Diuretics and renal tubular function

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The function of the kidney is to provide an ultrafiltrate of plasma which can then be modified, by selective absorption and secretion according to the patient's physiological needs, to produce urine. Diuretics are used to influence these processes and increase the volume of urine produced. Each class of diuretic influences the nephron in different regions, so an understanding of renal physiology is essential before diuretic drugs can be discussed in any detail.

Anatomy and physiology

Nephron

The basic functional unit of the kidney is the nephron that consists of the Bowman's capsule, proximal convoluted tubule (PCT), loop of Henle, distal convoluted tubule (DCT) and collecting duct (CD). The nephron begins as a blind-ended tube that forms the Bowman's capsule around a knot of capillaries (glomerulus) that arise from the afferent arteriole. The glomeruli, PCT and DCT are all situated in the renal cortex. The loops of Henle and CD extend down into the medulla. Cortical nephrons, originating in the outer two-thirds of the cortex, have short loops that may not extend into the medulla. Juxtamedullary nephrons, arising from the inner third of the cortex, have loops that pass deep into the medulla. These nephrons (~15%) are responsible for the kidney's concentrating abilities.

Glomerulus

In health, the glomerulus produces an ultrafiltrate of plasma into Bowman's capsule at a rate of 180 l day^{-1} (125 ml min^{-1}). The ultrafiltrate must pass through 3 layers: (i) the endothelial lining of the glomerular capillaries; (ii) glomerular basement membrane (lamina densa); and (iii) the visceral epithelial cells (podocytes). The endothelial cells are fenestrated to allow the passage of molecules in solution but to prevent blood cells and platelets coming into contact with the basement membrane which is the main filter. The basement membrane carries a negative charge and allows the passage of molecules depending on their molecular weight, size and shape. The podocytes maintain the basement membrane and may affect the passage of other molecules. The ultrafiltrate that passes into Bowman's capsule contains almost no protein. The molecular weight cut off for the basement membrane is approximately 70 kDa. Albumin (molecular weight 69 kDa) is negatively charged and so does not pass into the ultrafiltrate. The initial glomerular filtrate contains small molecules and ions (glucose, amino acids, Na^+, K^+, Cl^-, HCO_3^- and urea) in concentrations similar to that in the afferent arteriole.

Proximal tubule

The glomerular filtrate is subjected to selective re-absorption and secretion in the PCT, loop of Henle and DCT. Many of these processes require transporter proteins to carry the ions and molecules and energy derived from the hydrolysis of adenosine triphosphate (ATP). The most important active transport process in the nephron is Na^+K^+ATPase located on the basal and basolateral membranes of the cells lining the nephron. It enables the kidney to re-absorb 99% of the total Na^+ filtered and accounts for most of the oxygen consumed by the kidney. Other renal active transport systems include Ca^{2+}ATPase, H^+ATPase and H^+K^+ATPase. The absorbed Na^+ generates a concentration gradient which 'drives' other transport processes. This is termed secondary active transport with symport describing a solute moving in the same

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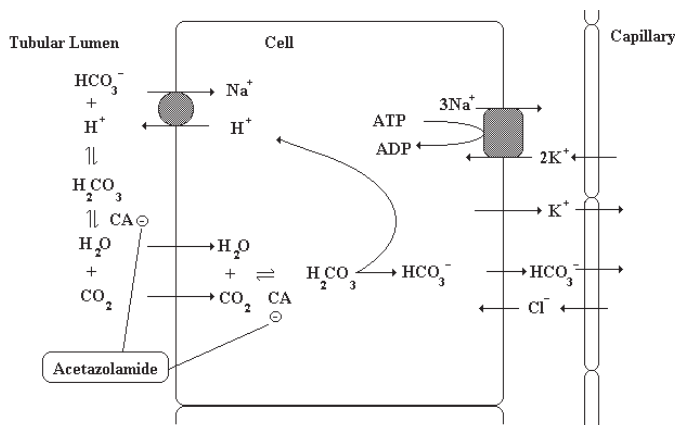St James's University Hospital,
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Fig. I Bicarbonate (HCO_3^-) re-absorption from the proximal tubule. Carbonic anhydrase (CA) is present in the brush border of the tubule cell in the lumen and also in the cytosol of the proximal tubule cell. HCO_3^- must be converted to CO_2 (via carbonic acid) before it can be absorbed into the cell where it is converted back into carbonic acid. Carbonic acid then dissociates into H^+ and HCO_3^-. H^+ is then exchanged with Na^+ in the tubular lumen. Some bicarbonate leaves the cell into the bloodstream and is exchanged with Cl^-.

