

جامعة الانبار

كلية : الصيدلة

قسم : فرع الادوية والسموم

اسم المادة باللغة العربية: السموم العامة

اسم المادة باللغة الإنكليزية: **General toxicology**

المرحلة: الرابعة

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عنوان المحاضرة باللغة العربية: الاستجابات السامة للكلى.

عنوان المحاضرة باللغة الإنكليزية: **Toxic Responses of the kidney**

Toxic Responses of the Kidney

Lecture 6

The functional integrity of the mammalian kidney is vital to total body homeostasis because the kidney plays a principal role in the excretion of metabolic wastes and in the regulation of extracellular fluid volume, electrolyte composition, and acid–base balance. In addition, the kidney synthesizes and releases hormones, such as renin and erythropoietin, and metabolizes vitamin D₃ to the active 1,25-dihydroxy vitamin D₃ form. A toxic insult to the kidney therefore could disrupt any or all of these functions and could have profound effects on total body metabolism.

FUNCTIONAL ANATOMY

Gross examination of a sagittal section of the kidney reveals three clearly demarcated anatomic areas: the cortex, medulla, and papilla (Figure 1). The cortex constitutes the major portion of the kidney and receives a disproportionately higher percentage (90%) of blood flow compared to the medulla (6%–10%) or papilla (1%–2%). The functional unit of the kidney, the nephron, may be considered in three portions: the vascular element, the glomerulus, and the tubular element.

The afferent and efferent arterioles, arranged in a series before and after the glomerular capillary tuft, respectively, are ideally situated to control glomerular capillary pressure and glomerular plasma flow rate. Indeed, these arterioles are innervated by the sympathetic nervous system and contract in response to nerve stimulation, angiotensin II, vasopressin, endothelin, adenosine, and norepinephrine, affecting glomerular pressures and blood flow. The efferent arterioles draining the cortical glomeruli branch into a peritubular capillary network, whereas those draining the juxtamedullary glomeruli form a capillary loop, the vasa recta, supplying the medullary structures.

These post-glomerular capillary loops provide an efficient arrangement for delivery of nutrients to the post-glomerular tubular structures, delivery of wastes to the tubule for excretion, and return of reabsorbed electrolytes, nutrients, and water to the systemic circulation.

The glomerulus is a complex, specialized capillary bed composed primarily of endothelial cells that are characterized by an attenuated and fenestrated cytoplasm, visceral epithelial cells characterized by a cell body (podocyte) from which many trabeculae and pedicles (foot processes) extend, and a glomerular basement membrane (GBM), which is a trilamellar structure sandwiched between the endothelial and epithelial cells (Figure 2). A portion of the blood entering the glomerular capillary network is fractionated into a virtually protein-free and cell-free ultrafiltrate, which passes through Bowman's space and into the tubular portion of the nephron.

The formation of such an ultrafiltrate is the net result of the Starling forces that determine fluid movement across capillary beds, that is, the balance between transcapillary hydrostatic pressure and colloid oncotic pressure.

