Physiology of Urine Formation

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OBJECTIVES

1) To review the physiology of renal function and urine formation, including hemodynamics, control processes and oliguria as a physiologic response to stress. 2) To review the renal response to hypovolemia, hypervolemia and diuretic therapy. 3) To relate renal autoregulation and certain pathophysiologic states (sepsis, acute tubular necrosis) to the physiology of urine formation.

CASE PRESENTATION

GLOMERULAR STRUCTURE , FUNCTION AND REGULATION

Glomerular Ultrafiltration

The kidneys contain approximately 2 x10^6 nephrons, each of which consists of a glomerulus and a tubule emptying into a collecting duct. Urine is formed by the combination of glomerular ultrafiltration and tubular reabsorption and secretion. The afferent arteriole supplies a highly convoluted tuft of capillary loops, which subsequently drains into the efferent arteriole. Glomerular filtrate requires passage through three distinct layers, which are size-selective and charge-selective[1]: (1) the fenestrated capillary endothelium (which restricts the passage of cells only), (2) the basement membrane (which filters plasma proteins), and (3) the epithelial podocytes. The central mesangial cells have myofilaments of actin and myosin (which contract in response to angiotensin II) and regulate the effective glomerular surface area for filtration[2]. Molecules with radius < 18 Å (water, sodium, urea, glucose, inulin) are freely filtered, whereas those > 36 Å (hemoglobin, albumin) are not. Filtration of molecules 18 - 36 Å depends on their electrical charge. In the glomerulus, negatively charged glycoproteins retard the passage of other negatively charged proteins, so cations are filtered but anions are not. In glomerulonephritis, negatively charged glycoproteins are destroyed, polyanionic proteins are filtered, and proteinuria ensues.

Glomerular filtration rate (GFR) depends on (1) the permeability of the filtration barrier; and (2) the net difference between the hydrostatic forces pushing fluid into Bowman′s space and the osmotic forces keeping fluid in the plasma:

$$GFR = K_{UF} [(P_{GC} - P_{BS}) - (\pi_{GC} - \pi_{BS})].$$

K_{UF} is the ultrafiltration coefficient, which reflects capillary permeability and glomerular surface area. P_{GC} is the glomerular hydrostatic pressure, determined by the renal arterial pressure. π_{GC} is the plasma oncotic pressure: it is lowered by increased renal plasma flow, which washes out osmotically effective molecules. P_{BS} and π_{BS} reflect the hydrostatic and oncotic pressure in Bowman's space, which oppose the plasma pressures.

Regulation of Renal Blood Flow and Glomerular Filtration

Renal blood flow (RBF) and renal perfusion pressure are regulated by two control mechanisms: extrinsic and intrinsic.

The extrinsic mechanism involves complex interactions between opposing vasomotor effects. A series of vasoconstrictor, salt-retaining systems protect against hypovolemia, hypotension and hyponatremia. These include the sympathoadrenal axis, the renin-angiotensin-aldosterone system and arginine vasopressin (AVP). Opposing these are vasodilator, salt-excreting systems that protect against hypervolemia, hypertension and hypernatremia, consisting of the prostaglandins, atrial natriuretic peptide (ANP) and nitric oxide. The interaction of these systems regulates blood pressure, salt and water homeostasis[3].

The intrinsic mechanism is renal autoregulation, which depends on changes in afferent arteriolar tone in response to renal perfusion pressure.

Extrinsic Regulation and the Juxtaglomerular Apparatus (JGA)

The juxtaglomerular apparatus (JGA) consists of the afferent and efferent arterioles and the interposed macula densa, a modified portion of the medullary thick ascending loop (mTAL) of Henle.

