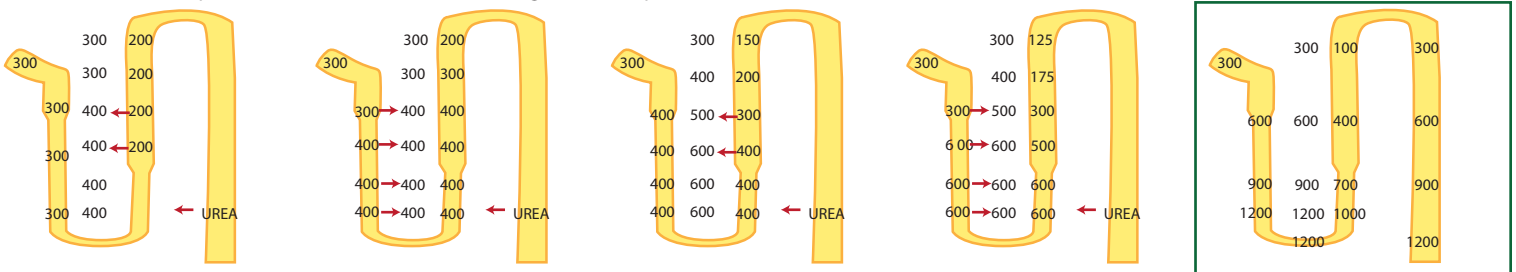
RENAL PHYSIOLOGY 2

Glomerular filtration and measurement Glomerular filtration is one of the key steps in the function of the kidney. The glomerulus is a specialised capillary bed with two important characteristics. Firstly it is located between two arterioles. This means that it is able to operate at higher pressures then normal capillary beds, and that variations in either the afferent or efferent branches creates variable pressure differentials which will increase or decrease the hydrostatic pressure within the glomerulus also acting as the effector of autoregulatory mechanisms. Secondly, it has very high permiability which decreases as molcule size increases from 7kDa (very little albumin is filtered as it is 70kDa), which is a function of the capillary epithelium, a layer of basement membrane, and the capsular endothelial cells (podocytes). The permiability is quantified by the ultra-filtration coefficient K_f. What ultimately determines glomerular filtration is the product of the filtration coefficient and the net starling forces (also known as the net filtration pressure). It is important to note that because limited large molecules are filtered their is negligable oncotic pressure towards Bowman's Space, therefore the net filtration pressure is the sum of the opposing hydrostatic pressures minus the oncotic pressure towards the plasma. It should also be noted that there is a slight negative charge on the glomerular membrane and that this predisposes to positive ions being filtered. The percentage that is filtered at the glomerulus may be quantified by the filtration fraction (FF) and is usually 15-20% renal plasma flow (RPF). Measurement Renal clearance is the volume of plasma completely cleared of a substance by the kidney per unit time (similar definition to liver). This can be represented by the formula; Clearance = UV/P where U is the urine concentration, P is the plasma concentration and V is the volume of urine produced per unit time. A substance which is filtered at the glomeruli, and neither reabsorbed or secreted by the tubules will represent the glomerular filtration rate. Inulin, a plant polysaccharide is often quoted as the best candidate but the measurement is problematic because the substance is exogenous and requires a steady state scenario to give an effective measurement. Creatinine, a byproduct of creatine breakdown in the muscles is an endogenous alternative. A small amount is secreted by the tubules into the lumen although this is often evened out by overestimation is the measurement of plasma creatinine. Creatinine varies significantly with muscle bulk and therefore it is often corrected for these age, weight and sex by formulas such as the Cockroft-Gault. There is also a non linear relationship between serum creatinine and creatinine clearance. There can be a decline of almost 50% of renal function before there is a significant increase in serum creatinine.

The countercurrent mechanism relates to a physiological process which sets up a concentration gradient from the cortex through to the medulla. Countercurrent mechanism is based on several assumptions

1) No flow of water in the ascending limb of the loop of Henle
2) Active transport of solutes out of the ascending loop of Henle creating gradient of 200mOsmol across the membrane
3) Urea from the cortical collecting duct augments the concentration in the medulla (650 of the 1400mOsmol total)
4) The vasa recta is organised such that it does not wash away the interstitual medullary gradient

The final concentration is dependent on the length of the loop, the capacity of the active pumps in the thick ascending limb and the rate of flow through the tubules and a maximum figure of 1400mOsmol is usually quoted. The result of this physiological process is the kidney is able to concentrate urine up to a concentration 1400 via ADH induced reabsorption of water in the cortical collecting duct. A simplified model is shown below.