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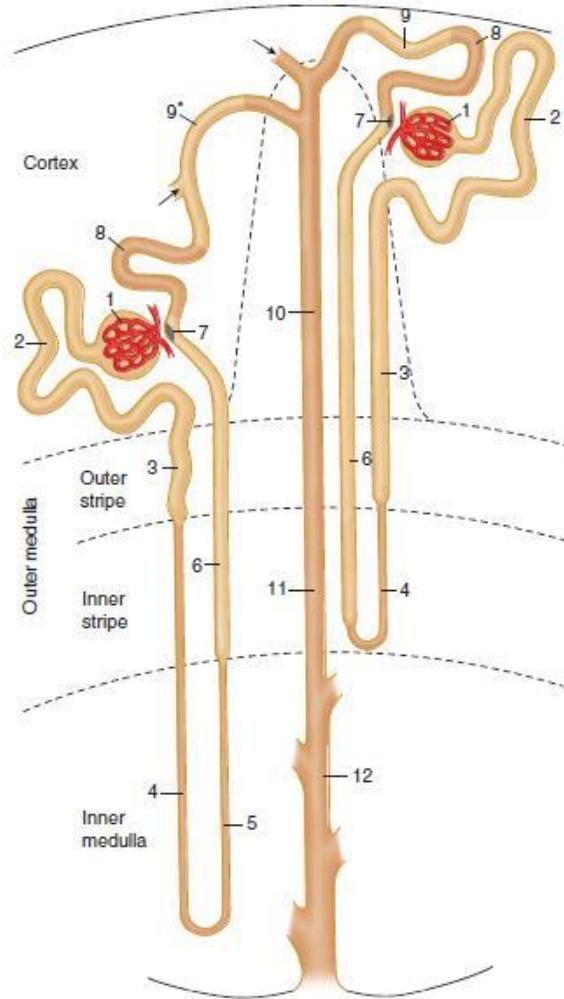


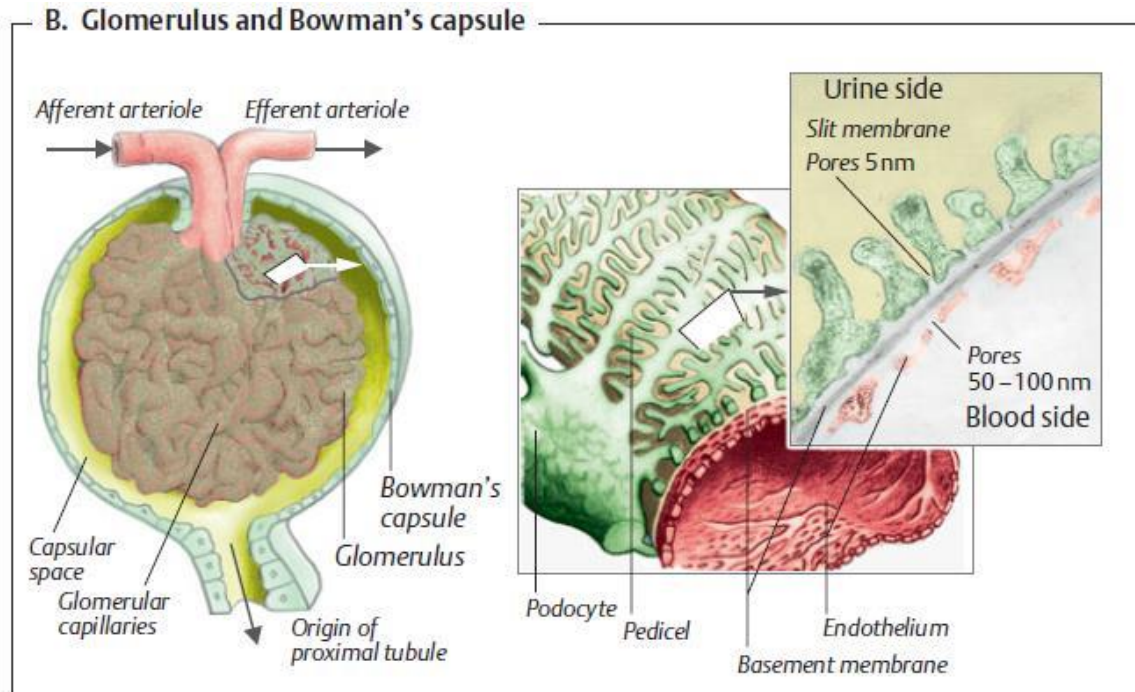
Figure 1. Schematic of short- and long-looped nephrons and the collecting system.

The filtration of macromolecules is inversely proportional to the molecular weight of a substance; thus, small molecules, such as inulin (molecular weight [MW] ~5,500), are freely filtered, whereas large molecules, such as albumin (MW 56,000–70,000), are restricted.