The afferent arterioles contain renin-producing granular cells and baroreceptors and are innervated by sympathetic fibers. The glomerular mesangial cells contain actin fibers, which can be stimulated to constrict via a G-protein coupled-phospholipase C receptor by norepinephrine, angiotensin II and endothelin[2]. This decreases glomerular surface area and thus GFR. The cells of the macula densa are chemoreceptors. When the tubular chloride concentration is increased, renin-angiotensin elaboration is triggered and arteriolar constriction ensues, which decreases GFR (tubuloglomerular feedback). This could be a protective mechanism to prevent polyuria and dehydration in acute tubular necrosis (ATN) referred to as “acute renal success”[4].

The GFR is largely determined by the glomerular filtration pressure (GFP), which depends on the balance between afferent and efferent arteriolar tone.

Moderate hypovolemia (e.g. anesthetic induction, positive pressure ventilation) induces a low level of sympathetic activity and angiotensin II, which causes preferential efferent arteriolar constriction. This differential effect may be explained by increased nitric oxide activity in the afferent arteriole, which confers relative resistance to vasoconstriction[5]. This is an important compensatory mechanism that maintains GFP in the face of decreased afferent arteriolar pressure or blood flow. It is reflected by an increase in filtration fraction (FF), which is the GFR as a fraction of the renal plasma flow (RPF). Compensatory efferent arteriolar constriction may be abolished by inhibitors of angiotensin converting enzyme (ACE), e.g. captopril, enalapril, or angiotensin receptor blockers, e.g. losartin, and result in deteriorating GFR with hypovolemia.

With severe stress (i.e. shock), high levels of catecholamines and angiotensin II cause afferent as well as efferent arteriolar constriction, and compound the decrease of renal perfusion pressure on GFP[6]. The FF decreases and GFR worsens. Severe arterial hypotension stimulates the release of AVP to plasma levels between 10-100 pg/mL, and induces vasoconstriction via the V_1-receptor. AVP also preferentially constricts the efferent arteriole at lower levels and the afferent arteriole and glomerular mesangium at higher levels. However, efferent arteriolar constriction predominates through most of its concentration-response curve[7], so in shock preservation of GFR is more likely with AVP than norepinephrine-induced vasoconstriction.

Intrinsic Regulation (Autoregulation)

Renal autoregulation implies that renal blood flow (RBF) and GFR are kept constant and maintain solute and water regulation independently of wide fluctuations of mean arterial pressure (MAP)[8]. The resistance of the preglomerular afferent arteriole decreases as MAP decreases (myogenic response). When MAP increases it enhances delivery of chloride to the macula densa of the juxtaglomerular apparatus (JGA), which induces afferent arteriolar constriction and decreases RBF and GFR (tubuloglomerular feedback)[1]. However, urinary flow rate is not autoregulated - it is subject to the peritubular hydrostatic pressure and decreases with hypotension.

Although not abolished by most anesthetic agents, autoregulation appears to be impaired in severe sepsis[9] possibly because of the generation of massive amounts of endogenous nitric oxide[5]; in acute renal failure[10] and perhaps during cardiopulmonary bypass[11]. In these situations, RBF is dependent on renal perfusion pressure, acutely falls during hypotension, and is restored by vasoconstrictor therapy.

TUBULAR STRUCTURE AND FUNCTION

The tubule has four distinct segments: (1) the proximal tubule (PT); (2) the loop of Henle, which comprises the pars recta, the descending and ascending thin limb segments, and the mTAL; (3) the distal tubule (DT); and (4) the collecting duct, which courses through the cortex, outer medulla, and inner medulla before entering the renal pelvis at the papilla. The more numerous outer cortical nephrons have short loops of Henle and receive about 85% of the RBF. The juxtamedullary nephrons, which receive < 10% of the RBF have long loops of Henle that dive deeply into the inner medulla together with the vasa recta, and generate the countercurrent mechanism for medullary hypertonicity and renal concentrating ability.

Tubular Reabsorption and Secretion

Each day the glomeruli produce 180 L of ultrafiltrate, of which the tubules reabsorb 99% of the salt and water. Many other filtered substances are completely reabsorbed, but some have a maximum rate of tubular reabsorption (T_{max}). For glucose the T_{max} is 375 mg/dL, above which glycosuria results in direct proportion to the filtered load.

