How can we model water transport through the kidney?

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The kidney is a major organ for the excretion of unwanted/toxic chemicals and the recovery of useful chemicals. Basically it carries out three functions: filtration, reabsorption and secretion. It is also a key organ in homeostasis, including the control of water balance in the body. The kidney comprises about a million individual units (nephrons) each with a blood filtration unit (glomerulus) with the capability to re-absorb wanted chemicals or actively secrete various unwanted chemicals in to the tubules post-filtration. Normal kidneys are able to filter about 125 ml/min of blood, whilst only excreting (on average) about 1ml/min of urine. However, the kidney is quite capable in short periods of time of giving 20-30 fold differences in the urine flow rate (as ardent beer drinkers or those visiting hot countries can testify). The tubules in the kidney, both proximal and distal, have important roles in controlling these acute changes in rate of fluid excretion. Past the kidney, the bladder can largely be considered as an impermeable bag with a maximum volume capacity. Usually when the bladder gets towards full, the brain is signalled about the need to urinate, so the time between micturition is also dependent of the urine flow rate.

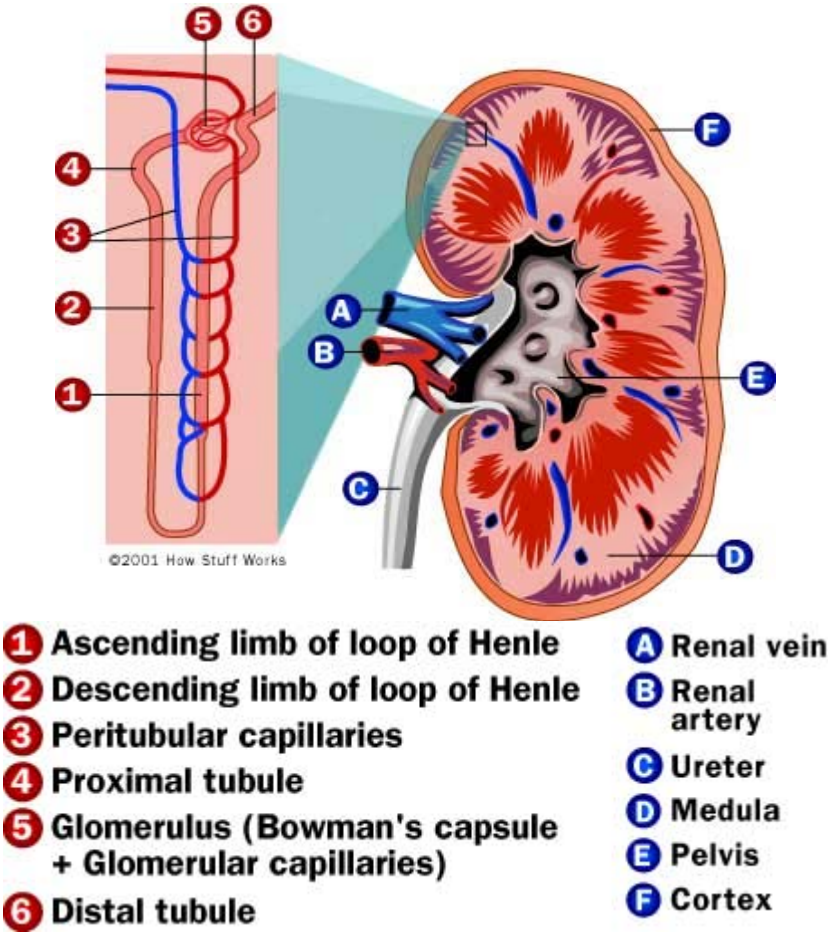

Diagram of the kidney and a single nephron unit- showing filtration of arterial blood through the glomerulus, the proximal tubule where absorption or secretion of chemical can occur, the ascending and descending limbs of Henle and the distal tubule where water balance is largely controlled. The formed urine is discharged from the distal tubule into collecting ducts, the ureter and finally the bladder.

In many branches of toxicology and clinical medicine the measurement of the concentration of a chemical or drug in urine is used as an index of the body burden of that chemical. The index is traditionally expressed as the excretion of chemical as amount per time period (e.g. mass per 24 hour) or amount per hour averaged over a significant time-frame. This is done to lessen the influence of fluctuations in urine flow rate on the measured excretion of chemical. The practical difficulties of collecting accurately timed and complete urine collections from humans and animals are well known. In occupational medicine assessing occupational exposure to chemicals generally relies on the analysis of chemicals/metabolites in an end of work-shift urine sample. It has been common to ratio the urine concentration of chemical to that of creatinine, which is a substance produced at a relatively constant rate by the body and with relatively little tubular secretion or absorption (i.e the excretion rate of creatinine is relatively constant and its concentration reflects urine flow rate). If such a correction was not done, the measured concentration of chemical in urine may reflect urine production rate rather than the body burden of the chemical. However creatinine is not a perfect chemical for this purpose as elements of tubular secretion of creatinine can be found at extremes of urine flow rates and total creatinine production in the body depends on muscle mass and is therefore variable between subjects.

Complications also arise because the excretion of some chemicals is strongly influenced by secretion or reabsorption in the tubules rather than by filtration of the blood by the glomeruli (e.g. ethanol passively diffuses into urine across cell walls in the tubule and therefore the rate of urine excretion of ethanol is not dependent on flow rate and body burden can be simply reflected by urine ethanol concentration).

However many toxic chemicals do largely enter urine through glomerular filtration with relatively little tubular absorption or excretion, leading to the chemical's excretion being urine flow rate dependent and, typically, these results are normalised against creatinine excretion to overcome the concentration/dilution effects that may be caused by the kidneys' key role in ensuring water balance.

The interpretation of urine measurements of chemicals and the value of creatinine correction would therefore be greatly improved by a mathematical model for water transport and creatinine handling through the kidney. Subsequent models can be developed to include the renal handling of specific toxic chemicals and the influence of the bladder.

Any model needs to be able to reflect the influence over time of various control systems that modify the functions of the kidney as a principal organ of water homeostasis. For example, glomerular filtration rate (rate of blood filtration) can be modified with normal boundary limits, water reabsorption in the loops of Henle are hormonally mediated responding to sodium concentration in the blood.