Filtration of anionic molecules tends to be restricted compared to that of neutral or cationic molecules of the same size. In particular, charge-selective properties of the glomerulus appear to be related to the anionic groups of the GBM coupled with the anionic coating of the epithelial and endothelial cells (Figure 2). These highly anionic components produce

electrostatic repulsion and hinder the circulation of polyanionic macromolecules, thereby markedly retarding passage of these molecules across the filtration barrier.

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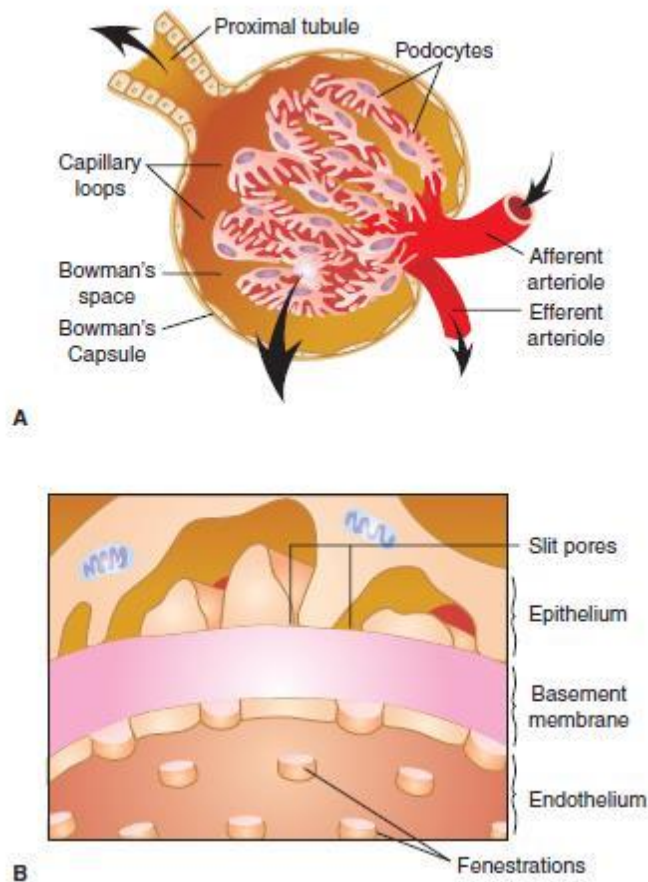


Figure 2.

(A) Bowman's capsule (B), Schematic of the ultrastructure of the glomerular capillaries. (C), Cross-section of the glomerular capillary membrane with the capillary endothelium, basement membrane, and epithelium podocytes

Proximal Tubule

The proximal tubule consists of three discrete segments: the S 1 (pars convoluta), S 2 (transition between pars convoluta and pars recta), and S 3 (the pars recta) segments (Figure 1). The formation of urine is a highly complex and integrated process in which the volume and composition of the glomerular filtrate is progressively altered as fluid passes through each of the different tubular segments. The proximal tubule is the workhorse of the nephron, as it reabsorbs approximately 60% to 80% of solute and water filtered at the glomerulus. Toxicant-induced injury to the proximal tubule therefore will have major consequences to water and solute balance. The proximal tubule contains numerous transport systems capable of driving concentrative transport of many metabolic substrates, including amino acids, glucose, and citric acid cycle intermediates.

The proximal tubule also reabsorbs virtually all the filtered low molecular-weight proteins by specific endocytotic protein reabsorption processes. In addition, small linear peptides may be hydrolyzed by peptidases associated with the proximal tubular brush border. An important excretory function of the proximal tubule is secretion of weak organic anions and cations by specialized transporters that drive concentrative movement of these ions from postglomerular blood into proximal tubular cells, followed by secretion into tubular fluid.

Loop of Henle, Distal Tubule and Collecting Duct

The thin descending and ascending limbs and the thick ascending limb of the loop of Henle are critical to the processes involved in urinary concentration (Figure 1). Approximately 25% of the filtered Na^+ and K^+ and 20% of the filtered water are reabsorbed by the segments of the loop of Henle.

