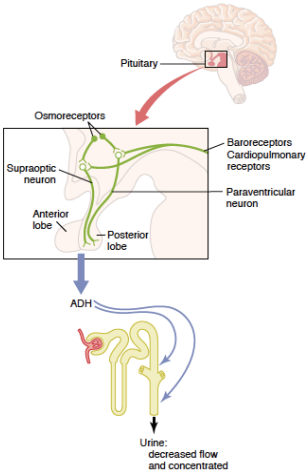
RENAL PHYSIOLOGY 3

Body water homeostasis refers to the overall balance of fluid intake and output. This includes all body water in both the extra and intracellular compartments (44L in 70 kg man). The system for maintaining this homeostasis may be considered a simple control system with sensors, a central controller and effectors. The most important sensor is the osmoreceptors located in the hypothalamus. It follows that the osmolality is the key determinant in maintaining total body water balance, a net increase in total body water will lead to a decrease in osmolality and a decrease in TBW will lead to an increase. The main molecule responsible for osmolality is sodium, hence its primacy in our appreciation of diuretic actions. Other sensors are more specialised and are determined by pressure and volume only on the related intravascular compartment, these include the low pressure sensors located in the right atrium and veins and the high pressure sensors in the aortic arch and carotid sinus. These augment the response, (and have other actions such as stimulating renin release from the kidney and causing vasoconstriction and increased TPR in low pressure states as well as the release of atrial naturetic peptide and brain naturetic peptides in high volume states). The central controller is the hypothalamus. The effectors are thirst and antidiuretic hormone. Anti diuretic hormone is a naturally occuring peptide released from the posterior pituitary also known as vasopressin. In addition to the main driver of release which is osmolality and the augmenting effects of the intravascular sensors (responding to hypovolaemia and hypotension) ADH is also released in response to stress. ADH acts on GPCR located on smooth muscle, platelets and importantly on the distal convoluted tubule and cortical collecting duct (V2 receptors). Because of the countercurrent mechanism setting up a large osmotic gradient in the medulla of the kidney the V2 receptors in the DCT and more so in the CCT are able to increase water reabsorption through activation of water channels called aquaporins. This enables urine to be concentrated to up to 1400 mOsmol and become as dilute as 50-100 mOsmols in the setting of hypervolaemia. Thirst is the physiological urge to drink. It is usually unneccesary because of hedonistic water intake due to social and behavioural factors, but can be a potent back up mechanism if intake due to hedonstic factors is insufficient.



Glucose handling glucose is completely reabsorbed in the proximal tubule by co-transport with sodium ions. at concentrations below 12mmol/L. The proximal tubule resorbs all of its glucose in the tubular fluid. However, the specific carrier mechanism for glucose can be overloaded as the proximal tubule has a transport maximum for glucose (and other nutrients). If the filtered load exceeds the proximal tubule transport maximum, as may occur in DM, glucose appears in the urine. In humans, at a normal GFR of 125mL/min, glucose begins to appear in the urine at a plasma glucose concentration of 10-12 mmol/L and becomes saturated at 15 mmol/L.

Urea and creatinine handling The liver produces urea in the urea cycle as a waste product of the digestion of protein (50g per day). Urea is passively reabsorbed from the tubule. As water is reabsorbed from the tubules (by osmosis coupled to sodium reabsorption), urea concentration in the tubular lumen increases. This creates a concentration gradient favoring the reabsorption of urea. However, urea does not permeate the tubule as readily as water. In some parts of the nephron, especially the inner medullary collecting duct, passive urea reabsorption is facilitated by specific urea transporters. Yet only about one half of the urea (25g) that is filtered by the glomerular capillaries is reabsorbed from the tubules. The remainder of the urea passes into the urine, allowing the kidneys to excrete large amounts of this waste product of metabolism. Another waste product of metabolism, creatinine (2g per day), is an even larger molecule than urea and is essentially impermiable to the tubular membrane. Therefore, almost none of the creatinine that is filtered is reabsorbed, so that virtually all the creatinine filtered by the glomerulus is excreted in the urine.

Renal excretion of drugs and metabolites in the urine involves three distinct processes: glomerular filtration, active tubular secretion, and passive tubular reabsorption. Changes in overall renal function generally affect all three processes to a similar extent. Almost all drugs are filtered at the glomerulus. Filtration is directly related to the rate and unlike the liver it is possible to estimate filtration rate using the cockroff-gault formula or eGFR. If a drug is in a lipid soluble form during its passage down the tubules a significant portion will be reabsorbed by simple passive diffusion. It may be therefore advantageous to have a drug in its ionised form which will increase removal of a drug in an overdose situation or non inonised form to extend its duration by alkanising or acidifying the urine. Pancuronium is the only anaethetic extensively execreted renally.

Physiological response to acute renal failure Symptoms of acute renal failure are not detected until less than 40% of normal functioning nephrons remain, and uraemic symptoms do not occur until less than 5% of normal functioning nephrons remain. Acute renal failure is attributed to several mechanisms (1) diseases that cause renal hypoperfusion, resulting in decreased function without frank parenchymal damage (prerenal ARF, or azotemia) (~55%); (2) diseases that directly involve the renal parenchyma (intrinsic ARF) (~40%); and (3) diseases associated with urinary tract obstruction (postrenal ARF) (~5%). Typically an early compensatory phase of normal renal adaptation progresses to ARF. Depending on renal function reserve this may occur over a period of hours to days. At this point the decline in renal function results in the retention of nitrogenous and end products of metabolism and an inability to maintain fluid and electrolyte homeostasis. Physiological responses to the most common cause of ARF (hypoperfusion) are as follows. In states of mild hypoperfusion, glomerular perfusion and the filtration fraction are preserved through several compensatory mechanisms. In response to the reduction in perfusion pressure, stretch receptors in afferent arterioles trigger afferent arteriolar vasodilatation through a local myogenic reflex (autoregulation). Macula densa sensors in the juxtaglomerular feedback mechanism sense a decrease in sodium delivery and release renin, as well as augment the dilation of the afferent arteriole. Angiotensin II increases biosynthesis of vasodilator prostaglandins (e.g., prostaglandin E2 and prostacyclin), and induces preferential constriction of efferent arterioles. As a result, the fraction of plasma flowing through glomerular capillaries that is filtered is increased (filtration fraction), intraglomerular pressure is maintained, and GFR is preserved. The renin release also which increases total body water via the RAAS (but may be blocked by medications already). With more severe hypoperfusion, these compensatory responses are overwhelmed and GFR falls, leading to prerenal ARF.

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