GLOMERULOTUBULAR BALANCE

In the dog and probably many other species as well, the glomerular filtration rate (GFR) varies markedly with the diet. The filtration rate in dog may be increased nearly 100% 4-5hrs after a meal of raw beef. Changes in GFR of this magnitude results in a very large increase in the Na load presented to the tubules. If the tubules are unable to adjust their Na reabsorption ability accordingly, the resulting severe Na loss in the urine cannot be tolerated. To prevent such wide fluctuation, the tubules are able to adjust their Na reabsorption proportionately.

Therefore, if GFR increases, tubular reabsorption of kidney increases proportionately and less Na is lost in the urine than would have occurred if Na reabsorption were fixed. This proportionality between Na reabsorption by the tubule and the GFR is termed Glomerulotubular balance.

Changes in Na reabsorptive capacity occurs primarily in the PCT. DCT and CD can only partially alter their reabsorptive rate for Na and the modest changes in GFR may be due at least in part to these incomplete adjustments at the DCT and CD. Glomerulotubular balance appears to be intact over a range of filtration rate, but during acute reductions or elevations in GFR some deviations from perfect balance occurs. How the tubules are informed of the necessity to readjust their reabsorptive ability when the filtration rate changes is still under investigation.

The hypothesis on which there is some evidence suggests that the interactions of some hydrostatic and colloid osmotic pressure at the peritubular capillaries surrounding the PCT are of primary importance. A change in these forces may be brought about by a change in the GFR relative to the renal blood flow.

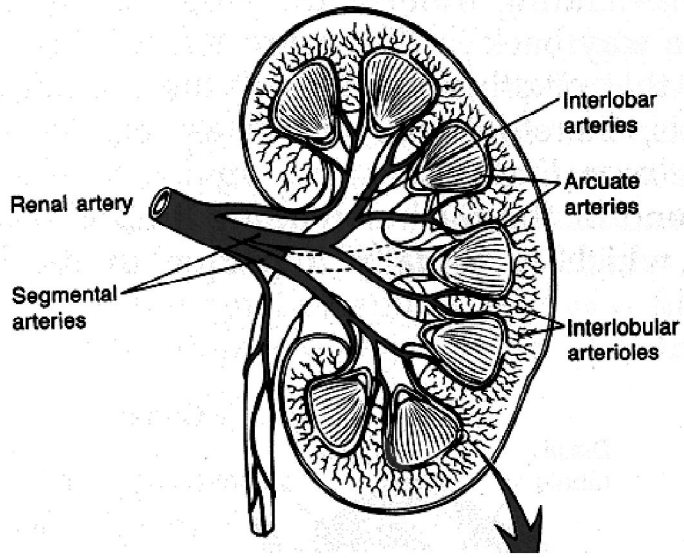
Also, The association of the glomerular arterioles with the macula densa of the DCT provides a system that may participate in the adjustment of glomerular filtration to tubular reabsorption.