Fig. 2 Cell from the ascending loop of Henle. Loop diuretics exert their effect from within the lumen of the tubule to inhibit the $Na^+2Cl^-K^+$ transporter.

direction as Na^+ and antiport if the solute moves in the opposite direction. The tubule cells also contain specific ion channels that allow ions (Na^+, K^+ and Cl^-) to move faster than the transport ATPases. The cell membranes contain proteins that transport only one specific molecule across (uniporters) which use the concentration gradient of the substance to drive the process of facilitated diffusion. Uniporters exist for glucose in the PCT and for urea in the CD.

In health, all the filtered load of glucose is re-absorbed by the end of the PCT. In diabetes mellitus, plasma glucose can be so high that the re-absorptive capacity of the PCT is exceeded. Glucose then passes further down the nephron, where there are no transport processes available, and it acts osmotically active within the tubule lumen preventing water re-absorption. This leads to polyuria and occurs when plasma glucose exceeds 10 mmol l^{-1}.

Sodium re-absorption assumes great significance because it is linked to the absorption of other substances such as Cl^-, amino acids, glucose and K^+. Na^+ can enter the cell passively down its electrochemical gradient and by active transport processes. Most of the Na^+ absorbed is in exchange for H^+ secretion. This in turn leads to Cl^- and HCO_3^- absorption. HCO_3^- moves as CO_2 (Fig. 1). The Na^+K^+ATPase then extrudes Na^+ against its electrochemical gradient from the cell, accompanied by entry of K^+ into the cell (Na^+:K^+ ratio 3:2). Accumulation of K^+ does not occur in the cell, as it is freely permeable to K^+ which can diffuse out along its concentration gradient. Around 60–70% of filtered water is re-absorbed in the PCT. The PCT also contains
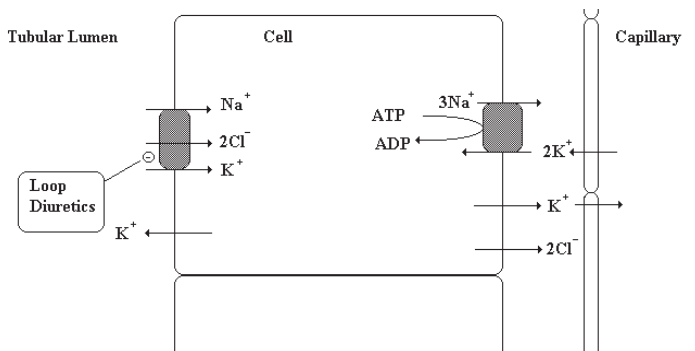
transporter proteins for organic acids that secrete these substances into the lumen of the tubule; this is how many of the diuretic drugs reach their site of action.

Loop of Henle

The loop of Henle delivers hypotonic fluid into the DCT. Its function is to manufacture hypertonic interstitial fluid in the renal medulla by the process of countercurrent multiplication. The loop of Henle produces a small transverse gradient between the ascending and descending limbs. This transverse gradient is then multiplied into a large longitudinal gradient by the countercurrent arrangement in the loop (*i.e.* flow in the opposite direction). The ascending limb secretes Na^+ into the interstitium, but is impermeable to water. This causes the osmolality of the interstitium to increase and that of the ascending limb to decrease. Na^+ is absorbed from the ascending limb by $Na^+K^+2Cl^-$ co-transporter. Na^+K^+ATPase then secretes the accumulated Na^+ into the interstitium of the medulla (Fig. 2).