Initally, sodium is transported from the ascending loop to the interstitium

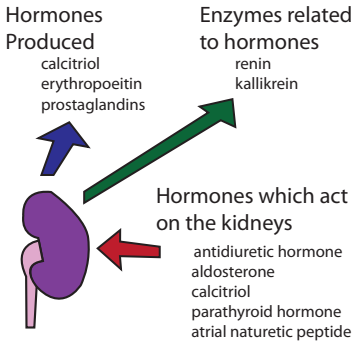
Water is then removed osmotically to the interstitium to balance the concentrations

Step one again, as solute is removed the intra-tubular concentration drops

Step two again, the medullary concentration increases with urea augmenting the process

After the process occurs multiple times the final concentrations are set as shown.

Endocrine functions of the kidney may be divided into three separate categories. The first of these categories is hormones produced by the kidney this includes calcitriol, erythropoietin and prostaglandins. Calcitriol, also known as 1,25 dihydroxycholecalciferol is the final step in the activation of vitamin D, it is initially formed by the skin, the first step in activation occurs in the liver and the final activation in the kidney. It is involved in the regulation of calcium, in particular the absorption from the gut, the reabsorption in the kidneys and action on the bones. Erythropoeitin is is a glycoprotein synthesized in response to arterial hypoxemia, and it stimulates RBC production in the bone marrow. Prostaglandins are unsaturated fatty acids containing 20 carbon atoms and a five-membered carbon ring at one end. In addition to the kidneys they are synthesised in most tissues from arachidonic acid and have a multitude of roles. The second category are the enzymes released by the kidney which directly contribute to the production and release of hormones. Renin is released from the juxtaglomerular aparatus in response to decreased renal perfusion and through a number of steps forms angiotensin I and II and stimulates the release of ADH and aldosterone. Kallikreins are serine proteolytic enzymes in plasma and tissue which produce kinins from kininogens, such as bradykinin which has important circulatory effects including vasodilation and increased vessel permiability. The final category is hormones which have there site of action at the kidneys - antidiuretic hormone, aldosterone, calcitriol, parathyroid hormone & atrial naturetic peptide. Anti diuretic hormone increases water loss in the CCD via aquaproins. Aldosterone acts on the distal tubule and the CCD to exchange hydrogen and potassium from salt and water. Parathyroid hormone increases calcium reabsorption from the distal tubule. Atrial naturetic peptide is produced by the right atrium in response to increase blood volume and this causes an increased secretion of sodium from the kidney. The mechanism is not well understood.



Kidney acid-base functions daily acid production is greater than 500 moles, but most of this is instantly turned over in reactions such as ATP and mitochondrial activity. The net production represents the excess production and is divided into the volatile component and fixed or non-volatile component. The volatile component is derived from the metabolism of fats and carbohydrates which produce CO_2 and H_2O - the former of which is removed by the lungs (roughly 12-15 moles per day depending on metabolic demands). The non-volatile or fixed component is derived from a range of different sources and is immediately neutralised via the bicarbonate buffering system and is removed from the body via the kidneys (roughly 0.1-0.15 moles per day). The kidneys role in acid base functions is to excrete an amount of acid equal to the non volatile acid production and in doing so replenish the the HCO_3^- by both reabsorption (mostly in the proximal tubule and thick ascending limb) and formation of new bicarbonate (mostly as a byproduct of phosphate buffering). Quantitatively the reabsorption of the HCO_3^- is more significant with the amount filtered at the glomerulus around 4300 mEq/day with only approximately 100mEq/day required per day for non volatile acid balance. As there is ultimately a net excretion of acid urine generally has a low pH. Urine is usually no more acidic than pH 4, and this equates to a total H^+ only 0.1 mEq/day. The work around for this is through titratable acids which is the collective term for urinary buffers (of which phosphate is the most important) and the excretion of ammonium. From this understanding we can see that the actual net acid excretion (which is equal to the non volatile acid production) may be represented by the formula

Net Acid Excretion = titratable acid + ammonium - HCO_3^- loss.

Acid secretion is regulated by a number of different factors including endothelin and cortisol which are released in response to acidosis and increase the transcription of transporters that facilitate acid transport from the apical membrane. Aldosterone's primary action is on the DCT and CCD to stimulate Na^+ reabsortion and as a side effect increase intercalated cells H^+ release. Parathyroid hormone acutely inhibits H secretion (by blocking the Na^+-H^+ antiporter) and in the long term stimulates H excretion in the TAL of the loop of Henle. Potassium regulates the system, hyperkalaemia inhibits H^+ secretion and hypokalaemia stimulates H^+ secretion.

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