Pathophysiology of Nephrotoxic Acute Renal Failure

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Humans are exposed intentionally and unintentionally to a variety of diverse chemicals that harm the kidney. As the list of drugs, natural products, industrial chemicals and environmental pollutants that cause nephrotoxicity has increased, it has become clear that chemicals with very diverse chemical structures produce nephrotoxicity. For example, the heavy metal $HgCl_2$, the mycotoxin fumonisin B_1, the immunosuppresant cyclosporin A, and the aminoglycoside antibiotics all produce acute renal failure but are not structurally related. Thus, it is not surprising that the cellular targets within the kidney and the mechanisms of cellular injury vary with different toxicants. Nevertheless, there are similarities between chemical-induced acute tubular injury and ischemia/reperfusion injury.

The tubular cells of the kidney are particularly vulnerable to toxicant-mediated injury due to their disproportionate exposure to circulating chemicals and transport processes that result in high intracellular concentrations. It is generally thought that the parent chemical or a metabolite initiates toxicity through its covalent or noncovalent binding to cellular macromolecules or through their ability to produce reactive oxygen species. In either case the activity of the macromolecule(s) is altered resulting in cell injury. For example, proteins and lipids in the plasma membrane, nucleus, lysosome, mitochondrion and cytosol are all targets of toxicants. If the toxicant causes oxidative stress both lipid peroxidation and protein oxidation have been shown to contribute to cell injury.

In many cases mitochondria are a critical target and the lack of adenosine triphosphate (ATP) leads to cell injury due to the dependence of renal function on aerobic metabolism. The loss of ATP leads

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to disruption of cellular ion homeostasis with decreased cellular K^+ content, increased Na^+ content and membrane depolarization. Increased cytosolic free Ca^{2+} concentrations can occur in the early or late phase of cell injury and plays a critical role leading to cell death. The increase in Ca^{2+} can activate calcium activated neutral proteases (calpains) that appear to contribute to the cell injury that occurs by a variety of toxicants. During the late phase of cell injury, there is an increase in Cl^- influx, followed by the influx of increasing larger molecules that leads to cell lysis. Two additional enzymes appear to play an important role in cell injury, particularly oxidative injury. Phospholipase A_2 consists of a family of enzymes in which the activity of the cytosolic form increases during oxidative injury and contributes to cell death. Caspases are a family of cysteine proteases that are activated following oxidative injury and contribute to cell death. Following exposure to a chemical insult those cells sufficiently injured die by one of two mechanisms, apoptosis or oncosis.

Clinically, a vast number of nephrotoxicants can produce a variety of clinical syndromes-acute renal failure, chronic renal failure, nephrotic syndrome, hypertension and renal tubular defects. The evolving understanding of the pathophysiology of toxicant-mediated renal injury has implications for potential therapies and preventive measures. This chapter outlines some of the mechanisms thought to be important in toxicant-mediated renal cell injury and death that leads to the loss of tubular epithelial cells, tubular obstruction, "backleak" of the glomerular filtrate and a decreased glomerular filtration rate. The recovery from the structural and functional damage following chemical exposures is dependent on the repair of sublethally-injured and regeneration of noninjured cells.

Clinical Significance of Toxicant-Mediated Acute Renal Failure

CLINICAL SIGNIFICANCE OF TOXICANT–MEDIATED RENAL FAILURE

- Nephrotoxins may account for approximately 50% of all cases of acute and chronic renal failure.
- Nephrotoxic renal injury often occurs in conjunction with ischemic acute renal failure.
- Acute renal failure may occur in 2% to 5% of hospitalized patients and 10% to 15% of patients in intensive care units.
- The mortality of acute renal failure is approximatley 50% which has not changed significantly in the last 40 years.
- Radiocontrast media and aminoglycosides are the most common agents associated with nephrotoxic injury in hospitalized patients.
- Aminoglycoside nephrotoxicity occurs in 5% to 15% of patients treated with these drugs.

FIGURE 15-1
Clinical significance of toxicant-mediated renal failure.

REASONS FOR THE KIDNEY'S SUSCEPTIBILITY TO TOXICANT INJURY

- Receives 25% of the cardiac output
- Sensitive to vasoactive compounds
- Concentrates toxicants through reabsorptive and secretive processes
- Many transporters result in high intracellular concentrations
- Large luminal membrane surface area
- Large biotransformation capacity
- Baseline medullary hypoxia

FIGURE 15-2
Reasons for the kidney's susceptibility to toxicant injury.

