsible for Na + K + exchange and for H + secretion and K + reabsorption, respectively
- Stimulation of aldosterone receptors in the principal cells results in Na + reabsorption and K + secretion.
- Antidiuretic hormone (ADH, vasopressin) receptors promote the reabsorption of water from the collecting tubules and ducts.

KIDNEY FUNCTION IN DISEASE

- In many diseases the amount of sodium chloride reabsorbed by the kidney tubules is abnormally high
- This leads to the retention of water, an increase in blood volume, and expansion of the extravascular fluid compartment, resulting in edema of the tissues

Diuretics are effective in the treatment of following:

- Edema due to CCF, Pregnancy and Nutritional
- Nephrotic syndrome
- Diabetes Insipidus
- Hypertension
- Cirrhosis of the Liver

CLASSIFICATION

Diuretics are Classified as:

1. High ceiling /Loop diuretics…
2. Thiazides.
3. Carbonic anhydrase inhibitors.
4. Potassium –sparing diuretics.
5. Osmatic diuretics.

LOOP OR HIGH-CEILING DIURETICS

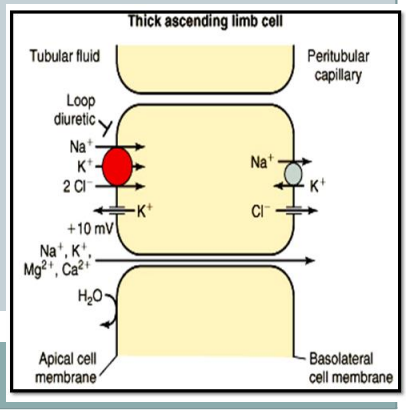
1. LOOP/HIGH CEILING DIURETICS:

(Inhibitors of Na+,K+,2Cl- cotransport)

Mechanism of action:

- Loop diuretics inhibit the Na+/K+/CI - cotransport of the luminal membrane in the ascending limb of the loop of Henle.
- Therefore reabsorption of Na +, K +, and CI- is decreased
- Inhibits reabsorption of 25% of the glomerular filtration

Examples : Furosemide, Bumetanide, Torasemide ,Ethacrynic acid.

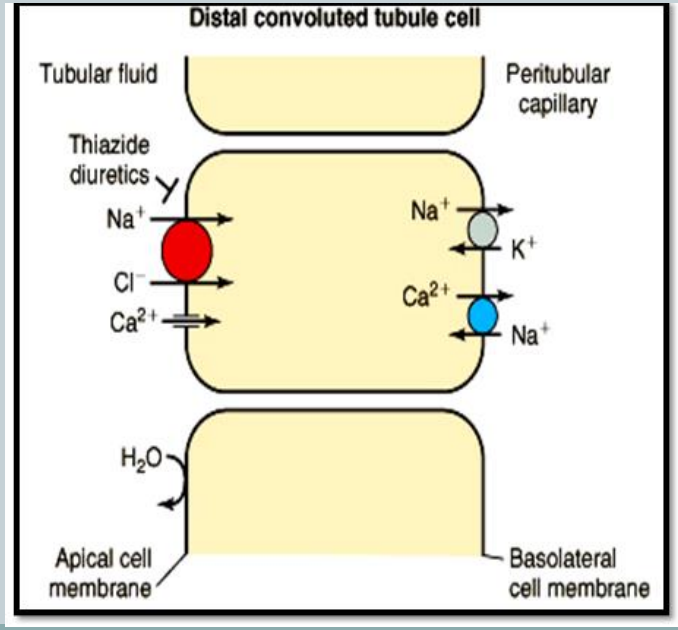


LOOP OR HIGH-CEILING DIURETICS

- The loop diuretics act promptly, patients with poor renal function or who have not responded to thiazides or other diuretics.
- Loop diuretics increase the Mg++ and Ca ++ content of urine, while thiazide diuretics decrease the Ca ++ concentration of the urine.
- The loop diuretics cause decreased renal vascular resistance and increased renal blood flow

Therapeutic Uses

- Edema; Pulmonary, cardiac, renal
- Chronic Renal failure
- Hypertension
- Hypercalcemia
- Acute and Chronic Hyperkalemia



