DIURETICS

Dr. Kushan Medagoda

Nephron is the most important part of the kidney that regulates fluids and electrolites

- URINE FORMATION
  - Glomerular filtration how many litres per 24 hours
  - Tubular reabsorption (around 98%)
  - Tubular secretion

- **HOW COULD URINE OUTPUT BE INCREASED**
- Increase glomerular filtration vs decrease tubular reabsorption(the most important clinically)

- **PURPOSE OF USING DIURETICS**

1.to maintain urine volume(eg:-Renal failure)

2.to mobilize oedema fluid

Eg:- Heart failure, liver failure, nephrotic syndrome

3.to control high blood pressure

FACTS OF RENAL PHYSIOLOGY

- Kidney
  - Weight-0.5% of body
  - Receive 25% of cardiac output
- Kidney functions
  - **B**alance of electrolytes , plasma volume , acid base
  - **A**ctivation of vit B
  - **S**ynthesis of erythropoietin urokinase
  - **E**xcretion of urea uric acid creatinine etc
- Transport types
  - Passive
    - Simple, channel mediated and facilitated diffusion, solvent drag
  - Active
    - Primary and secondary (symports and secondary counter transports

FACTS RELATED TO RENAL PHYSIOLOGY

- **Pressure difference** at bowman's capsule 20mmHG
- **Filter** = Plasma proteins
- **Volume** of
  - Filtered 180l
  - Urine 1.5l(1%)
- **Kidneys**
  - Renal blood flow 1200ml per minute
  - Renal plasma flow 650ml per minute
  - GFR 120ml per minute
  - Reabsorb NaCl and bicorbonates > 99%
  - While K about 85%

TERMINOLOGY

- **NATRIURESIS** – increase sodium excretion
- **KALIURESIS** – Increased Potassium excretion
- **DIURETICS** – Drugs which cause a net loss of sodium and water in urine (exception – osmotic dry uretics (Mannitol) don’t cause natriuresis but produce dry uresis

PROXIMAL TUBULE

- Leaky – Freely permeable to Water , Solutes
- Active absorption of
  - Sodium chloride
  - -sodium bicarbonate
  - -Glucose
  - -Amino acids
  - -Organic solutes
    - followed by passive absorption of water

LOOP OF HENLE

- Descending limb
  - Permeable to water
- Thick ascending limb
  - Impermeable to water but
  - Permeable to sodium by **Na+K+2Cl- co transport**
  - About 25% of filtered sodium is absorbed here

Nephron parts and their functions

SEGMENT	FUNCTION
Glomerulus	Formation of glomerular filtrate
Proximal convoluted tubule (PCT)	Reabsorption of 65% of filtered Na+/K+/ Ca2+, and Mg2+; 85% of $NaHCO_3$, (activity of Carbonic an-hydrase enzyme) and nearly, 100% of glucose and amino acids. Iso-osmotic reabsorption of water., Secretion and reabsorption of organic acids and bases, including uric acid and most diuretics
Thin descending limb of Henle's loop	Passive reabsorption of water
Thick ascending limb of Henle's loop (TAL)	**Active reabsorption of 25% of filtered $Na^+/K^+/2Cl^-$; secondary re-absorption of Ca2+ and Mg2+**
Distal convoluted tubule (DCT)	Active reabsorption of 4–8% of filtered Na^+ Cl^-; Ca2+ reabsorption under parathyroid hormone control
Cortical collecting tubule (CCT)	Na+ reabsorption (2–5%) coupled to K+ and H+ secretion (under **Aldosterone**)
Medullary collecting duct	Water reabsorption under **Vasopressin** control

MACULA DENSA and JUXTAGLOMERULAR APPARATUS

- Contact between ascending limb with afferent arterioles - by specialized columnar epithelial cells **macula densa**
- Macula densa sense NaCl conc. Infiltrate
- Give signal to **J.G cells** present in afferent arterioles
- J.G cells of afferent arterioles secrete Renin

