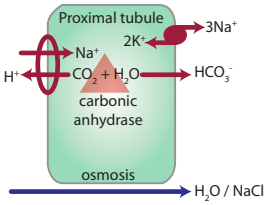
DIURETICS

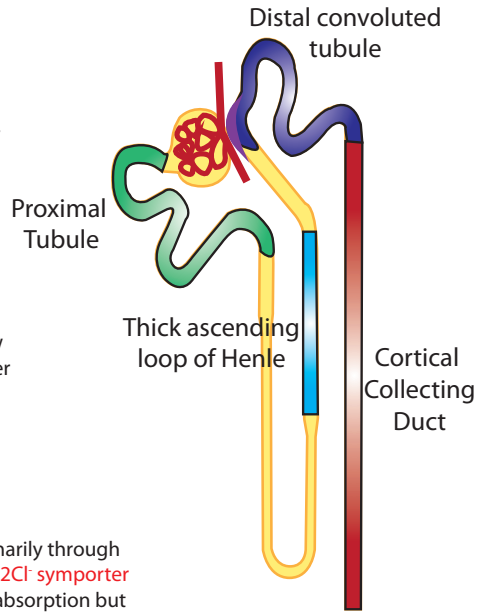
Diuretics are drugs that increase the rate of urine flow; clinically useful diuretics also increase the rate of excretion of Na+ (natriuresis) and an accompanying anion, usually Cl–. Most clinical applications of diuretics aim to reduce extracellular fluid volume by decreasing total-body NaCl content. As previously described the osmolality is the most important determinant of total body water. Although continued administration of a diuretic causes a sustained net deficit in total-body Na+, the time course of natriuresis is finite because renal compensatory mechanisms bring Na+ excretion in line with Na+ intake, a phenomenon known as diuretic braking. Compensatory mechanisms include activation of the sympathetic nervous system, activation of the renin–angiotensin–aldosterone axis, decreased arterial blood pressure (which reduces pressure natriuresis), hypertrophy of renal epithelial cells, increased expression of renal epithelial transporters, and perhaps alterations in natriuretic hormones such as atrial natriuretic peptide. Therefore several days after initiation of a diuretic a new steady state is established with lower overall TBW. Diuretics are typically classified in two ways. Firstly into two groups based on the principle action, which is either naturesis (loss of sodium) or aquaresis (loss of water directly). The most common slassification system is based on the site of action in the kidneys and specific mechanisms. This is shown below.

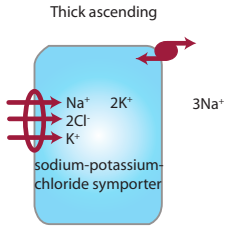


Proximal tubule

Carbonic anhydrase inhibitors (acetazolamide) reduce Na^+ reabsorption by their effect on carbonic anhydrase. This is because up to a third of PT Na^+ reabsorption occurs in exchange for H (through the Na-H antiporter) and is thus dependent on CA. Even though this represents a large amount of Na , the total diuresis for CA inhibitors and osmotic agents as well is much lower because there is significant compensation by the more distal tubules which will reabsorb increased sodium if it is delivered due to decreased reabsorption proximally. CA inhibitors are responsible for a 5-10% excretion increase in the filtered load.

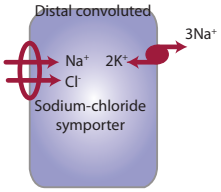
Osmotic Agents the most common osmotic agent is mannitol. As the name implies they inhibit the reabsorption of solute and water by altering osmotic driving forces along the nephron. Unlike other classes of diuretics, osmotic diuretics do not inhibit a specific membrane transport protien. Osmotics like mannitol are freely filtered at the glomerulus but are poorly reabsorbed. Because the proximal tubule is involved in the reabsorption of 60-70% of the filtered load this is the most important site of action. When there is an osmotic diuresis the blood flow to the medulla is increased and this reduces the effectiveness of the countercurrent mechanism, as a result less water in reabsorbed in the thin descending limb of the loop of Henle and the cortical collecting duct.





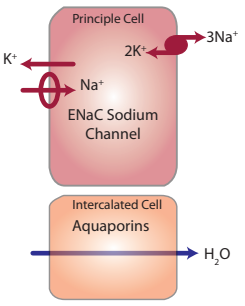
Thick ascending loop of Henle

Loop Diuretics (Frusemide) are organis ions that enter the tubular lumen primarily through secretion into the proximal tubule. They inhibit Na^+ reabsorption by blocking the $Na^+.K^+.2Cl^-$ symporter located in the apical membrane of these cells. By this action they not only inhibit Na^+ reabsorption but also interupt the countercurrent mechanism and he body's ability to dilute or concentrate urine. This also leads to decreased urine reabsorption in the TAL and the CCD. Loop diuretics are the most potent diuretics available, and are responsible for an 25% increase in the excretion of sodium filtered load. This reflect the fact that there is limited opportunities for reabsorption distal to the TAL.



Distal convoluted tubule

Thiazide diuretics (hydrochlorothiazde) are, like the loop diuretics organic anions. They are also mostly bound to plasma protiens, and they gain access to the tubule via secretion in the proximal tubule. They act to inhibit Na^+ reabsorption in the early portion of the distal tubule by blocking the $Na^+.Cl^-$ symporter in the apical membrane of these cells. Because water cannot cross this portion of the nephron, it is a site where urine is diluted. Therefore thiazides reduce the ability to dilute the urine maximally by inhibiting NaCl reabsorption. Because they act in the cortex they do not effect the ability of the kidneys to concentrate the urine maximally. Naturesis with thiazide diuretics is 5-10% of the filtered load.



Cortical collecting duct (and late distal tubule)

Potassium sparing diuretics these are divided into two classes, those which antagonise the action of aldosterone (spironolactone) and those which which block entry of Na^+ into the same cells through the Na^+ selective channels (ENaC) in the apical membrane (amiloride). Aldosterone stimulates both Na^+ resorption and K^+ secretion by the principles cells of the CCD. Thus the presence of a aldosterone antagonist these effects are reduced. The result of drugs such as amiloride is similar but rather than antagonise aldosterone they act directly on the ENaC channel. The result of both is decreased reabsorption of Na^+ which leads to decreased extrusion by the $Na^+.K^+$.ATPase pump and therefore less intracellular K^+, and ultimately less K^+ secretion into the tubular fluid.

Aquaretics are a more recent development and involve the direct antagonism of the V2 receptor which responds to ADH and is responsible for increasing the numbers of intergral membrane proteins called aquaporins. Aquaporins, especially when located in the CCT, enable the recovery of water by osmotic processes facilitated by the counter current mechanism. These drugs may be especially helpful in the treatment of patients with serious complications associated with SIADH.

Christopher Andersen 2012