Pharmacokinetics

- Routes of admin: Oral, IV, IM
- Rapid on Set of action about 1-1.5hours e.g Fuseromide
- Bind to plasma proteins and can displace warfarin
- Increase toxicity of Cephalosporin and Lithium
- Additive toxicity with other ototoxic drugs
- Inhibitors of organic acid reduce potency e.g. probenecid and NSAIDS

Adverse effects ;

- Ototoxicity
- Hyperuricemia:
  - Furosemide and ethacrynic acid compete with uric acid for the renal and biliary secretory systems, thus blocking its secretion and thereby causing or exacerbating gouty attacks.
- Acute hypovolemia
- Hyponatremia
- Metabolic Alkalosis
- Potassium depletion (Hypokalemia)

THIAZIDE DIURETICS

2.Medium efficacy diuretics :(Inhibitors of Na+,Cl- symport)

- Examples Chlorthiazide (Prototype), Hydrochlorothiazide, Most widely used of the diuretic drugs.

Mechanism of Action

- They are sulfonamide derivatives and are related in structure to the carbonic anhydrase inhibitors, but more diuretic effect
- Thiazide derivatives act mainly in the distal tubule to decrease the reabsorption of Na + by inhibition of a Na+/CI - cotransporter on the luminal membrane
- Increase Na+ and Cl- Excretion
- Weak inhibitor od Carbon anhydrous, increased HCO_3 excretion
- Increased Mg++ and K+ excretion
- Decrease calcium excretion

Therapeutic Uses

- Hypertension:
  - mainstay treatment; inexpensive, convenient to administer, and well tolerated.
- Congestive heart failure:
- Hypercalciuria:
  - beneficial for patients with calcium oxalate stones in the urinary tract.
  - Osteoporosis

Pharmacokinetics:

- The drugs are effective orally.
- Most thiazides take 1 to 3 weeks to produce a stable reduction in blood pressure,
- Exhibit a prolonged biological half-life (40 hours).
- All thiazides are secreted by the organic acid secretory system of the kidney

Adverse Effects

- Hypokalemia
- Hyponatremia
- Hyperglycemia
- Diminished insulin secretions
- Hypercalcemia
- Hyperuricemia

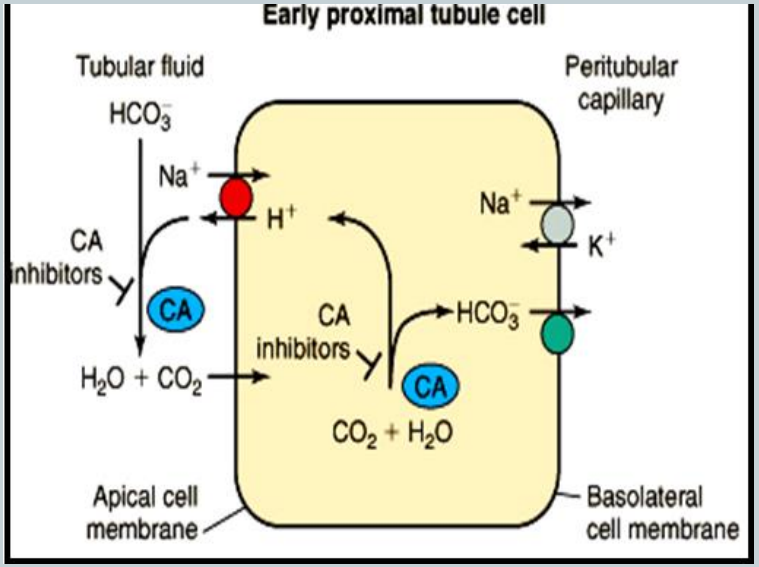
WEAK OR ADJUNCTIVE DIURETICS

Weak or adjunctive diuretics:

1. Carbonic anhydrase inhibitors: Acetazolamide
2. Potassium –sparing diuretics:
   - ❑ Aldosterone antagonist:
     a) Spironolacton
     b) Eplerenone.
   - ❑ Inhibitors of renal epithial Na+ channel:
     a) Trimterene.
     b) Amiloride.

CARBONIC ANHYDRASE INHIBITORS

- Acetazolamide is a sulfonamide without antibacterial activity.
- Its main action is to inhibit the enzyme carbonic anhydrase in the proximal tubular epithelial cells.
- This results in several effects including bicarbonate retention in the urine.
- Potassium retention in urine.
- Decreased sodium absorption.