RAAS IN RESPONES TO LOW BP , or LOW Na

Renin

Angiotensinogen ->->->Angiotensin 1

ACE

Angiotensin 1->->-> Angiotensin 2

Effects of angiotensin

Early distal tubule

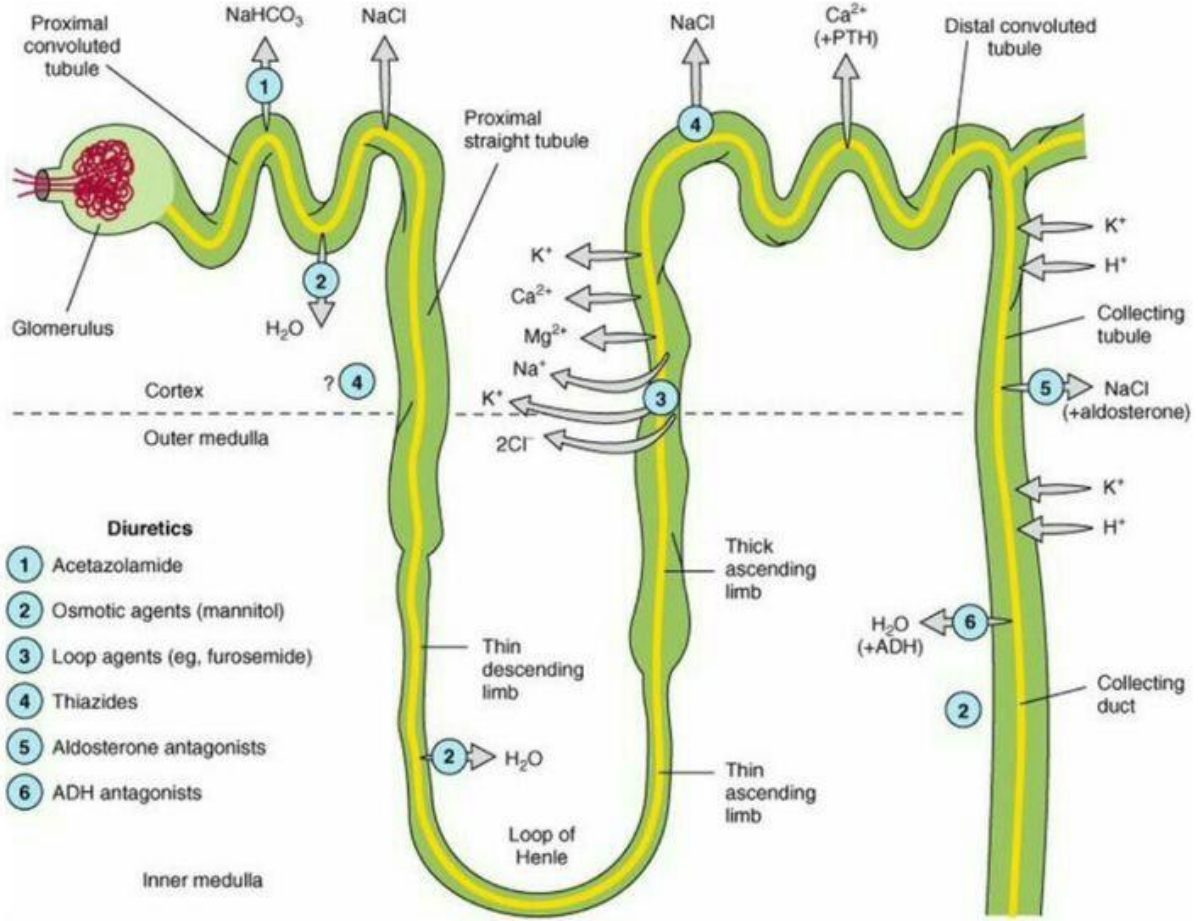
- Active transport of sodium by **NaCl symport**
- Calcium excretion is regulated (poarathomone and calcitriol, increase absorption of calcium)

Collecting tubules and collecting ducts

- Aldosterone- on membrane receptor and cause sodium absorption by Na+ / H+/ K+ Exchange

- ADH- collecting tubular epithelium permeable to water (Water enters to aquaporin 2)

