

Al-Rasheed University/ Collage of
Pharmacy

Kidney toxicity

by:

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TOXIC RESPONSES OF THE KIDNEY

Introduction

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

Introduction (cont.)

- Kidneys are equipped with a variety of detoxification mechanisms and have considerable functional reserve and regenerative capacities.
- The nature and severity of the toxic insult may be such that these detoxification and compensatory mechanisms are overwhelmed.
- Renal failure can be profound; permanent renal damage may result, requiring chronic dialysis treatment or kidney transplantation.

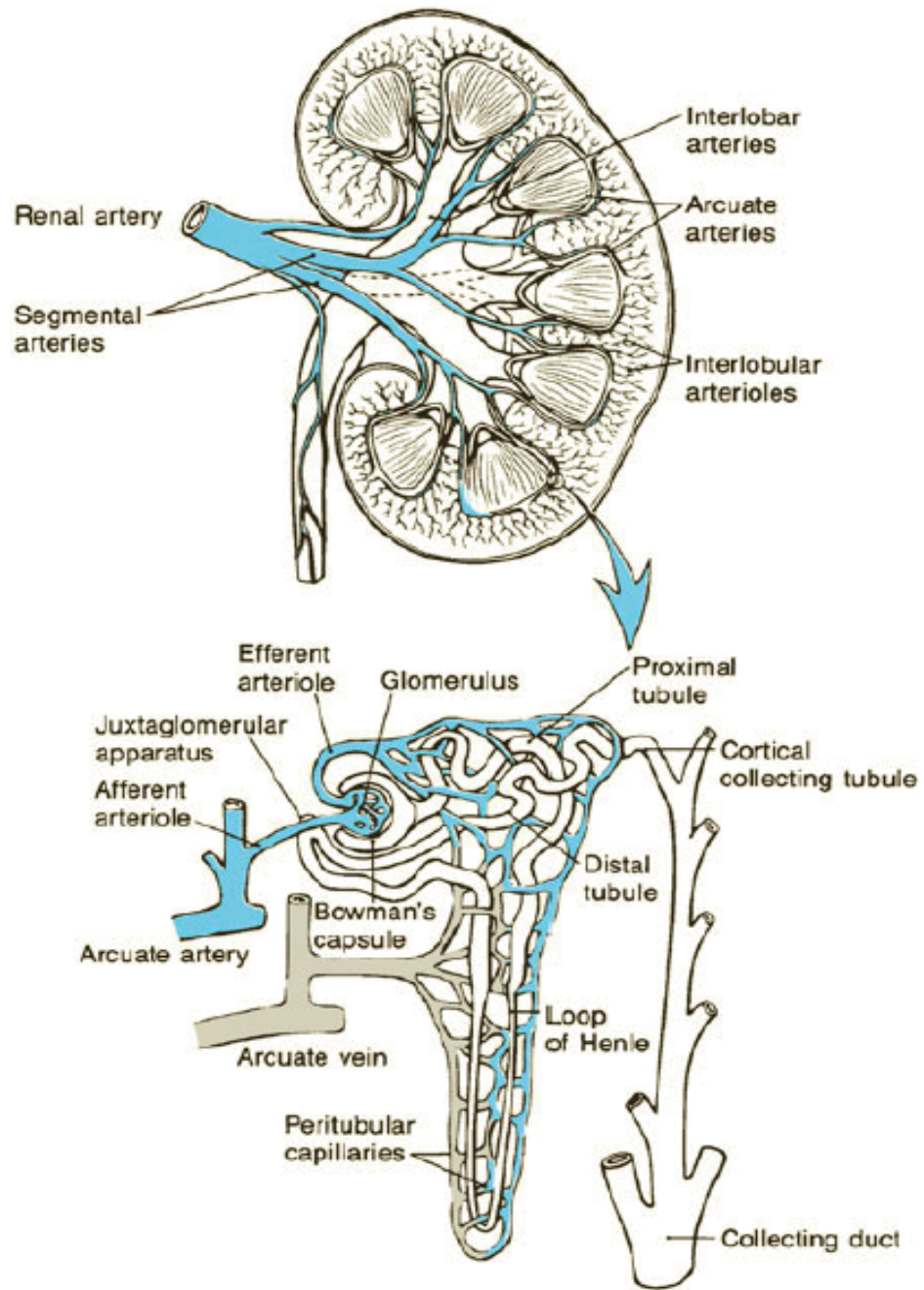
Filtration, Reabsorption, and Excretion Rates of Different Substances by the Kidneys*

	FILTERED (meq/24 h)	REABSORBED (meq/24 h)	EXCRETED (meq/24 h)	REABSORBED (%)
Glucose (g/day)	180	180	0	100
Bicarbonate (meq/day)	4320	4318	2	>99.9
Sodium (meq/day)	25,560	25,410	150	99.4
Chloride (meq/day)	19,440	19,260	180	99.1
Water (L/day)	169	167.5	1.5	99.1
Urea (g/day)	48	24	24	50
Creatinine (g/day)	1.8	0	1.8	0

*Glomerular filtration rate: 125 mL/min = 180 L/24 h.

FUNCTIONAL ANATOMY

- The kidney reveals three clearly demarcated anatomic areas: the cortex, medulla, and papilla.
- 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%).
- Thus, when a blood-borne toxicant is delivered to the kidney, a high percentage of the material will be delivered to the cortex and will have a greater opportunity to influence cortical rather than medullary or papillary functions.

