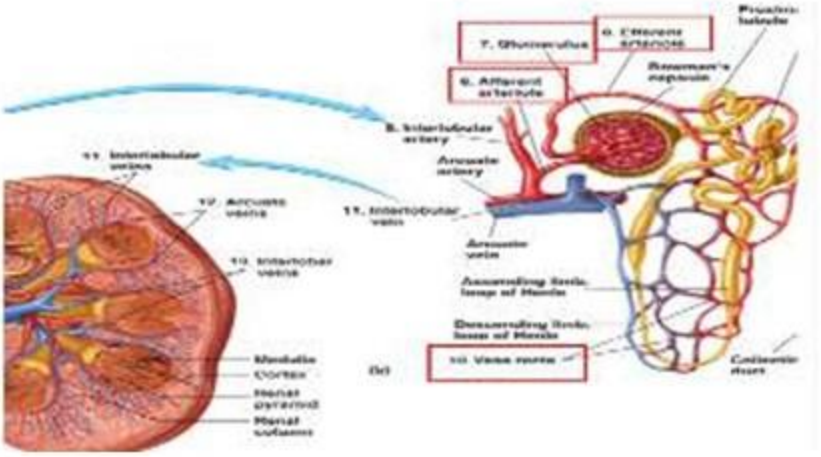
Toxic Responses of the Kidney



Adaptation after Toxic Insult:

The kidney has a remarkable ability to compensate for a loss in single-nephron GFR, Where are accompanied by proportionate increases in proximal tubular water and solute reabsorption, so that renal function appears normal on standard clinical tests. The changes in renal function may not be detected until these compensatory mechanisms are overwhelmed by significant nephron loss and/or damage. There are a number of cellular and molecular responses to a nephrotoxic insult (cell death by apoptosis or oncosis) in addition cellular proliferation.

Two of the most notable cellular adaptation responses are:

- metallothionein induction
- stress protein induction(Heat-shock proteins) and glucose-regulated proteins (Grps) are two examples of stress protein families that are induced in response to a number of pathophysiologic states such as heat shock, anoxia, oxidative stress, toxicants, heavy metal exposure, and tissue trauma.

These proteins are involved in normal structure and the degradation of damaged proteins and provide a defense mechanism against toxicity by facilitating recovery and repair.

ASSESSMENT OF RENAL FUNCTION

Nephrotoxicity can be assessed by tests includes measurement of urine volume and osmolality, pH, and urinary composition (e.g., electrolytes, glucose, and protein). Urinary excretion of high-molecular-weight proteins, such as albumin is suggestive of glomerular damage, whereas excretion of low molecular-weight proteins, such as β2-microglobulin, suggests proximal tubular injury where urinary excretion of enzymes localized in the brush border (e.g., alkaline phosphatase, y- glutamy I transpeptidase) may reflect brush-border damage, whereas urinary excretion of other enzymes (e.g., lactate dehydrogenase) may reflect more generalized cell damage.

GFR can be measured directly by determining creatinine or inulin clearance. Inulin an exogenous compound that is completely filtered with no reabsorption or secretion. Indirect markers of GFR are serial blood urea nitrogen (BUN) and serum creatinine concentrations. Chemically induced increases in BUN and/or serum creatinine may not necessarily reflect renal damage but rather may be secondary to dehydration, hypovolemia, and/or protein catabolism.

Glomerular Injury:

A number of nephrotoxicants , alter glomerular permeability to proteins. Cyclosporine, amphotericin B, and gentamicin impair glomerular ultrafiltration without a significant loss of structural integrity and decreased GFR. Amphotericin B decreases GFR by causing renal vasoconstriction and decreasing the glomerular capillary ultrafiltration coefficient (Kf). Gentamicin interacts with the anionic sites on endothelial cells, decreasing Kf and GFR. Cyclosporine not only causes renal vasoconstriction and vascular damage but is injurious to the glomerular endothelial cell.

Proximal Tubular Injury:

The proximal tubule is the most common site of toxicant-induced renal injury. 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. Drugs such as aminoglycosides, B-lactam antibiotics, and cisplatin: environmental chemicals such as ochratoxin and metals such as cadmium and mercury. The nephrotoxic potential of xenobiotics depends on the intrinsic reactivity of the drug with subcellular or molecular targets. Both cytochrome P450 and cysteine conjugate B-lyase are localized almost exclusively in the proximal tubule, and bioactivation contributes at least in part to the proximal tubular lesions produced by chloroform (via cytochrome P450) and haloalkene S-conjugates (via cysteine B-lyase).