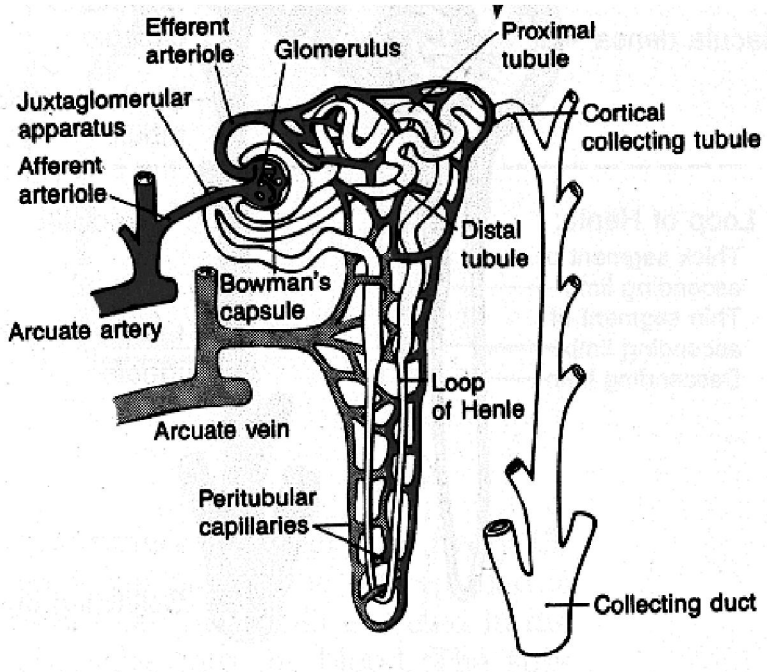
RENAL CIRCULATION

The renal arteries branch off the abdominal aorta and enter the kidneys. They give rise to several interlobar arteries which pass between the renal pyramids. The interlobar arteries give rise to arcuate arteries which arch between the cortex and medulla. Interlobular arteries branch off the arcuate arteries to project into the cortex.

The afferent arterioles, arise from branches of the interlobular arteries and extends to the glomerular capillaries. Efferent arterioles extend from the glomerular capillaries to the peritubular capillaries, which surround the PCT, DCT and LH. Blood from the peritubular

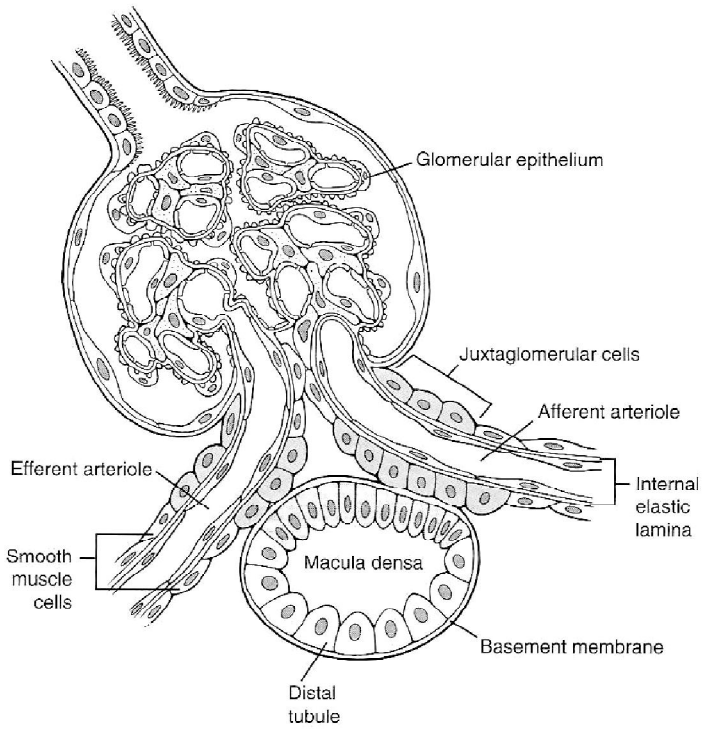
capillaries enters the interlobular veins. The veins of the kidney run parallel to the arteries and have similar names.





Section of the human kidney showing the major vessels that supply the blood flow to the kidney and schematic of the microcirculation of each nephron

JUXTAGLOMERULAR APPARATUS / COMPLEX



This is composed of specialized cells in the walls of the afferent glomerular arterioles which are in intimate contact with the distinctive portion of the DCT known as macula densa. The specialized cells in the arteriolar walls are designated as granular or agranular cells because of the presence or absence in their cytoplasm secretory granules. Endoplasmic reticulum is present in both cell types which suggests the presence of active protein formation. The agranular cells may represent less active cell types. Cells of the macula densa may be differented from other cell type of DCT by special staining characteristics. The cells of the macula densa contain fewer mitochondria than the other cells of the DCT. Renin is produced in the macula densa which acts on angiotensinogen (produced by the liver) to produce angiotensin I. Angiotensin I is further hydrolyzed to angiotensin II by angiotensin converting enzyme. Cells of the macula densa exert control on the renin-angiotensin system, which is done through the sensing of changes in Na^+ concentration in tissue fluids. Increased Na^+ leads to decreased renin release, and vice versa.

URINE FORMATION

Formation of urine begins as an ultra filtrate of plasma a cross the glomerular capillary walls and Bowman's capsule into the Glomerular capillary networks.

Energy for this filtration process is provided by the heart in the form of blood pressure within the glomerular capillary and is opposed by the colloid osmotic pressure (COP) of plasma protein plus the intrinsic tissue pressure of the kidney.