Distal tubule

Na^+, K^+ and Cl^- re-absorption occurs in the initial part of the DCT. In the more distal part, K^+ is secreted into the lumen by a passive process along its concentration gradient. The rate of K^+ secretion is limited by the luminal K^+ concentration and fluid flow through it (*i.e.* greater flow results in greater K^+ secretion). There is also a Na^+K^+ exchange transporter that couples K^+ secretion with Na^+ re-absorption.

Collecting duct

The CD cells are impermeable to Na^+, Cl^-, urea and water. Water permeability is influenced by antidiuretic hormone (ADH). Na^+ re-absorption occurs with secretion of H^+ or K^+. It is under the influence of aldosterone.

Classification of diuretics

Drugs may produce a diuresis indirectly by their effect on cardiac output (*e.g.* digoxin) or body fluids (*e.g.* infusion of electrolytes). This review will concentrate on diuretics that have a direct action on the kidney. They can be classified according to the mechanism or site of action, *i.e.* osmotic, loop, thiazide, K^+-sparing, aldosterone antagonists and carbonic anhydrase (CA) inhibitors. This does not include drugs such as dopamine and methylxanthines that also have diuretic actions.

Osmotic diuretics

These are pharmacologically inert molecules with low molecular weights which enter the filtrate, are poorly re-absorbed and remain within the lumen of the tubule to be osmotically active, *e.g.* glucose, urea, sucrose and mannitol. Osmotic diuretics increase the amount of water excreted, with a relatively smaller increase in Na^+ excretion.

Mannitol is the most commonly used osmotic diuretic and is derived from *Dahlia* tubers. It acts by three mechanisms: (i) in the tubule lumen, it exerts an osmotic effect reducing the effective Na^+ concentration and thus reducing the re-absorptive gradient for Na^+; (ii) increasing the flux of Na^+ from the interstitial fluid back into the tubular fluid; and (iii) expanding extracellular and intravascular fluid volumes, thus decreasing blood viscosity and increasing medullary blood flow. The latter impairs the medullary concentration gradient, resulting in decreased concentrating ability and increased urine flow.

Mannitol is available as 10% or 20% solutions and the usual dose is 0.5–1 g kg^{-1} over 30 min. The diuretic effects usually occur within 30 min and can last for up to 6 h. Activity relies on the nephron being permeable to mannitol. It does not work if the nephron is blocked by disease, *e.g.* late in severe rhabdomyolysis when precipitated myoglobin crystals may block the tubules.

Mannitol redistributes rapidly resulting in mobilisation of intracellular fluid into the extracellular compartment. Fluid overload and pulmonary oedema may occur, especially in patients with impaired cardiac function. It may also have toxic effects on the cells of the DCT and CD resulting in vacuolisation of the epithelial cells.

Loop diuretics

Loop diuretics act by inhibiting the $Na^+K^+2Cl^-$ co-transporter in the ascending loop of Henle (Fig. 2) leading to increased Na^+ and water delivery to the DCT. The drugs need to be secreted into the tubular lumen by the organic acid transporter to exert their effect. The renal medullary concentration gradient diminishes, decreasing renal concentrating capacity by reducing the amount of water that can be re-absorbed by the CD. In high doses, loop diuretics can lead to excretion of over 30% of the filtered load of Na^+ and water. Drugs in this class include furosemide, bumetanide, torasemide, piretanide and ethacrynic acid.

Loop diuretics are the most powerful diuretics available at present. They are used in patients with salt and water overload due to pulmonary oedema, heart failure, cirrhosis with ascites, nephrotic syndrome, renal failure, hypertension and in the treatment of acute hypercalcaemia. In the critically ill, loop diuretics are administered parenterally by bolus or by infusion. After administration of loop diuretics, oxygen consumption in the loop of Henle is reduced to basal levels. This may protect the kidney from ischaemia. It may also protect the cell at the mitochondrial level, preventing the influx of calcium that occurs in ischaemia. Loop diuretics are used to convert oliguric renal failure to a non-oliguric state, assisting in fluid management. In the treatment of acute pulmonary oedema, loop diuretics lead to an improvement in breathlessness before diuresis occurs because they also cause vasodilatation, thus reducing ventricular preload.

