General Toxicology

Toxic Responses of the Kidney

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Specific nephrotoxicants:

- Heavy metals:
  - Mercury
  - Cadmium

- Halogenated hydrocarbons:
  - Chloroform
  - Tetrafluoroethylene

- Therapeutic agents:
  - Acetaminophen
  - NSAIDs
  - Aminoglycosides
  - Amphotericin B

Mercury:

- Due to its high affinity for sulfhydryl groups, virtually all of the Hg^{2+} found in blood is bound to cells—albumin, other sulfhydryl-containing proteins, glutathione, & cysteine.

- The S_3 segment of the proximal tubule is the initial site of Hg^{2+}, toxicity. As the dose or duration of treatment increases, the S_1 & S_2 segments may be affected.

- Early markers of $HgCl_2$-induced renal dysfunction include an increase in the urinary excretion of brush-border enzymes such as alkaline phosphatase & γ-glutamyl transpeptidas (γ-GT), suggesting that the brush border may be an initial target of $HgCl_2$.

- As injury progresses, tubular reabsorption of solutes & water decreases & there is an increase in the urinary excretion of glucose, amino acids, albumin, & other proteins.

- There is progressive decline in the glomerular filtration rate (GFR) resulting from the glomerular injury, tubular injury, &/or vasoconstriction.

- Mitochondrial dysfunction is an early & important contributor to inorganic mercury-induced cell death along the proximal tubule.

Cadmium:

- Cadmium has a half-life of greater than 10 years in humans & thus accumulates in the body over time. Approximately 50% of the body burden of cadmium can be found in the kidney.
- Cadmium produces proximal tubule dysfunction (S_1 & S_2 segments).
- Metallothionein binds to cadmium & thereby renders it biologically inactive. This assumes that the unbound or “free” concentration of cadmium is the toxic species. Once the renal metallothionein pool is saturated, “free” Cd2+ initiates injury.

Chloroform:

- The primary cellular target is the proximal tubule, with no primary damage to the glomerulus or the distal tubule.

- Proteinuria, glucosuria, & increased BUN levels are all characteristic of chloroform-induced nephrotoxicity.

- The nephrotoxicity produced by chloroform is linked to its metabolism by renal cytochrome P450, which biotransforms chloroform to trichloromethanol, which is unstable & releases HCl to form phosgene which injuriously reacts with cellular macromolecules.

Tetrafluoroethylene:

- Tetrafluoroethylene is conjugated with glutathione in the liver.

- The cysteine S-conjugate is the penultimate nephrotoxicant of tetrafluoroethylene.

- This nephrotoxicant is a substrate for the cytosolic & mitochondrial forms of the enzyme cysteine conjugate β-lyase. The products of this reaction are ammonia, pyruvate, & a reactive thiol that is capable of binding covalently to cellular macromolecules causing cellular damage.

Acetaminophen:

- There is be a marked species difference in the nature & mechanism of APAP nephrotoxicity.

- Morphologically, the primary targets in the mouse kidney are the S_1 & S_2segments of the proximal tubule, whereas in the rat kidney the S_3 segment is the target.

- In the mouse, renal cytochrome P4502E1 has been associated with APAP biotransformation to a reactive intermediate, N-acety-*p*-amino-benzoquinoneimine (NAPQI), that arylates proteins in the proximal tubule & initiates cell death.

Types of nephrotoxicity caused by nonsteroidal anti-inflammatory drugs (NSAIDs):

I. Acute kidney injury (AKI):

- It may occur within hours of a large dose of a NSAID, usually reversible upon withdrawal of the drug, & is characterized by decreased renal blood flow (RBF) & GFR & by oliguria.

- A number of risk factors (eg, renal insufficiency, congestive heart failure, hemorrhage, hypertension) are known to facilitate the development of AKI following NSAIDs consumption.

II. Analgesic nephropathy:

- Chronic consumption of combinations of NSAIDs &/or APAP (>3 years) results in an often irreversible form of nephrotoxicity known as analgesic nephropathy.

- Impaired urinary concentration & acidification are the earliest clinical manifestations.

- The primary lesion in this nephropathy is papillary necrosis with chronic interstitial nephritis.

III. Interstitial nephritis:

- The third, even though rare, type of nephrotoxicity associated with NSAIDs is an interstitial nephritis with a mean time of NSAID exposure to development of approximately five months.

- This nephrotoxicity is characterized by a diffuse interstitial edema with mild-to-moderate infiltration of inflammatory cells. Patients normally present with elevated serum creatinine, proteinuria, & nephritic syndrome.

- If NSAIDs are discontinued, renal function improves in one to three months.

Aminoglycosides:

- The incidence of renal dysfunction following aminoglycoside administration ranges from 0% to 50%, but seldom leads to a fatal outcome.

- Renal dysfunction by aminoglycosides is characterized by a nonoliguric renal failure with reduced GFR & an increase in serum creatinine & BUN. Polyuria is an early event following aminoglycoside administration.

- Within 24 hours, increases in urinary brush border enzymes, glucosuria, aminoaciduria, & proteinuria are observed.

- Histologically, there is damage to the brush border, endoplasmic reticulum, mitochondria, & cytoplasm, ultimately leading to tubular cell necrosis.

- The earliest lesion observed following clinically relevant doses of aminoglycosides is an increase in the size & number of lysosomes, which contain phospholipids leading to renal phospholipidosis.

Amphotericin B:

- Amphotericin B administration is associated with decreases in RBF & GFR. Amphotericin B nephrotoxicity is characterized by anti-diuretic hormone (ADH)-resistant polyuria, renal tubular acidosis, hypokalemia, & either acute or chronic renal failure.

- Amphotericin B nephrotoxicity is unusual in that it impairs the functional integrity of the glomerulus & of the proximal & distal portions of the nephron.

Cyclosporine:

- Nearly all patients who receive the drug exhibiting some form of nephrotoxicity.

- Clinically, calcineurin inhibitor (CNI)-induced nephrotoxicity may manifest as:
  - acute reversible renal dysfunction,
  - acute vasculopathy (thrombotic) microangiopathy), &
  - chronic CNI nephrotoxicity with interstitial fibrosis.

- Vasoconstriction probably plays a contributing role in nephrotoxicity induced by cyclosporine.

  Studies have also suggested that oxidative stress plays a role in cyclosporine nephrotoxicity in rats.


Thank
you