Net filtration pressure = Capillary bp – (C.O.P + Tissue pressure)

Under normal circumstances, in which the renal arterial pressure varies between 90 and 100mmHg with mean pressure as blood enters the glomerular afferent arterioles of 75mmHg, then the net filtration pressure will be approximately 45mmHg.

= 75 – (25 + 5)

= 45 mmHg

N.B.: The mean capillary blood pressure ranges between 60-70mmHg (this promotes filtration).

COP range between 25-30mmHg (this opposes filtration)

Tissue pressure ranges between 5-15mmHg (this opposes filtration)

The net filtration pressure represents the measurement of pressure across the glomerulus. Within the glomerulus there is an additional redistribution of pressures. The hydrostatic pressure drops as blood flows from the afferent arterioles into the glomerular capillaries and COP increases in the efferent portions of glomerular capillaries as fluid is lost during the filtration process.

The ultrafiltration pressure, the net pressure available to force an ultra-filtrate of plasma into the Bowman's space, will be greatest in afferent portions of the glomerular capillaries. Increasing the tissue pressure within the kidney decreases filtration rate by reducing the net filtration pressure. Clamping the ureter permits fluid to accumulate within the nephron. Assuming no change in blood pressure and continued filtration, the pressure within the nephron increases until the intra- tubular pressure reach 45mmHg. At this point, net filtration pressure should be abolished. Ureteral obstruction decreases the filtration rate but continued absorption of tubular fluid into the peritubular blood flow generally prevents complete cessation of the plasma filtering process.

Estimates of regional blood flow, indicates that at least 85% of the effective renal blood flow perfuse the cortex. Total renal blood flow determined quantitatively in unaneasthetized dog was found to be 642ml / 100g/min which represent 20% of the cardiac output. This indicates the magnitude of blood flow to an organ that comprises 0.3% of the total body mass.

Area	Blood Flow
Cortex	472ml / 100g/min
Outer medulla	132ml/100g/min
Inner medulla	17ml/100g/min
Hilus and perirenal fat	21ml/100g/min

Blood flow in different parts of the Kidney (Thorburn *et.al.*1963)

Medullary blood flow does not only differ quantitatively from cortical blood flow, but also shows qualitative changes that reflects both the composition of the area it perfuse and the singular arrangement of the vasa recta into a counter current exchange system.

Blood taken by micro puncture from the vasa recta near the medullary crest has an osmolality approximating the osmolality of the medullar interstitium. Generally, blood samples taken at varying levels of the medulla have osmolality indicative of the corticomedullary osmotic gradient.

MechanisMs of ionic ReabsoRption

Na Transport / reabsorption: this is a specific function of the tubular epithelium involving specific enzyme system and which also requires energy. Na is completely reabsorbed in the tubule and is absent in the secondary urine.