The late distal tubule, cortical collecting tubule, and medullary collecting duct perform the final regulation and fine-tuning of urinary volume and composition. The remaining Na^+ is reabsorbed in conjunction with K^+ and H^+ secretion in the late distal tubule and cortical collecting tubule. The combination of medullary and papillary hypertonicity generated by countercurrent multiplication and the action of antidiuretic hormone (ADH, vasopressin) serve to enhance water permeability of the medullary collecting duct. Chemicals that interfere with ADH synthesis, secretion, or action therefore may impair concentrating ability.

PATHOPHYSIOLOGIC RESPONSES OF THE KIDNEY

Acute Kidney Injury

One of the most common manifestations of nephrotoxic damage is acute renal failure or acute kidney injury (AKI). AKI is a group of syndromes that comprises multiple causative factors and occurs in a variety of settings with varied clinical manifestations ranging from a minimal elevation in serum creatinine to anuric renal failure.

Any decline in GFR is complex and may result from prerenal factors (renal vasoconstriction, intravascular volume depletion, and insufficient cardiac output), postrenal factors (ureteral or bladder obstruction), and intrarenal factors (glomerulonephritis, tubular cell injury, death, and loss resulting in back leak; renal vasculature damage, interstitial nephritis) (Figure 3).

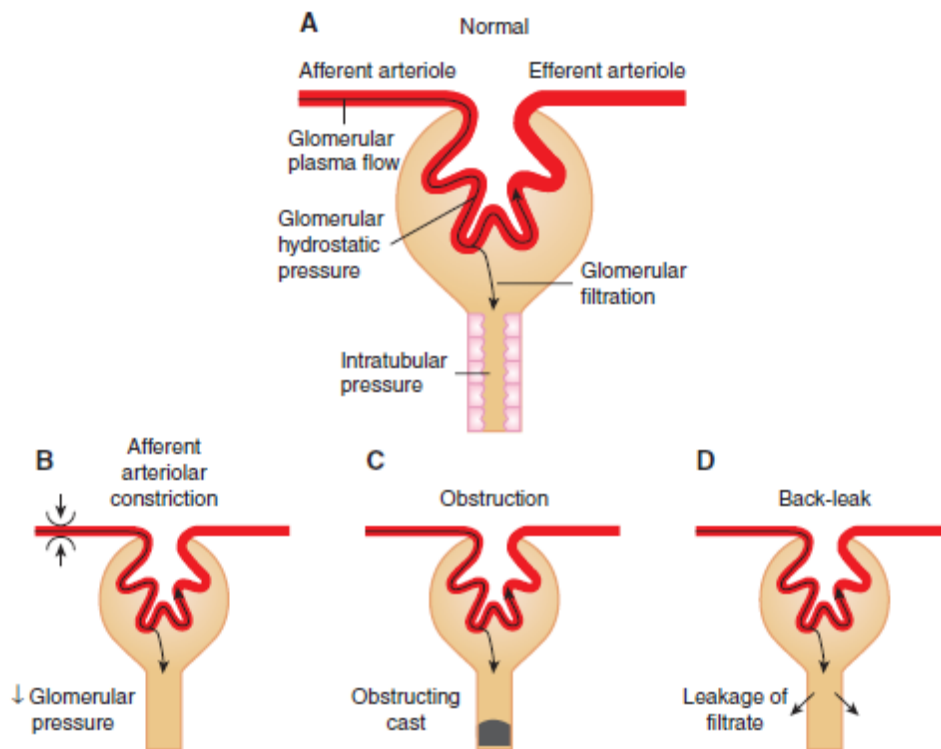
The pre- and postrenal factors can lead to decreased GFR. If a chemical causes tubular damage directly, then tubular casts can cause tubular obstruction, increased tubular pressure, and decreased GFR. The tubular damage may result in epithelial cell death/loss, leading to back leak of glomerular filtrate and a decrease in GFR.