Loop of Henle/Distal Tubule/Collecting Duct Injury:

Functional abnormalities at these sites manifest primarily as impaired concentrating ability and/or acidification defects. Amphotericin B, cisplatin, and methoxyflurane all of them caused induce an ADH-resistant polyuria, that causes the concentrating defect occurs at the level of the medullary thick ascending limb and/or the collecting duct. Amphotericin B is highly lipophilic and interacts with lipid sterols such as cholesterol, resulting in the formation of transmembrane channels or pores and disrupting membrane permeability. Thus amphotericin effectively transforms the tight distal tubular epithelium into one that is leaky to water and ions and impairs at these sites. The mechanism mediating cisplatin-induced polyuria by the first phase is responsive to vasopressin associated and inhibitors of prostaglandin synthesis.

Methoxyflurane nephrotoxicity: is associated with the inhibitory effects of the metabolite fluoride on solute and water reabsorption. Fluoride inhibits sodium chloride reabsorption in the thick ascending limb and inhibits ADH-mediated reabsorption of water, possibly due to disruption in adenylate cyclase.

Papillary Injury:

Occur because chronic injurious effects when susceptible to abusive consumption of analgesics. The initial target for analgesics was the medullary interstitial cells, followed by degenerative changes in the medullary capillaries, loops of Henle, and collecting ducts. The important factor may contribute to this site selective injury, including high papillary concentrations of potential toxicants and inhibition of vasodilatory prostaglandins, compromising RBF to the renal medulla papilla and resulting in tissue ischemia.

Biochemical Mechanisms/Mediators of Renal cell Injury

Mediators of Toxicity:

Nephrotoxicants: the toxicant may have a high affinity for a specific macromolecule or class of macromolecules that result in altered activity (increase or decrease) of these molecules and cell injury. Chemical may initiate injury indirectly by inducing oxidative stress via increase reactive oxygen species in the cells directly or after being biotransformed into a reactive intermediate. The resulting increase in reactive oxygen species such as superoxide anion, hydrogen peroxide, and hydroxyl radicals causes oxidative stress nephrotoxicity is associated with ischemia/reperfusion injury, this is what are caused by gentamicin, cyclosporine, cisplatin, and haloalkene cysteine conjugates.

Amphotericin B reacts with plasma membrane sterols, increasing membrane permeability. Fumonisin B1 inhibits sphinganine (sphingosine) N-acyl transferase. Hg^{2+} binds to sulfhydryl groups on cellular proteins. alkylating agents, are electron-deficient compounds (electrophiles) that bind to cellular nucleophiles (electron-rich compounds) such as proteins and lipids For example, acetaminophen and chloroform are metabolized in kidney by cytochrome P450 to the reactive intermediates, N-acetyl-p-benzoquinoneimine and phosgene.

Mitochondria:

Numerous nephrotoxicants cause mitochondrial dysfunction. For example, pentachlorobutadienyl-1-cysteine initially uncouples oxidative phosphorylation in renal proximal tubular cells by dissipating the proton gradient, role in determining whether cells die by apoptosis or oncosis. Further, the release of apoptotic proteins such as apoptosis inducing factor (AIF), cytochrome c, Endonuclease G a key role in activating downstream caspases and executing apoptosis.

Lysosomes:

Which are key subcellular targets of aminoglycosides, unleaded gasoline, and d limonene, are believed to induce cellular injury through rupture and release of lysosomal enzymes into the cytoplasm after excessive accumulation of reabsorbed toxicant(s) and lysosomal overload.

Specific Nephrotoxicants

Mercury:

The kidneys are target organs for the accumulation of Hg^{2+}. The acute nephrotoxicity induced by $HgCl_2$ is characterized by proximal tubular necrosis and acute renal failure within 24 to 48 hr after administration. Early markers of $HgCl_2$-induced renal dysfunction include an increase in the urinary excretion of brush-border enzymes such as alkaline phosphatase and gamma-GT. Subsequently, when tubular injury becomes severe, intracellular enzymes such as lactate dehydrogenase and aspartate aminotransferase increase in the urine. As injury progresses, tubular reabsorption of solutes and water decreases.

Tetrafluoroethylene

It is conjugated with glutathione in the liver, and then secreted into the bile and small intestine, where it is degraded to the cysteine S-conjugate, reabsorbed, and transported to the kidney. After transport into the proximal tubule, the cysteine s-conjugate is a substrate for the cytosolic and forms of the enzyme cysteine conjugate b-lyase. That catalyzes beta-elimination reactions with cysteine S-conjugates that possess an electron-withdrawing group attached at the sulfur.