Therapeutic uses:

❖ Treatment of glaucoma:

- The most common use of acetazolamide is to reduce the elevated intraocular pressure of open- angle glaucoma.
- It is useful in the chronic treatment of glaucoma but should not be used for an acute attack

❖ Epilepsy

- Acetazolamide is used chronically in conjunction with antiepileptic medication to enhance the action of these other drugs.
- Sometimes used in epilepsy--both generalized and partial. It reduces the severity and magnitude of the seizures.

Adverse Effects

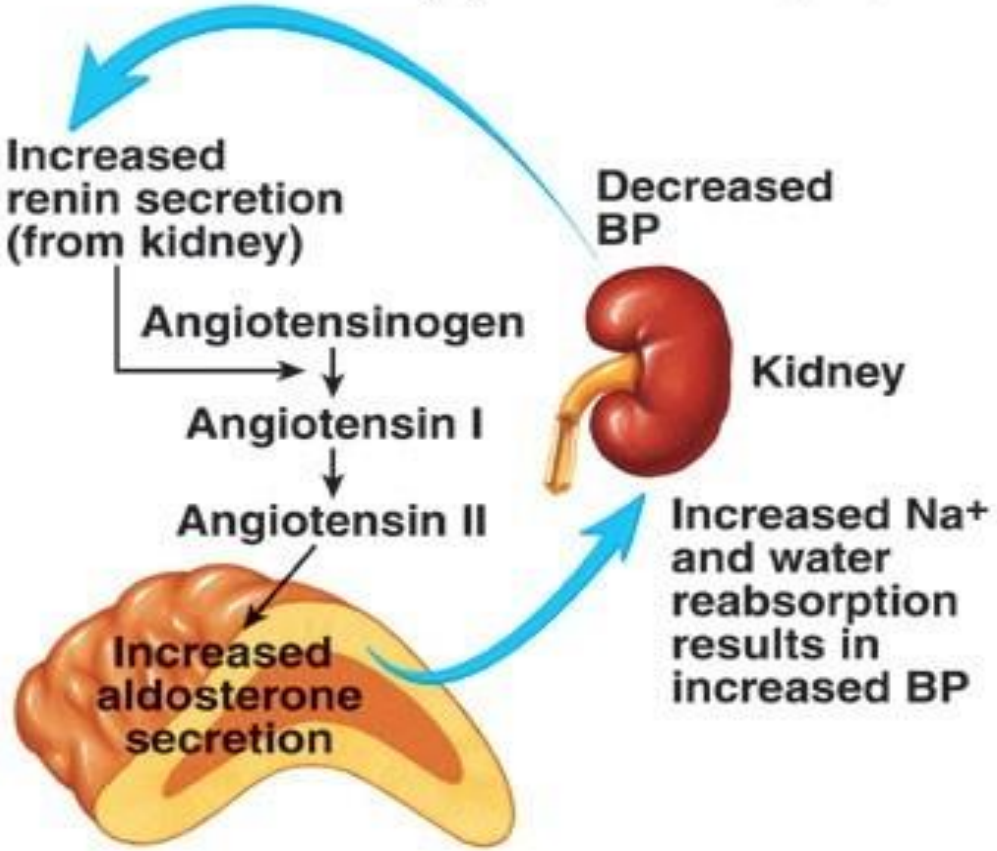
- Rapid tolerance
- Increased HCO_3 cause metabolic Acidosis
- Drowsiness
- Fatigue
- CNS depression
- Paresthesia (Pins and needles under the skin)
- Nephroliathsis (Renal Stones)