Diuretic	Site of Action	Adverse Effects	Special points
Carbonic anhydrase inhibitors	PTC (inhibition of CAE)	Metabolic Acidosis	Weak, Used in Glaucoma, Petit mal epilepsy, Acute mountain sickness, to alkaline the urine
Osmotic Diuretics	PTC, LOH, DCT (Osmotic retention of water, Dilates Afferent arterioles, Increased hydrostatic pressure in glomerulus	Shifting of fluid from intracellular to extracellular, Hyponatremia, Pulmonary edema	Potent Used in Glaucoma, Poisoning, Increased ICT, impending ARF
Loop Diuretics	Thick Ascending Limb of Henle (NaK2Cl inhibition) Weak CAI action	Hyponatremia Hypomagnesaemia Hypocalcaemia Hyperuricemia Hyperglycemia Hyperlipidemia Hyperuricemia Ototoxic (ECA)	Most potent, Most Potent is Bumetanide, Effective even in low GFR, All except Ethacrynic acid are sulphonamide related, Venodilatation, Decrease Left Ventricle Pressure, Used in Acute LVF, Pulmonary Edema, Nephrotic syndrome, ARF, NSAIDS blunt effect, Cerebral edema, short term tt of Hypertension, to reduce volume overload during transfusion,
Thiazide Diuretics	DCT (NaCl)	Hypokalemic metabolic alkalosis (Gitelman's Syndrome) Hypercalcemia	Moderate, Chlorthalidone is Longest acting, Paradoxical effect in Diabetes Insipidus First line in Hypertension,
Potassium Sparing Diuretics	CD	HyperKalemia Antiandrogenic effect	Weak, As supplement to other to counter the hypokalemia, Canrenone is active metabolite, used in Conn's syndrome (Primary Hyperaldosteronism) cirrhotic edema, polycystic ovary



Potassium-sparing Diuretics

For potassium-sparing diuretics, think of SEAT

Aldosterone antagonists	**S**pironolactone **E**plerenone
Epithelial sodium channel blockers	**A**miloride **T**riamterene

@PharmaFactz

Diuretics classification in order of site of action

"**COLT P**ee:"

· In their sequential site of action along the nephron:

Carbonic anhydrase inhibitors (at the proximal tubule)

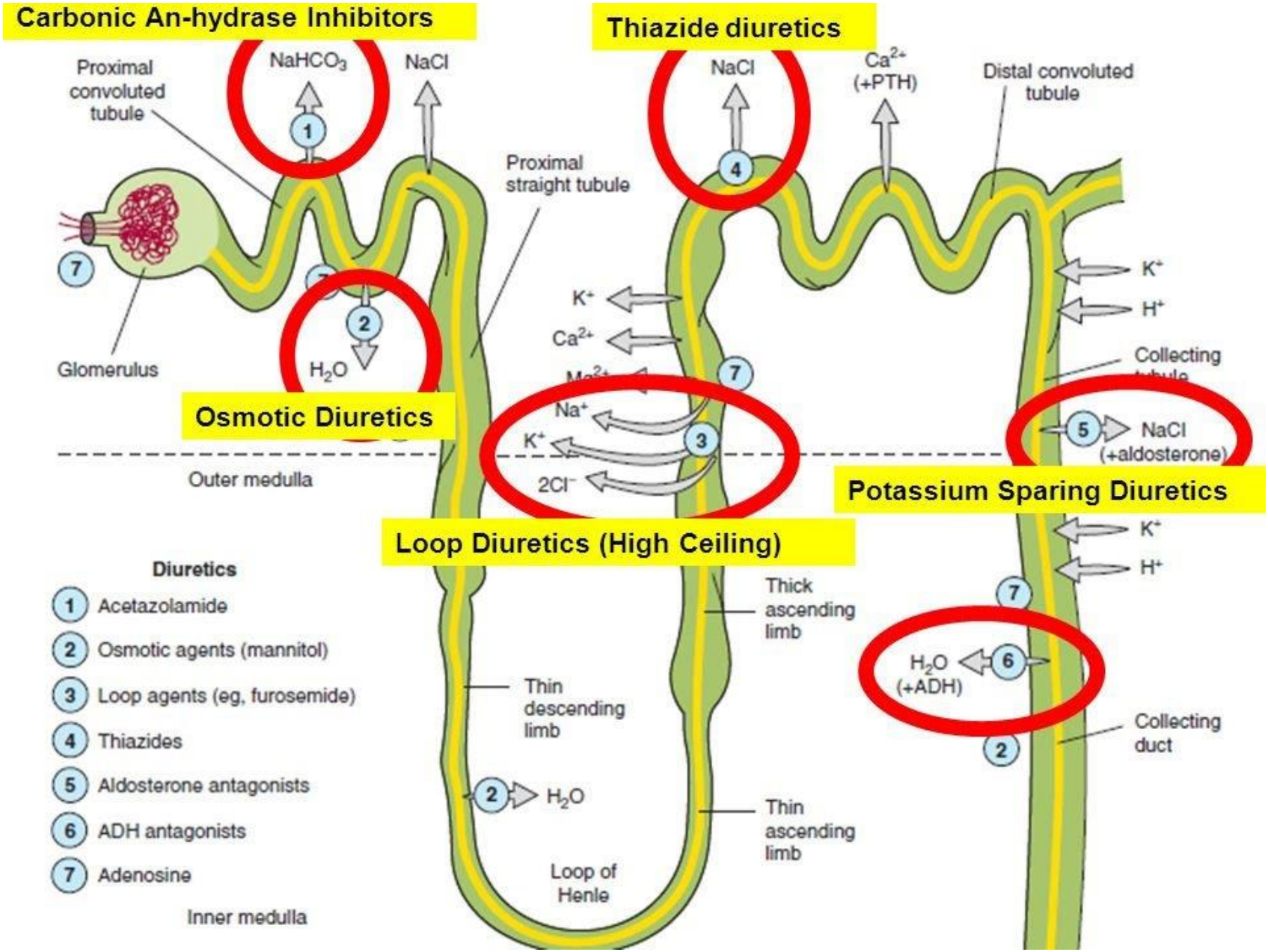
Osmotic diuretics (at the Loop of Henle)