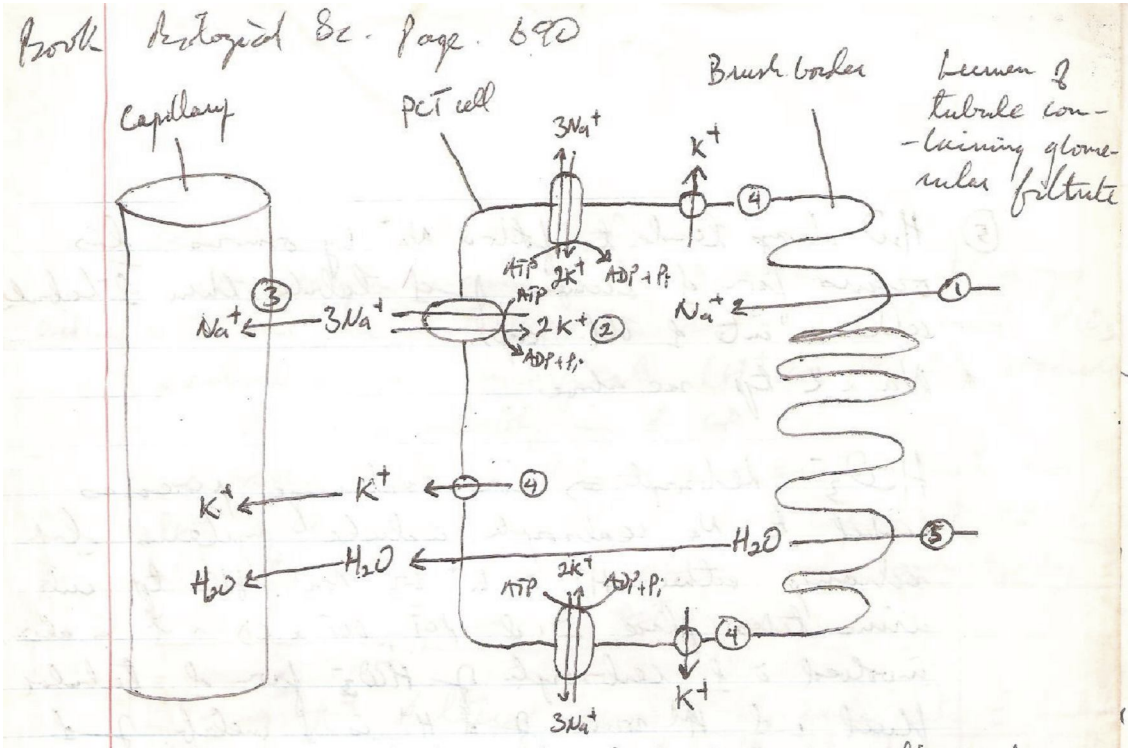
Active Na transport makes possible the reabsorption of Na back into the blood whose blood concentration is normal or higher than normal relative to their tubular concentration. Reabsorption of Na is independent of the concentration (mandatory reabsorption) in the PCT and LH, whereas in the DCT the reabsorption of Na varies with blood Na concentration (optional reabsorption). Therefore Na reabsorption occurs at several nephronal levels: PCT, thick ascending segment of the LH., DCT and CD. Quantitatively, the most significant component of Na reabsorption is accompanied by attendant chloride reabsorption.

Na reabsorption is also linked to ion exchange processes that are of great physiological significance in the maintenance of acid base and ionic equilibrium of the body's fluid compartment. Na transport against its concentration gradient is limited in the PCT and can be inhibited by diluting its concentration in the fluid of the PCT.

Na reabsorption from the DCT can proceed against a much greater concentration gradient. The hypotonic urine excreted during H_20 diuresis is virtually free of Na indicating that Na in the tubular fluid has been conserved despite an increasingly unfavorable concentration gradient.

N. B.: The electrical potential across the PCT has been recorded at approximately -20mV while that of the DCT may be > - 50mV (-35mv to -50mV) emphasizing further the great capacity of Na reabsorption to overcome this electrochemical gradient.

Diagram of Na transport



1. Diffusion of Na down its electrochemical gradient from higher concentration outside the cell to lower concentration inside and towards negatively charged interior of cell (all cells maintain a potential difference across their surface membranes, usually negative on the inside respect to the outside). Na enters through ion channels.
2. Na^+ /K^+ ion pumps in the base and sides of the cell, pump out $3Na^+$ for every $2K^+$ pumped in, using ATP as an energy source. This maintains the Na^+ diffusion gradient into the cell. (6% of the total ATP used in the body is used in the kidney by these pumps)
3. Na^+ diffuses into the blood capillaries find the spaces around the tubule cells.

4. K^+ diffuses back out of the cell passively through the K^+ channels.
5. H_20 always tends to follow Na^+ by osmosis. This occurs from the lumen of the tubule through the tubule cells and the blood capillaries.

HCO_3^- transport / reabsorption: ion exchange processes linked to Na reabsorption includes systems that exchange either H^+ or K^+ for Na^+. H^+ transport into urine takes place in the PCT, DCT and CD and it is also involved with the reabsorption of HCO_3^- from the tubular fluid. The source of the H^+ is the metabolism of the renal tubular cells and the hydration of CO_2 to carbonic acid and the dissociation of this acid into H^+ and HCO_3^-.