Nonsteroidal Anti-Inflammatory Drugs:

Three different types of nephrotoxicity have been associated with NSAID administration:
acute renal failure may occur within hours after a large dose of a NSAID, is usually reversible upon withdrawal of the drug, and is characterized by decreased RBF and oliguria. When the normal production of vasodilatory prostaglandins is inhibited NSAIDs, vasoconstriction induced by circulating catecholamines and angiotensin II is unopposed, resulting in decreased RBF and ischemia.

Chronic NSAIDs (>3years) results in an often irreversible of papillary necrosis nephrotoxicity. The mechanism by the process may result from chronic medullary/papillary ischemia the secondary to

renal vasoconstriction or from genesis of a reactive intermediate that in turn initiates an oxidative stress or binds to critical cellular macromolecule.

nephrotoxicity associated with NSAIDs is an interstitial nephritis. These patients normally present with elevated serum creatinine and proteinuria. If NSAIDs a discontinued, renal function improves in 1 to 3 months.

Aminoglycosides:

Nephrotoxic by aminoglycosides is characterized by nonoliguric renal failure because reduced GFR, an increase in serum creatinine and BUN, and polyuria. Polyuria an early event following aminoglycoside administration and may be due to inhibition of chloride transport in the thick ascending limb. aminoglycosides are highly polar cations; they are almost exclusively filtered by the glomerulus and excreted unchanged. Filtered aminoglycosides undergo proximal tubule reabsorption by binding to anionic phospholipids in the brush border, followed by endocytosis and sequestration in lysosomes. The earliest lesion observed following clinically relevant doses of aminoglycosides is an increase in the size and number of lysosomes. The renal phospholipidosis produced by the aminoglycosides is thought to occur through their inhibition of lysosomal hydrolases, such as sphingomyelinase and phospholipases.

Cyclosporine

cyclosporine-induced nephrotoxicity may manifest as acute reversible renal dysfunction

1. Acute renal dysfunction nephropathy with is characterized by dose-related decreased RBF& GFR & increases in BUN and serum creatinine. The decreased RBF& GFR is related to marked vasoconstriction induced by cyclosporine. In particular, increased production of the vasoconstrictor thromboxane A2 appears to play a role in cyclosporine- induced acute renal failure. Endothelin may contribute to constriction of the afferent arteriole because endothelin receptor antagonists inhibit cyclosporine-induced vasoconstriction.

2. Acute vasculopathy

Called thrombotic microangiopathy is a rather usual nephrotoxic lesion that affects arterioles and glomerular capillaries without inflammatory component, following cyclosporine treatment. Hyaline and/or fibroid changes, often with fibrinogen deposition, are observed in arterioles, whereas thrombosis with endothelial cell desquamation affects the glomerular capillaries.

3. Chronic nephropathy with interstitial fibrosis: Long-term treatment with it can result in chronic nephropathy with interstitial fibrosis and tubular atrophy. These lesions may not be reversible if cyclosporine therapy is discontinued and may result in end-stage renal disease.

Mycotoxins:

They are products of molds and fungi and a number of mycotoxins produce nephrotoxicity such as aflatoxin B1, citrinin, ochratoxins, fumonisins, and patulin. Citrinin nephrotoxicity is characterized by decreased urine osmolality, GFR and RBF, and increased urinary enzyme excretion. Interestingly, the location of citrinin-induced tubular damage (proximal, distal) varies among species. Whereas the mechanism of citrinin toxicity to the tubules, citrinin enters the cells through the organic anion transporter and causes mitochondrial dysfunction. While acute exposures of ochratoxin produce similar effects on the kidney as citrinin, chronic exposures result in tubular atrophy and fibrosis. Fumonisins B1 and B2 are commonly found on corn products & produce nephrotoxicity in rats and rabbits. Histologic examination of the kidney revealed disruption of the basolateral membrane, mitochondrial swelling. The fumonisins are structurally similar to sphingoid bases and are thought to

produce their toxicity through the inhibition of sphinganine (sphingosine) N-acyltransferase. the ratio of free Inhibition of this enzyme results in an increase in the ratio of free sphinganine to free sphingosine and a decrease in complex sphingolipids.

Skin toxicity

The skin protects the body against external insults maintain internal homeostasis. It participates directly in thermal, electrolyte, hormonal, metabolic, and immune regulation. The skin was affected with toxicant depend on a variety of intrinsic and extrinsic factors, including body duration of exposure, and other environmental conditions.

Factors Influencing Cutaneous Responses:

1-Body Site

-Thick stratum corneum-good, it considers physical barrier and common site of contact with chemicals.

-Enhanced percutaneous absorption in intertriginous areas (axillae, neck, finger webs, umbllicus, genitalia, Postauricular) because they are moist, occluded areas, chemicals trapping.

-Face Exposed frequently for chemicals, frequently chemicals transferred from hands

-Eyelids, Poor barrier function-thin epidermis, these areas more sensitive to irritants.