Each tubular cell has an apical (luminal) cell membrane with adjoining tight junctions, and a basolateral cell membrane, which interfaces with the peritubular capillary. There are many protein-based active transport systems, of which the most important is the sodium-potassium adenosine triphosphatase (Na-K ATPase) pump on the basolateral membrane. This pumps Na out of the tubular cell into the blood against a concentration and an electrical gradient in exchange for K. This decreases intracellular Na concentration and passively draws Na from the tubular lumen into the cell. The transport of virtually all solutes is coupled to that of Na. Active transport systems move solutes in the same direction (symporter) or in opposite directions (antiporter). Solutes are transported by both active and passive mechanisms, but water always diffuses passively along an osmotic gradient.

The most metabolically active components of the tubule are the PT, the mTAL and the first part of the DT.

Proximal Tubule

The first part of the PT reabsorbs about 100% of the filtered glucose, lactate, and amino acids as well as some phosphate by coupling with sodium-symporter systems[1]. About two-thirds of the filtered water, chloride and K are also reabsorbed, coupled with and strongly influenced by Na absorption. The PT is also an important site of secretion of many endogenous anions (bile salts, urate), cations (creatinine, dopamine) and drugs (diuretics, penicillin, probenecid, cimetidine). Organic ions compete for protein transport systems. For example probenecid impairs tubular secretion of penicillin and prolongs its action. In chronic renal insufficiency, excess organic acids compete for secretor proteins with drugs such as furosemide and confer “resistance” to loop diuretics.

Loop of Henle

The mTAL reabsorbs about 20% of filtered Na, chloride, K and bicarbonate. A Na-K ATPase pump in the basolateral membrane is the engine that drives its resorptive capacity. An important symporter protein system couples the reabsorption of Na, chloride and K across the apical membrane. This system is the major site of action of loop diuretics that inhibit Na chloride reabsorption in the mTAL.

The kidneys receive 20% of the total cardiac output but extract relatively little O_2 so that the renal arteriovenous O_2 difference [(a-v)O_2] is only 1.5 mL/dL. However, the medulla receives only 6% of the RBF, extracts a large proportion of O_2 and the tissue PO_2 is just 8 mmHg. Severe hypoxia may develop rapidly despite “adequate” total RBF. The metabolically active mTAL is particularly vulnerable to nephrotoxin-mediated hypoxic injury[12]. Endogenous vasoactive compounds normally direct blood flow to the medulla. Adenosine induces cortical vasoconstriction, while in the juxtamedullary zone prostaglandins and nitric oxide promote vasodilation. Prostaglandin inhibitors such as nonsteroidal anti-inflammatory agents (NSAIDs) can thus cause medullary ischemia.

The initial response to renal hypoperfusion is increased active Na chloride absorption in the mTAL, which increases oxygen consumption (VO_2) in the face of decreased oxygen delivery

(DO_2). When ATP stores become depleted, active Na chloride reabsorption winds down. This increases the chloride concentration in tubular fluid reaching the macula densa, resulting in angiotensin release and afferent arteriolar constriction (tubuloglomerular feedback). The resultant decrease in GFR benefits renal O_2 balance by decreasing solute reabsorption and mTAL VO_2[13]. Thus it is theoretically possible that loop diuretics or dopaminergic agents could alleviate ischemic or nephrotoxic insults to the tubules: by inhibiting active Na reabsorption in the mTAL, they might decrease tubular VO_2 and enhance O_2 balance[14].

Distal Tubule and Collecting Duct

The proximal segment of the DT is structurally and functionally similar to the mTAL. An apical cell membrane Na chloride symporter system is the site of action of thiazide diuretics. In the last part of the DT, principal cells reabsorb Na and water and secrete K (Na-K ATPase pump), while intercalated cells secrete H^+ and reabsorb bicarbonate (H^+ -ATPase pump).