Secretion of H^+ by the renaltubular cells may account for their relatively high intracellular pH. H^+ when transferred into urine may react with urinary constituent. Under normal conditions, plasma.HCO_3^- concentration in the dog is 24-26meq/L. The quantity of bicarbonate ion reabsorbed per minute varies with the GFR; assuming a constant G F R, tubular maximal HCO_3^- reabsorption in the dog($TmHCO_3^-$) is about

2 - 3mmol/min/dL filtrate. HCO_3^- reabsorption also depends on plasma PCO_2. Increased arterial PCO_2 increases the maximal rate of HCO_3^- reabsorption and conversely, decreases in the arterial PCO_2 decreases the kidneys capacity to reabsorb HCO_3^-.

HCO_3^- reabsorption and acidification of urine in the dog's kidneys (nephron) are initiated in the PCT. Continued HCO_3^- reabsorption and urine acidification (H^+ secretion) occurs in the DCT and probably in the CD.

The reactions of H^+ with HCO_3^- and anion such as phosphate and chloride occurs in both the PCT, DCT and CD. The ultimate pH (H^+ concentration) of urine is determined, however by the rate of H^+ transport into the PCT.

K^+ Reabsorption: K^+ filtered across the glomeruli into the tubular filtrate, are almost completely reabsorbed by the PCT via active transport. Reabsorption of K^+ occurs in the DCT and CD via a transport process which functions as an ion exchange process, or from the diffusion of K^+ down a favorable electrochemical gradient from the interior of the tubular cells into the tubular fluid.

The physiological stimulus for H^+ and K^+ secretion is the increased negativity of the tubular fluid which results from the transport of Na^+ from the tubular fluid.

H^+ and K^+ appear to utilize a common transport or diffusion pathway and in general a reciprocal relationship exists between the secretion of these ions. The metabolic state of the body, under normal circumstances determines whether H^+ or K^+ will be transferred preferentially into urine.

N.B.: The urinary excretion of ions, especially Na^+ and K^+ does not always conform to a stoichiometric relationship which would be anticipated on the basis of ion exchange mechanisms. Administration of excess K^+ salt to the dog is followed by the rapid excretion of the excess K^+ into the urine without corresponding increases in Na^+ reabsorption.

Ca^+ and Mg^+ reabsorption: They are reabsorbed primarily from the glomerular filtrate in the PCT. Ca^+ is also reabsorbed in the ascending limb of LH and in the DCT. Ca^+ transport is an active process and may be linked to the Na^+ transport system.

MeasureMent of renal Functions

Glomerular Filtration Rate: Glomerular filtration takes place in all the nephrons of both kidneys at the same time but the filtration process are not the same. Also the quality of the glomerular filtration varies from on nephron to another.

The quantity of the glomerular filtrate that is formed in all the nephrons of both kidneys per minute is the glomerular filtration rate.

If U_x = concentration of drugs or substance in urine (mg/ml)

V = flow rate of urine (ml/min) or urine volume

P_x = concentration of drugs / substance in plasma (mg/ml)

The relationship between these factors and glomerular filtration rate is:

$$GFR = \frac{U_x(\text{mg/ml})\text{urine} \times V(\text{ml/min})}{P_x\ (\text{mg/ml})\ \text{plasma}}$$

x can be inulin or creatinine, these 2 substances are physiologically inert.

Glomerular Filtration Rate can be measured in intact animals and humans by measuring the excretion of plasma level of a substance which is freely filtered through the glomerulus and should not be secreted nor reabsorbed by the tubules. The amount of such a substance in the urine per unit time must have been provided by filtering the exact number of *ml* of plasma which contains these amounts.

Characteristics of substances suitable for measuring glomerular filtration rate by determining its clearance are:

- Freely filtered
- Should not be a reabsorbed or secreted by the tubules
- Should not be a metabolite
- Should not be stored in the kidney
- Should not be protein bound (cause substance bound to albumin and globulin are not freely filtered)
- Should not be toxic
- Should not have effect on filtration rate
- Should be easy to measure in the plasma and urine

Renal Clearance / Plasma Clearance: Renal clearance expresses the ability of the kidneys to "clean" or "clear" the plasma of various substances. It is used to indicate the manner of disposition of a given substance known to be excreted into urine e.g. Evans dye.

$$P_c = \frac{U \times V}{P}$$

U = Concentration of substance in urine (mg/ml)

P = Concentration of substance in plasma (mg/ml)

V = Volume in ml of urine formed per minute (ml)

Plasma clearance of a substance is important in estimating kidney function.

Renal Blood Flow

See also Renal Circulation.

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