POTASSIUM-SPARING DIURETICS

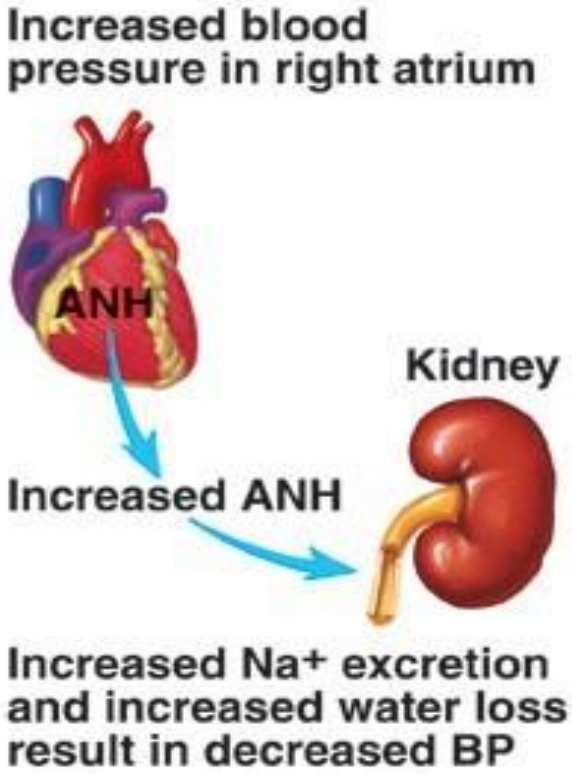
- These are diuretics which do not promote the secretion of potassium into the urine.
- Potassium is retained unlike other diuretics.
- The term potassium sparing refers to pharmacological effects rather than a mechanism or location.
- K+ sparing function in the Collecting tubes
- Decrease Na+ transport in the collecting tubes
- Eg: Aldosterone antagonists Spironolactone

Aldosterone antagonists Spironolactone

- K+ sparing diuretics decrease Na+ transport in the collecting tubules
- Spironolactone
  - Competitive inhibitor on mineralocorticoids receptor
  - Competitively binds to the Aldosterone receptor thus inhibiting the actions and effects of aldosterone
  - Prevents aldosterone stimulated increase of Na+ transport expression.
  - Inhibits distal Na+ retention and K+ secretion
  - Eg: Eplerenone.
- Epithelial sodium channel blockers
  - Eg: Amiloride, Triamterene



(a) Low blood pressure (BP) stimulates renin secretion from the kidney. Renin stimulates the production of angiotensin I, which is converted to angiotensin II, which in turn stimulates aldosterone secretion from the adrenal cortex. Aldosterone increases Na^+ and water reabsorption in the kidney.



(b) Increased blood pressure in the right atrium of the heart causes increased secretion of atrial natriuretic hormone (ANH), which increases Na^+ excretion and water loss in the form of urine.

Therapeutic uses

- Hyperaldosteronism
- Adrenal Adenoma, bilateral adrenal hyperplasia, Hirsutism.
- Congestive Heart Failure
- Cirrhosis
- Nephrotic syndrome togather with loop/ thiazide diuretics
- Can prevent hypokalemia when used with other diuretics (Loop/Thiazide)

Adverse Effects

- Hyperkalemia –Monitor K+ Plasma levels
- Spironolactone –Gynecomastia
- Triamterene - Megaloblastic anemia in cirrhosis patients
- Amirolide - Increase blood urea nitrogen, glucose intolerance in Diabetes Mellitus

OSMOTIC DIURETICS

- Do not directly inhibit a receptors or block renal transport
- Actively dependent on the development of osmotic pressure
- The compounds as Mannitol are filtered in the glomerulus, but cannot be reabsorbed.
- Their presence lead to an increases in the osmolality of the filtrate.

OSMOTIC DIURETICS

- To maintain osmotic balance ,water is retained in the urine.
- Glucose like mannitol behave as an osmotic diuretic.
- Glucosuria causes a loss of hypotonic water & Na+,
- leading to a hypertonic state with signs of volume depletion.
- Such as Hypotention,Tachycardia.
- Examples:
  - Mannitol
  - Glycerol
  - Urea
  - Isorsobide

Mechanism of action

- Osmotic diuretics are not reabsorbed
- Increases Osmotic pressure specifically in the proximal tubules and the loop Henle
- Prevents passive reabsorption of water
- Osmotic pressure in the lumen> Osmotic force of the reabsorbed sodium
- Increased water and Na+ excretion