Extensive evidence supports the idea that endothelial injury and inflammatory cells play a role in ischemia-induced AKI.

It is thought that more than 90% of AKI mediated by intrarenal factors is the result of ischemia/reperfusion injury or nephrotoxicity.

Although chemically induced AKI can be initiated by proximal tubular cell injury, nephrotoxicants may also delay the recovery of renal function by inhibiting cellular repair and regeneration. It was been demonstrated that cisplatin impaired tubular regeneration resulting in prolonged renal dysfunction, effects that were in contrast to the regenerative response and renal functional recovery following tobramycin-induced nephrotoxicity.

Figure 3. Mechanisms of reduction of the GFR. (A), GFR depends on 4 factors: (1) adequate blood flow to the glomerulus; (2) adequate glomerular capillary pressure; (3) glomerular permeability; and (4) low intratubular pressure. (B), Afferent arteriolar constriction decreases GFR by reducing blood flow, resulting in diminished capillary pressure. (C), Obstruction of the tubular lumen by cast formation increases tubular pressure; when tubular pressure exceeds glomerular capillary pressure, filtration decreases or ceases. (D), Back-leak occurs when the paracellular space between cells increases and the glomerular filtrate leaks into the extracellular space and bloodstream.



Chronic Kidney Disease

It is generally believed that progression to chronic kidney disease (CKD) and end-stage renal failure is not simply a function of a primary renal insult per se but rather is related to secondary pathophysiologic processes triggered by the initial injury.

A low level of injury or inflammation may exist following AKI that ultimately leads to CKD and/or may sensitize the kidney to a second insult.

Progressive deterioration of renal function may occur with long-term exposure to a variety of chemicals (eg, analgesics, lithium, and cyclosporine). The progression of chronic renal disease, for example, has been postulated to be a consequence of the glomerular hemodynamic response to renal injury.

That is, following nephron loss, there are adaptive increases in glomerular pressures and flows that increase the single-nephron GFR of remnant viable nephrons. Although these compensatory mechanisms serve to maintain whole-kidney GFR, evidence has accumulated to suggest that, with time, these alterations are mal-adaptive and foster the progression of renal failure.

The compensatory increases in glomerular pressures and flows of the remnant glomeruli may result in mechanical damage to the capillaries due to increased shear stress on the endothelium and damage to the glomerular capillary wall, leading to altered permeabilities, and mesangial thickening due to increased transcapillary flux and local deposition of macromolecules. Other factors likely to play a role in the pathogenesis of chronic renal failure include growth promoters and inhibitors, increased extracellular matrix deposition, reactive oxygen species (ROS), lipid accumulation, and tubulointerstitial injury.

Reasons for the Susceptibility of the Kidney to Toxicity

The unusual susceptibility of the mammalian kidney to the toxic effects of noxious chemicals can be attributed in part to the unique physiologic and anatomic features of this organ. Although the kidneys constitute only 0.5% of total body mass, they receive about 20% to 25% of the resting cardiac output. Consequently, any drug or chemical in the systemic circulation will be delivered to these organs in relatively high amounts. The processes involved in forming concentrated urine also serve to concentrate potential toxicants in the tubular fluid. As water and electrolytes are reabsorbed from the glomerular filtrate, chemicals in the tubular fluid may be concentrated, thereby driving passive diffusion of toxicants into tubular cells. Therefore, a nontoxic concentration of a chemical in the plasma may reach toxic concentrations in the kidney.

Finally, renal transport, accumulation, and metabolism of xenobiotics contribute significantly to the susceptibility of the kidney (and specific nephron segments) to toxic injury.

In addition to intrarenal factors, the incidence and/or severity of chemically induced nephrotoxicity may be related to the sensitivity of the kidney to circulating vasoactive substances. Under these conditions, vasoconstrictors such as angiotensin II or vasopressin are increased. Normally, the actions of high circulating levels of vasoconstrictor hormones are counterbalanced by the actions of increased vasodilatory prostaglandins; thus, renal blood flow (RBF) and GFR are maintained. However, when prostaglandin

synthesis is suppressed by NSAIDs, RBF declines markedly and AKI ensues, due to the unopposed actions of vasoconstrictors.