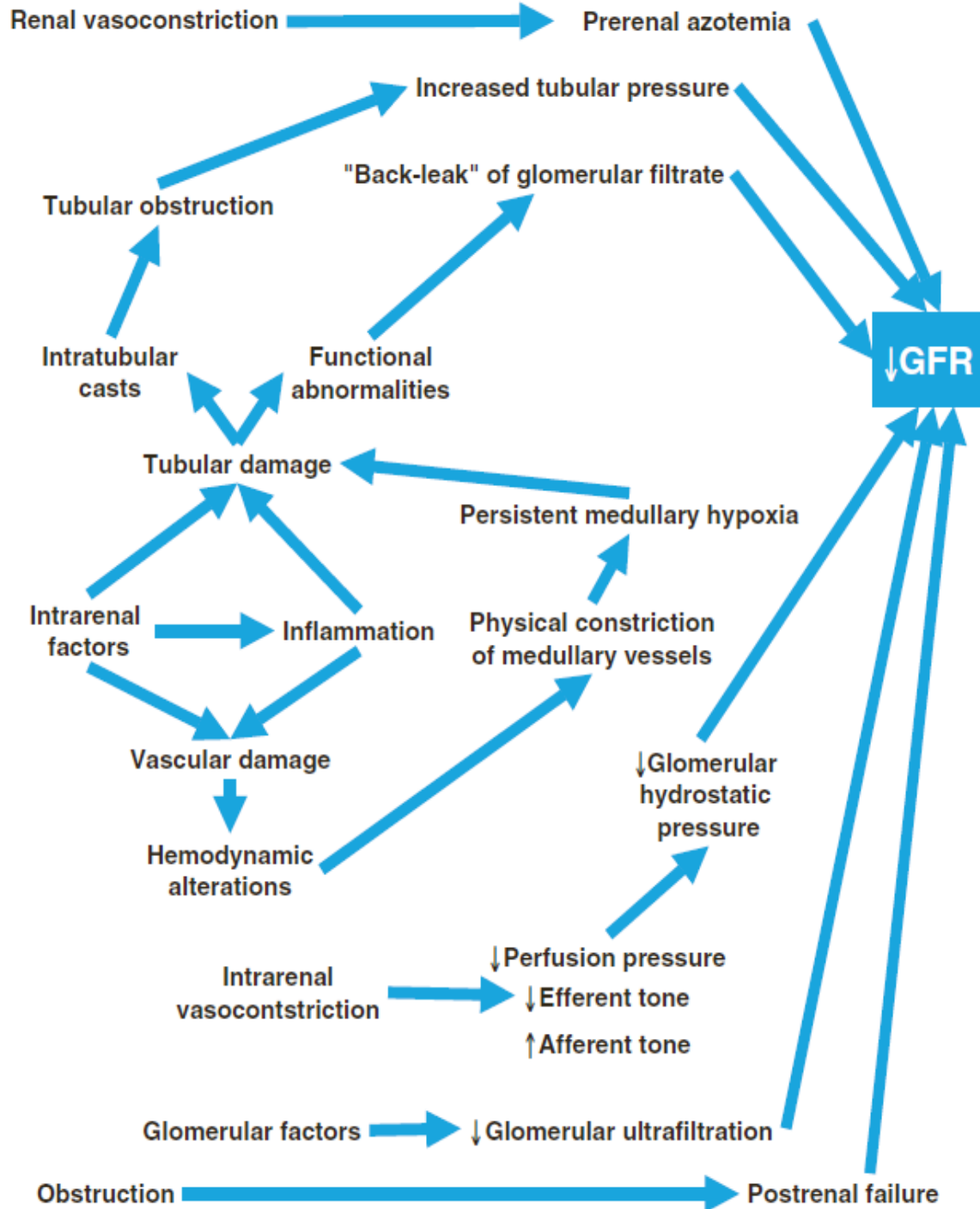


PATHOPHYSIOLOGIC RESPONSES OF THE KIDNEY

Acute Kidney Injury

- A decline in kidney function secondary to an injury that leads to a functional or structural change in the kidney.
- AKI is defined as a complex disorder 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)
 - ✓ Intrarenal factors (glomerulonephritis, tubular cell injury, death, and loss resulting in back leak; renal vasculature damage, interstitial nephritis).

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Acute Kidney Injury (cont.)

- It has been estimated that prerenal factors are responsible for AKI in 55–60% of patients, intrarenal factors are responsible for AKI in 35–40% of patients, and postrenal factors are responsible for AKI in <5% of patients.
- ❖ It is thought that more than 90% of AKI mediated by intrarenal factors is the result of ischemia/reperfusion injury or nephrotoxicity.

Mechanisms of Chemically Induced Acute Renal Failure

PRERENAL	VASOCONSTRICTION	CRYSTALLURIA	TUBULAR TOXICITY	ENDOTHELIAL INJURY	GLOMERULOPATHY	INTERSTITIAL NEPHRITIS
Diuretics	Nonsteroidal anti-inflammatory drugs	Sulfonamides	Aminoglycosides	Cyclosporine	Gold	Antibiotics
Angiotensin receptor antagonists		Methotrexate	Cisplatin	Mitomycin C	Penicillamine	Nonsteroidal anti-inflammatory drugs
Angiotensin-converting enzyme inhibitors	Radiocontrast agents	Acyclovir	Vancomycin	Tacrolimus	Nonsteroidal anti-inflammatory drugs	Diuretics
Antihypertensive agents	Cyclosporine Tacrolimus	Triamterene Ethylene glycol	Pentamidine Radiocontrast agents	Cocaine Conjugated estrogens		
	Amphotericin B	Protease inhibitors	Heavy metals Haloalkane- and Haloalkene-cysteine conjugates	Quinine		