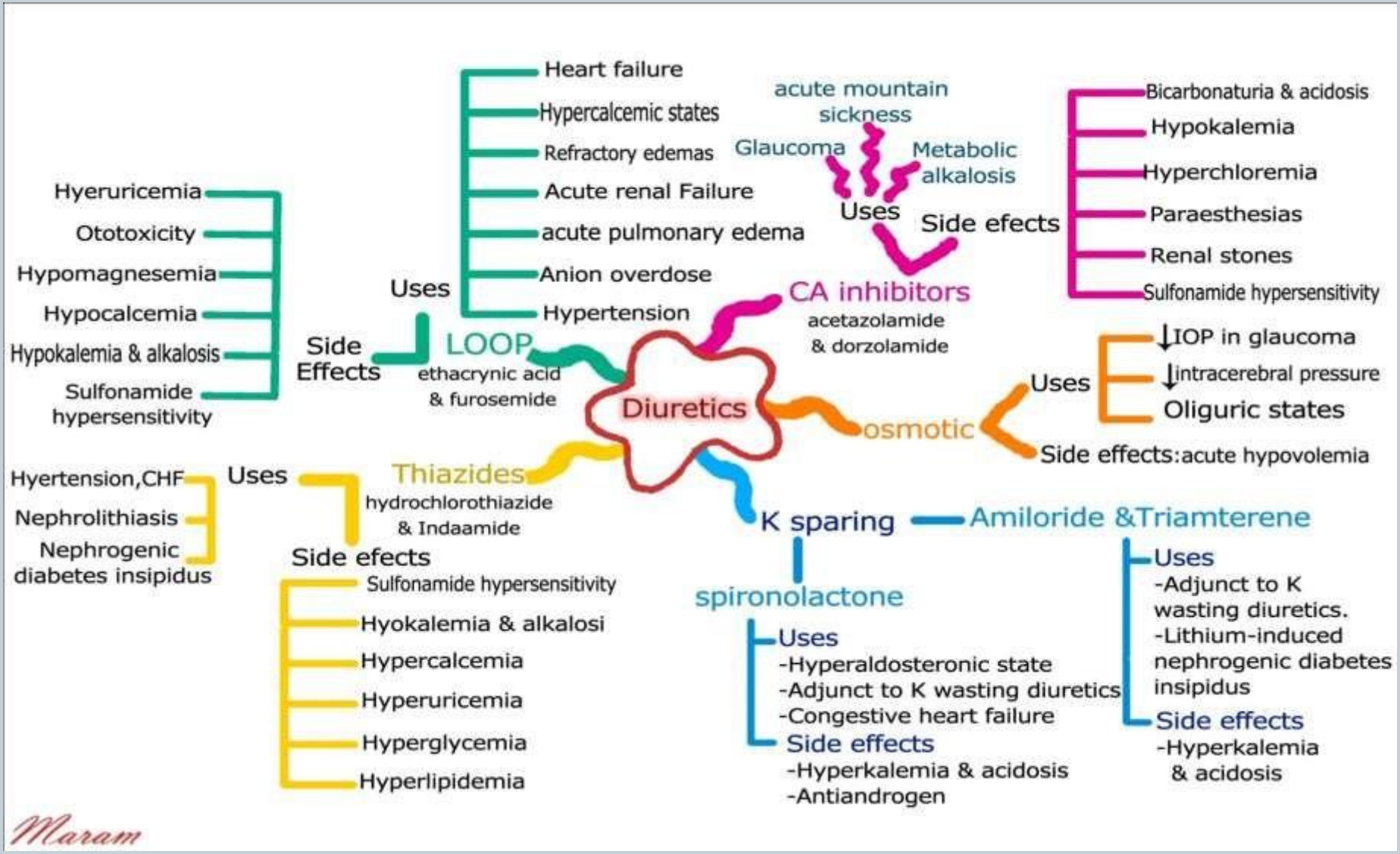
Therapeutic Uses : Mannitol

- Drug of choice, Non toxic, freely filtered, non reabsorbed, non metabolized
- Administered prophylactically for acute renal failure secondary to trauma, CVS Disease, Surgery, Nephrotoxic drugs
- Short term treatment of acute glaucoma
- Fused to lower intracranial pressure
- Urea, Glycerol and Isosorbide are less effective

Adverse Effects

- Increased extracellular fluids volume
- Cardiac failure
- Pulmonary edema
- Hypernatremia
- Hyperkalemia secondary to diabetes mellitus or renal impairment
- Headache, Nausea and Vomiting

USES AND SIDE EFFECTS OF DIURETICS



ANTI- DIURETICS HORMONE

1.Anti diuretic homone(ADH) and its analogues:

Vasopressin.

Desmopressin.