-Scalp considers chemical trapping and occlusion area. Hair follicles susceptible to metabolic damage.

2-Genetic Factors:

-Predisposition to skin disorders,

-Variation in sensitivity to irritants,

-Susceptibility to contact sensitization

3-Temperature: Vasodilation-improved percutaneous absorption, Increased sweating-trapping in the epidermis, these cells are stimulated by ultraviolet light to produce melanin granules, which leads to became pigmented skin. In addition Migrating through the epidermis are numerous Langerhans cells, which are important participants in the immune response of skin to foreign agents.

Percutaneous Absorption:

The stratum corneum is the primary barrier to percutaneous absorption. Diseases (e.g psoriasis) and other conditions (e.g., abrasion, wounding) that compromise this barrier can permit greatly increased uptake of poorly permeable substances.

Biotransformation:

The ability of the skin to metabolize agents that diffuse through it contributes to its barrier function. The epidermis and pilosebaceous units are the major sites of such activity in the skin. Enzymes participating in biotransformation that are mod in skin include multiple forms of cytochrome P450, epoxide hydrolase, UDP-glucuronosyltransferase, quinone reductase, and glutathione transferases. other metabolic enzyme such as sulfatases, B-glucuronidase, N-acetyltransferases, esterases, and reductases. Region of the stratum corneum has catabolic activities (e.g., proteases, lipase, glycosidases, phosphatase).

Contact Dermatitis:

Irritant and allergic contact dermatitis, two distinct inflammatory processes, result from adverse exposures of the skin. These syndromes have indistinguishable. Classically, erythema (redness), induration (thickening and firmness) scaling (flaking), and vesiculation (blistering) are present on areas in direct contact with the chemical agent.

1- Irritant Dermatitis:

is a non-immune related response caused by the direct action of an agent on the skin. Direct corrosives, solvents, oxidizing and reducing agents, and dehydrating agents act as irritants by disrupting the keratin ultrastructure or directly injuring critical cellular macromolecules or organelles. Marginal irritants (detergents, soaps, household cleaners).

Chemical Burns:

Extremely corrosive and reactive chemicals may produce immediate coagulative necrosis that results in substantial tissue damage, with ulceration and sloughing. The lesion is a direct result of the chemical insult. Resulting in either continued cutaneous damage or percutaneous absorption and systemic injury after exposure.

2- Allergic Contact Dermatitis:

Allergic contact dermatitis represents a delayed (type IV) hypersensitivity reaction. an immune reaction to a sensitizer, one must be genetically prepared to become sensitized, have sufficient contact with a sensitizing chemical, and then have repeated contact later, Common Contact Allergens (Bacitracin, Neomycin, Aminoglycosides, Sulfonamides, Benzalkonium chloride, chlorhexidine, chloroxylenol, chromium, Cobalt).

Phototoxicology:

the skin is exposed to radiation that spans the electromagnetic spectrum, including ultraviolet (UV), visible, and infrared radiation from the sun extends from 290 to 700 nm, artificial light sources, electromagnetic radiation, and heat sources, all these have capable of inducing skin changes. The absorption of light in deeper, more vital structures of the skin is dependent on chromophores, epidermal thickness, and water content that differ from region to region on the body, the chromophores melanin and amino acids are capable of absorbing UV-B (290 to 320 nm) radiation.

Adverse Responses to Electromagnetic Radiation:

After exposure, the most evident acute feature of UV radiation exposure is erythema (redness or sunburn). The minimal erythema dose (MED): the smallest dose of UV light that needed induce an erythematous response, varies greatly from person to person. The vasodilation responsible for the color change is accompanied by significant alterations in inflammatory mediators such as prostaglandins D2, E2 and F2; leukotriene and prosticyclin local Inflammatory cells as well as from injured keratinocytes.

1. **UV-B (290 to 320 nm)** is the most effective solar band in causing erythema human skin. Environmental conditions that affect uv-induced injury include duration of exposure, season, altitude, body site, skin pigmentation, and previous exposure substantially greater dosage

2. **UV-A (320 to 400 nm):** reached to the earth up to 100-fold compared with UV-B ; however, its efficiency in generating erythema in human bout 1000-fold less than that of UV-B. overt pigment darkening is typical response to UV-A exposure. This may be accomplished by enhanced melanin production by melanocytes or by the photooxidation of melanin. The tanning increased pigmentation usually occurs within 3 days of exposure to UV light whereas photo oxidation is evident immediately.

The tanning response is produced most readily by exposure in the UV-B band, serves to augment the protective effects of melanin in the skin. However, the immediate pigment darkening characteristic of UV-A and visible light exposure does not confer improved photoprotection.