FACTORS THAT PREDISPOSE THE KIDNEY TO TOXICANT INJURY

- Preexisting renal dysfunction
- Dehydration
- Diabetes mellitus
- Exposure to multiple nephrotoxins

FIGURE 15-3
Factors that predispose the kidney to toxicant injury.

EXOGENOUS AND ENDOGENOUS CHEMICALS THAT CAUSE ACUTE RENAL FAILURE

- Antibiotics
  - Aminoglycosides (gentamicin, tobramycin, amikacin, netilmicin)
  - Amphotericin B
  - Cephalosporins
  - Ciprofloxacin
  - Demeclocycline
  - Penicillins
  - Pentamidine
  - Polymixins
  - Rifampin
  - Sulfonamides
  - Tetracycline
  - Vancomycin
- Chemotherapeutic agents
  - Adriamycin
  - Cisplatin
  - Methotraxate
  - Mitomycin C
  - Nitrosoureas (*eg*, streptozotocin, lomustine)
- Radiocontrast media
  - Ionic (*eg*, diatrizoate, iothalamate)
  - Nonionic (*eg*, metrizamide)
- Immunosuppressive agents
  - Cyclosporin A
  - Tacrolimus (FK 506)
- Antiviral agents
  - Acyclovir
  - Cidovir
  - Foscarnet
  - Valacyclovir
- Heavy metals
  - Cadmium
  - Gold
  - Mercury
  - Lead
  - Arsenic
  - Bismuth
  - Uranium
- Organic solvents
  - Ethylene glycol
  - Carbon tetrachloride
  - Unleaded gasoline
- Vasoactive agents
  - Nonsteroidal anti-inflammatory drugs (NSAIDs)
  - Ibuprofen
  - Naproxen
  - Indomethacin
  - Meclofenemate
  - Aspirin
  - Piroxicam
  - Angiotensin-converting enzyme inhibitors
  - Captopril
  - Enalopril
  - Lisinopril
  - Angiotensin receptor antagonists
  - Losartan
- Other drugs
  - Acetaminophen
  - Halothane
  - Methoxyflurane
  - Cimetidine
  - Hydralazine
  - Lithium
  - Lovastatin
  - Mannitol
  - Penicillamine
  - Procainamide
  - Thiazides
  - Lindane
- Endogenous compounds
  - Myoglobin
  - Hemoglobin
  - Calcium
  - Uric acid
  - Oxalate
  - Cystine

FIGURE 15-4
Exogenous and endogenous chemicals that cause acute renal failure.

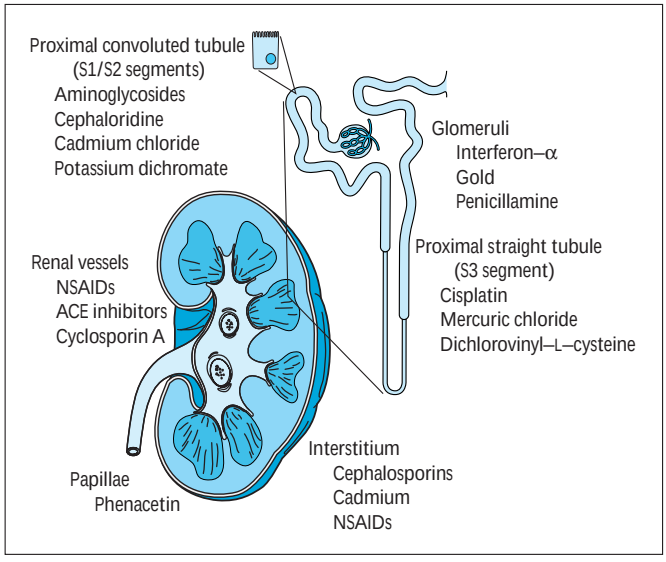

FIGURE 15-5
Nephrotoxicants may act at different sites in the kidney, resulting in altered renal function. The sites of injury by selected nephrotoxicants are shown. Nonsteroidal anti-inflammatory drugs (NSAIDs), angiotensin-converting enzyme (ACE) inhibitors, cyclosporin A, and radiographic contrast media cause vasoconstriction. Gold, interferon-alpha, and penicillamine can alter glomerular function and result in proteinuria and decreased renal function. Many nephrotoxicants damage tubular epithelial cells directly. Aminoglycosides, cephaloridine, cadmium chloride, and potassium dichromate affect the S1 and S2 segments of the proximal tubule, whereas cisplatin, mercuric chloride, and dichlorovinyl-L-cysteine affect the S3 segment of the proximal tubule. Cephalosporins, cadmium chloride, and NSAIDs cause interstitial nephritis whereas phenacetin causes renal papillary necrosis.