Lypressin.

Terlipressin.

2.Diuretics:

Thiazides.

Amiloride.

3. Miscellineous:

Chlorpropamide.

Carbamazepine.

ANTI- DIURETICS HORMONE AGONOST AND ANTAGONIST

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3. Miscellineous:

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Carbamazepine.

ANTI- DIURETICS HORMONE AGONOST AND ANTAGONIST

- Secretion of ADH increases in response to Increased plasma osmolarity
- Hypovolemia, Hypotension (Bleeding, dehydration
- Demecycline and conivaptan are ADH antagonist
- Lithium also has some antagonist effects but never used for this purpose

ANTI- DIURETICS HORMONE

- Hormone (protein) secreted by posterior pituitary (neurohypophysis)
- Rate of ADH Release controlled by:
  - Osmoreceptors present in hypothalamus
  - Volume receptors present in left atrium, ventricles and pulmonary veins
- Physiological Stimuli for ADH release:
  - Rise in plasma osmolarity
  - Contraction of plasma extracellular fluid (e.c.f.) volume

ADH receptors

- V 1 Receptors At all sites except for sites of V 2 (i.e. Collecting Duct cells)
  - vascular smooth muscles (including that of vasa recta in renal medulla), uterine, visceral smooth muscles, interstitial cells in renal medulla, cortical CD cells, adipose tissue, brain, platelets, liver, etc.
  - : anterior pituitary, certain areas in brain and in pancreas
- V2 Receptors: more sensitive
  - Collecting Duct Principal cells in Kidney:
  - Regulates their water permeability
  - Also present in AscLH cells: Activates Na+K+2Cl cotransporter
  - Endothelium: vasodilator

Action on Various Organs

- **Kidneys:**
  - Acts on CD principal cells -renders them water permeable -water
  - absorbed □ concentrated urine (equilibrating with hyperosmolar
  - medulla) passed
- **Blood Vessels:**
  - Constricts through V1 receptors : raises blood pressure
  - Dilates through V2 receptors: endothelium dependent NO production

ADH receptors

- **GIT:**
  - Increased peristalsis: evacuation and expulsion of gases
- **Uterus:**
  - Contracted by acting on oxytocin receptors
- **Central Nervous System**
  - Endogenous AVP may be involved in regulation of temperature,
  - systemic circulation, ACTH release, learning of tasks
- **Others:**
  - Induces platelet aggregation, hepatic glycogenolysis
  - Release of factor VIII and von Willebrand's factor from vascular
  - endothelium : V2 mediated

ADH receptors

V_2R:

- Principal cells of Collecting Duct: increased aquaporin expression leading to
- increased water absorption -decreased urine formed.
- Augmented by concurrent decrease in endocytosis and degradation of aquaporins
- Continued stimulation leads to increased production of aquaporins
- Increased Vasopressin regulated urea transporter expression in terminal CD cells
- increased medullary hypertonicity - increased water absorption - decreased

Mechanism of action

V_2 urine formed

i. Increased translocation and synthesis of Na+K+2Cl- channels in ascending limb of

ii. loop of Henle → increased medullary hypertonicity → concentrated urine formed

V_1R

i. Constricts vasa recta: diminished blood flow to inner medulla: reduces washing off effect and helps in maintaining high osmolarity; contributing to antidiuresis

USES

- Based on V2 Actions:
  - Diabetes Insipidus (Neurogenic)
  - Bedwetting in children and nocturia in adults
  - Renal Concentration Test
  - Hemophilia, von Willebrand's Disease
- Based on V1 Actions:
  - Bleeding Esophageal Varices
  - Before abdominal radiography