Diuresis may precipitate significant hypovolaemia and electrolyte disturbances are common, i.e. hypokalaemia, hyponatraemia, hypomagnesaemia and metabolic alkalosis. Ototoxicity with irreversible sensorineural deafness can occur with excessive doses, rapid i.v. administration or impaired excretion. It is also more common with ethacrynic acid or if loop diuretics are used with aminoglycoside antibiotics.

Thiazide diuretics

Thiazide diuretics (*e.g.* bendrofluazide, hydrochlorothiazide, metolazone) inhibit Na^+Cl^- co-transport in the DCT (Fig. 3). They
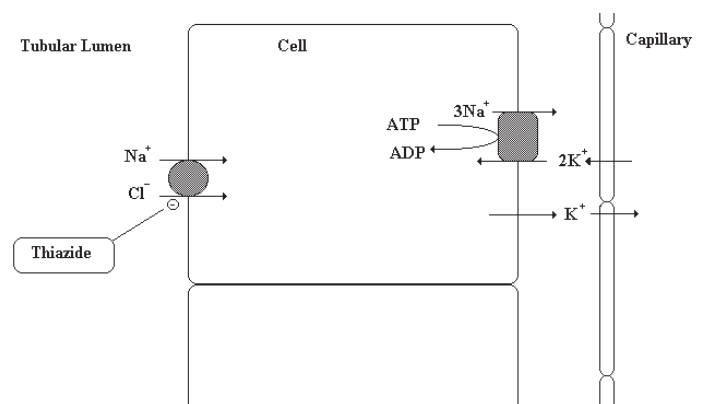

Fig. 3 NaCl co-transport in the proximal tubule, highlighting the action of thiazide diuretics from within the lumen acting on the NaCl co-transporter on the apical membrane.

are not as powerful as loop diuretics but K^+ loss may be severe, because the increased Na^+ load is delivered to the Na^+K^+ exchanger in the DCT. They also have vasodilator properties. There are used mainly for hypertension and are synergistic with loop diuretics, *e.g.* metolazone is used in resistant heart failure. Paradoxically, they reduce urine volume in nephrogenic diabetes insipidus.

Thiazides can cause severe hyponatraemia and hypokalaemia. Acute gout may be precipitated (increased plasma uric acid) and hyperglycaemia and hypercholesterolaemia may occur with long-term use. Blood dyscrasias and rashes are described and hepatic encephalopathy may be precipitated in patients with liver failure.

Potassium-sparing diuretics

Amiloride and triamterene have weak diuretic actions by blocking Na^+ absorption in the DCT in exchange for H^+ or K^+, independent of aldosterone (Fig. 4). When used in combination with loop diuretics or thiazides, they reduce the severity of hypokalaemia. They may cause hyperkalaemia and a metabolic acidosis.

Aldosterone antagonists

Drugs in this class include spironolactone and potassium canrenoate (parenteral form of spironolactone). They antagonise the actions of aldosterone at its nuclear receptor. The synthesis of Na^+ and K^+ channels for luminal membranes and $Na^+K^+ATPase$ for basal membranes is reduced. Spironolactone also inhibits aldosterone-induced ATP turnover making less available for $Na^+K^+ATPase$. Aldosterone mediated synthesis of Na^+H^+ co-transporter is inhibited resulting in reduced Na^+ absorption and decreased K^+ secretion. This causes a weak diuresis, retention of K^+ and, to a lesser extent, H^+. Its effects take days to occur, because spironolactone exerts its effect by preventing aldosterone-induced gene expression.

Spironolactone is often used in primary hyperaldosteronism (Conn's syndrome) and in secondary hyperaldosteronism (*e.g.* hepatic cirrhosis with ascites, chronic heart failure). However, angiotensin converting enzyme inhibitors are more commonly used in heart failure.

The main side-effect of aldosterone antagonists is hyperkalaemia and they are commonly administered to counteract K^+ loss induced by loop diuretics.