The Countercurrent Mechanism and Osmotic Equilibrium

Urinary concentrating ability is dependent on (1) development of a hypertonic medullary interstitium (countercurrent mechanism, urea recycling); (2) subsequent tubular fluid dilution by active Na chloride reabsorption and water impermeability in the mTAL; and (3) the antidiuretic effect of arginine vasopressin (AVP) in increasing water permeability in the DT and collecting ducts.

The hypertonic medullary interstitium is created by the countercurrent multiplier effect of the loop of Henle, in which solute is separated from water (the single effect). The mTAL actively reabsorbs Na but is impermeable to water, which becomes trapped so that as the tubular fluid ascends it becomes more and more dilute. By the end of this “diluting segment”, tubular fluid osmolality has decreased to 1% increase in serum osmolality and at plasma levels of 1-5 pg/mL, AVP stimulates specific V_2-receptors in the collecting ducts to induce water reabsorption and a decreased flow of concentrated urine[16]. However, AVP release is also triggered by decreased venous stretch receptor activity (e.g. mechanical ventilation) and psychic stress (via cortical input), and may result in inappropriate water retention and hypoosmolality (SIADH)[17].

Hypovolemia

In the PT, sympathetic activity and angiotensin II increase Na reabsorption from about 66% to 80%. In the mTAL, DT and collecting duct, aldosterone and AVP also increase Na reabsorption. Release of AVP and activation of V_2 receptors causes avid reabsorption of water in the collecting duct, so that the urine becomes highly concentrated (> 600 mOsm/kg) with virtually no sodium (10 mEq/L). This is a classic prerenal syndrome, indicating intact tubular function and a perfectly appropriate response to intravascular hypovolemia. In severe dehydration this may persist despite the administration of “low dose” dopamine18 (i.e., dopamine is not a substitute for rehydration!).

Diuretic agents abolish urinary concentrating ability by washing out the hypertonic medulla. Osmotic diuretics (mannitol) prevent water reabsorption, loop diuretics (furosemide, bumetanide) inhibit active Na chloride transport in the mTAL, and thiazide diuretics (hydrochlorthiazide, metolazone) inhibit it in the first part of the DT. An early and important manifestation of ATN is the loss of urinary concentrating ability caused by the breakdown of the energy-requiring Na-K ATPase pump in the mTAL.

Hypervolemia

The tubular response to an expanded extracellular volume is controlled by a series of vasodilator, salt-excreting neurohormonal systems (prostaglandins, atrial natriuretic peptide).
The vasodilator prostaglandins (PGD_2, PGE_2, and PGI_2) oppose the effects of the vasoconstrictor systems and promote vasodilation and salt excretion[19]. They also provide endogenous renal protection in conditions of stress by maintaining perfusion to the oligemic renal medulla[20]. ANP is synthesized in specialized atrial myocytes and is released in response to atrial stretch[21]. It promotes the formation of cyclic GMP, which opposes the vasoconstrictor and salt-retaining effects of norepinephrine and angiotensin II, and inhibits renin, aldosterone and AVP release.

Reflex decreases in sympathetic and angiotensin II activity and the release of ANP cause RBF, GFR and the filtered Na load to increase, while Na reabsorption in the PT decreases from 66% to 50%. Decrease aldosterone and AVP limit Na absorption in the mTAL, DT and collecting duct. The absence of AVP (and the presence of ANP) impairs water absorption at the collecting duct, so that a dilute urine (300 mOsm/kg) with abundant Na (80 mEq/L) is produced. This urine profile (low osmolality, high urine Na) may be encountered in hypovolemia if loop diuretics have been given which depress tubular resorptive capacity. It is also pathognomonic of oliguric ATN, where it indicates complete loss of the normal ability of the tubules to conserve Na and water in the face of intravascular hypovolemia.

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