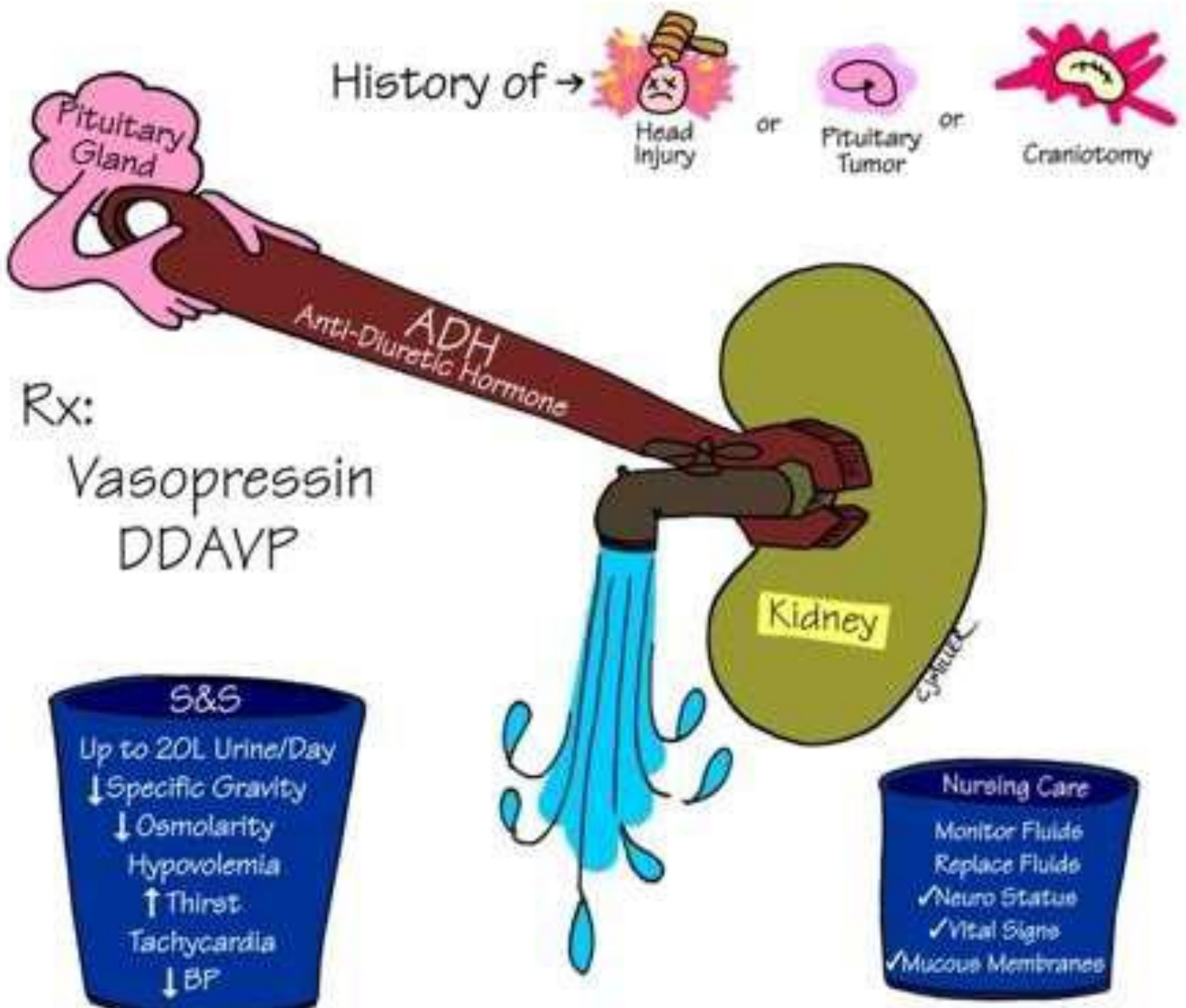
Vasopressin: Adverse Effects

- Selective drugs produce lesser side effects
- Transient headache and flushing: frequent
- Local Application: Nasal irritation, congestion, rhinitis, ulceration, epistaxis
- Systemic Side effects: belching, nausea, vomiting, abdominal cramps, pallor, urge to defecate, backache in females (uterine contraction)
- Fluid retention, hyponatremia
- Contraindicated in patients with Ischaemic heart disease,
- hypertension, chronic nephritis, psychogenic polydipsia

Other Antidiuretics

- Indomethacin
  - Reduces renal PG synthesis ☐ reduced polyuria in nephrogenic DI.
  - Combined with thiazide +/- amiloride
  - Other NSAIDs less active
- Chlorpropamide
  - Long acting sulfonylurea oral hypoglycaemics
  - Effective in neurogenic DI: sensitizes kidney to ADH
- Carbamazepine
  - Antiepileptic
  - Effective in neurogenic DI
  - Higher Doses needed: marked adverse effects

DIABETES INSIPIDUS

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YOU