Carbonic anhydrase inhibitors

Carbonic anhydrase (CA) is the enzyme which catalyses the conversion of HCO_3^- and H^+ into carbonic acid, and then car-
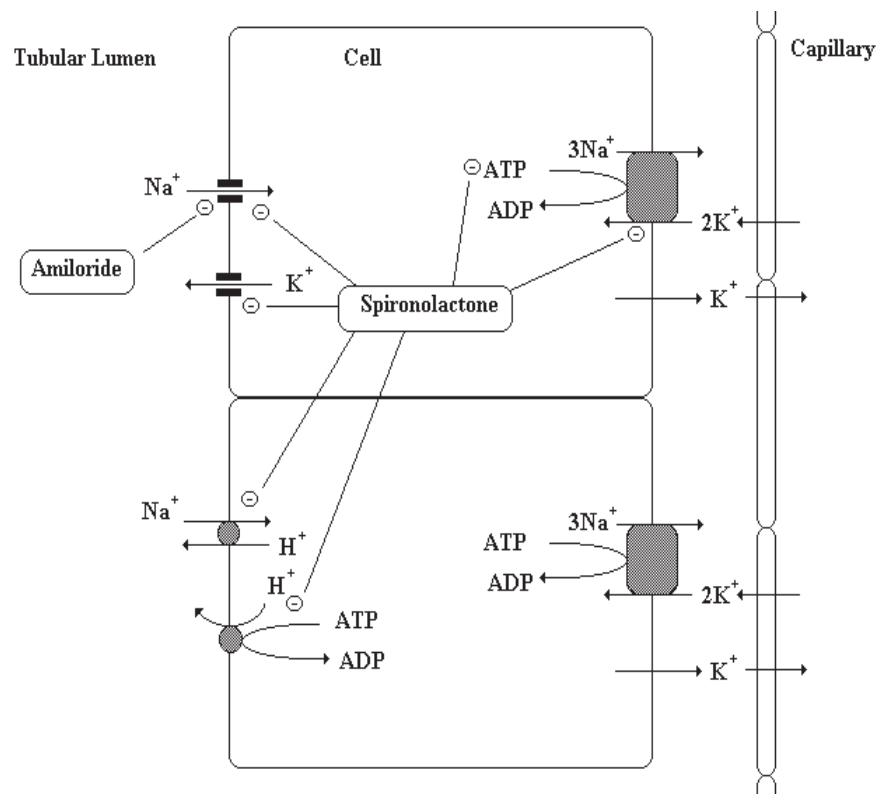

Fig. 4 Distal renal tubular cell showing ion channels on the luminal side of the cell and $Na^+K^+ATPase$ on the basolateral membrane. Amiloride acts on the luminal side of the ion channel to block Na^+ entry. Spironolactone inhibits the aldosterone-mediated synthesis of Na^+ and K^+ ion channels, ATP turnover, $Na^+K^+ATPase$ synthesis, Na^+H^+ co-transporter and $H^+ATPase$ in the distal tubule cell. Two cells are drawn for clarity.

bonic acid to carbon dioxide and water (Fig. 1). It is situated within the cytosol of the cell and on the brush border of PCT epithelium. It allows HCO_3^- to be re-absorbed. When the enzyme is inhibited, *e.g.* with acetazolamide, Na^+ accompanies the non-absorbable HCO_3^- and passes to the more distal nephron. In the DCT, K^+ secretion is enhanced due to increased Na^+ delivery. Also, H^+ secretion is impaired because of CA inhibition.

Acetazolamide is a weak diuretic and is used in the treatment of raised intra-ocular pressure in glaucoma, acute mountain sickness and some rare forms of epilepsy. Its side-effects include hypokalaemia and metabolic acidosis.

Dopamine

Dopamine promotes a diuresis via dopaminergic receptors (DA_1) on both the luminal and basal membranes of the PCT. Dopaminergic stimulation promotes a natriuresis by inhibiting $Na^+K^+ATPase$. This effect is blocked by phenothiazines. Dopamine has been used for many years for renal protection, but recent studies and editorials have challenged this indication.

There is no evidence from any randomised controlled study that dopamine provides renal protection and it is not used routinely for this indication. Its effects on DA_1, α and β receptors are unpredictable and it may provoke arrhythmias and worsen renal ischaemia.

Methylxanthines

Historically, drugs such as theophylline have been used as weak diuretics. They probably act by elevating cAMP in renal tubular cells and inhibiting electrolyte re-absorption.

Key references

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See multiple choice questions 58–61.