Loop diuretics (at the ascending loop)

Thiazides (at the distal tubule)

Potassium-sparing diuretics (at the collecting tubules)

· Diuretics make patient pee like a horse, hence "Colt Pee".


Carbonic An-hydrase Inhibitors
Thiazide diuretics
Proximal convoluted tubule
$NaHCO_3$
NaCl
NaCl
Ca^{2+} (+PTH)
Distal convoluted tubule
Proximal straight tubule
Glomerulus
H_2O
K^+
Ca^{2+}
Na^+
K^+
$2Cl^-$
K^+
H^+
Collecting tubule
NaCl (+aldosterone)
Osmotic Diuretics
Outer medulla
Potassium Sparing Diuretics
Loop Diuretics (High Ceiling)
Thick ascending limb
Thin descending limb
H_2O
Thin ascending limb
Loop of Henle
H_2O (+ADH)
Collecting duct
Inner medulla
Diuretics
1 Acetazolamide
2 Osmotic agents (mannitol)
3 Loop agents (eg, furosemide)
4 Thiazides
5 Aldosterone antagonists
6 ADH antagonists
7 Adenosine

Classification of diuretics

- The best way to classify diuretics is to look for their site of action in the nephron.

- Diuretics that inhibit transport in the proximal convoluted tubule(Osmotic diuretics M; carbonic anhydrase inhibitors)
- Diuretics that inhibit Na+ /K+ 2Cl – co transporters in the medullary ascending limb of the loop Henle.(Loop diuretics)
- Diuretics that inhibit Na+/Cl- co transporter in the distal convoluted tubule (Thiazides, Indapamide, Metolazone)
- Diuretics that inhibit Na+/K+ transport in the cortical collecting tubule by inhibiting action of aldosterone(K+ spring diuretics) spironolactone.

Classification of Diuretics

- The best way to classify diuretics is to look for their Site of action in the nephron

A) Diuretics that inhibit transport in the Proximal Convoluted Tubule (Osmotic diuretics, Carbonic Anhydrase Inhibitors)

B) Diuretics that inhibit transport in the Medullary Ascending Limb of the Loop of Henle(Loop diuretics)

C) Diuretics that inhibit transport in the Distal Convoluted Tubule(Thiazides : Indapamide , Metolazone)

D) Diuretics that inhibit transport in the Cortical Collecting Tubule (Potassium sparing diuretics)