Site-Selective Injury

Many nephrotoxicants have their primary effects on discrete segments or regions of the nephron. For example, the proximal tubule is the primary target for most nephrotoxic antibiotics, antineoplastics, halogenated hydrocarbons, mycotoxins, and heavy metals, whereas the glomerulus is the primary site for immune complexes, the loop of Henle/collecting ducts for fluoride ions, and the medulla/papilla for chronically consumed analgesic mixtures. The reasons underlying this site-selective injury are complex but can be attributed in part to site-specific differences in blood flow, transport and accumulation of chemicals, physicochemical properties of the epithelium, reactivity of cellular/molecular targets, balance of bioactivation/detoxification reactions, cellular energetics, and/ or regenerative/repair mechanisms.

Glomerular Injury

The glomerulus is the initial site of chemical exposure within the nephron, and a number of nephrotoxicants produce structural injury to this segment. In certain instances, chemicals alter glomerular permeability to proteins by altering the size- and charge- selective functions.

The decrease in charge selectivity is thought to result from a decrease in negatively charged sites, while the loss of size selectivity is thought to result from focal detachment of podocytes from the GBM. Cyclosporine, amphotericin B, and gentamicin are examples of chemicals that impair glomerular ultrafiltration without significant loss of structural integrity and decrease GFR.

A chemical may function as a hapten attached to some native protein (eg, tubular antigens released secondary to toxicity) or as a complete antigen and elicit an antibody response.

Proximal Tubular Injury

The proximal tubule is the most common site of toxicant-induced renal injury. The reasons for this relate in part to the selective accumulation of xenobiotics into this segment of the nephron. For example, in contrast to the distal tubule, which is characterized by a relatively tight epithelium with high electrical resistance, the proximal tubule has a leaky epithelium, favoring the flux of compounds into proximal tubular cells. More importantly, tubular transport of organic anions and cations, low-molecular-weight proteins and peptides, GSH conjugates, and heavy metals is localized primarily if not exclusively to the proximal tubule. Thus, transport of these molecules will be greater in the proximal tubule than in other segments, resulting in proximal tubular accumulation and toxicity.

In addition to segmental differences in transport, segmental differences in cytochrome P450 and cysteine conjugate β -lyase activity also are contributing factors to the enhanced

susceptibility of the proximal tubule. Both enzyme systems are localized almost exclusively in the proximal tubule, with negligible activity in the glomerulus, distal

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tubules, or collecting ducts. Thus, nephrotoxicity requiring P450 and β -lyase-mediated bioactivation will most certainly be localized in the proximal tubule. Indeed, the site of proximal tubular bioactivation contributes at least in part to the proximal tubular lesions produced by chloroform (via cytochrome P450) and by haloalkene *S*-conjugates (via cysteine β -lyase).

Finally, proximal tubular cells appear to be more susceptible to ischemic injury than distal tubular cells. Therefore, the proximal tubule will likely be the primary site of toxicity for chemicals that interfere with RBF, cellular energetics, and/or mitochondrial function.

Loop of Henle/Distal Tubule/ Collecting Duct Injury

Chemically induced injury to the more distal tubular structures, compared to the proximal tubule, is an infrequent occurrence. Functional abnormalities at these sites manifest primarily as impaired concentrating ability and/or acidification defects. Drugs that have been associated with acute injury to the more distal tubular structures include amphotericin B, cisplatin, and methoxyflurane. Each of these drugs induces an ADH-resistant polyuria, suggesting that the concentrating defect occurs at the level of the medullary thick ascending limb and/or the collecting duct.

Fluoride inhibits sodium chloride reabsorption in the thick ascending limb and inhibits ADH-mediated reabsorption of water, possibly due to disruption in adenylate cyclase.