TOXIC RESPONSES OF THE LIVER

The liver's strategic location between intestinal tract and the rest of the body facilitates the performance of its enormous task of maintaining metabolic homeostasis of the body. Venous blood from the stomach and intestine flows into the portal vein and then through the liver before entering the systemic circulation. Thus the liver is the first organ to encounter ingested nutrients, vitamins,metals, drugs, and environmental toxicants as well as waste products of bacteria that enter portal blood. Efficient scavenging or uptake processes extract these absorbed materials from the blood for catabolism, storage, and/or excretion into bile. The liver is the main organ where exogenous chemicals are metabolized and eventually excreted. As a consequence, liver cells are exposed to significant concentrations of these chemicals which can result in liver dysfunction, cell injury, and even organ failure.

Many factors make liver the target site for so many chemicals: Location, specialized processes for uptake , biliary secretion produce higher exposure levels in the liver than in other tissues of the body & abundant capacity for bioactivation reactions influences the rate of exposure to proximate toxicants. To recognize potential liver cell dysfunction and injury, it is necessary to have a general knowledge of liver physiology and function**.**

Hepatic Functions

Two concepts exist for organization of the liver into operational units, namely, the lobule and the acinus. Classically,the liver was divided into hexagonal lobules oriented around terminal hepatic venules (also known as central veins). At the corners of the lobule are the portal triads (or portal tracts), containing a branch of the portal vein, a hepatic arteriole, and a bile duct . Blood entering the portal tract via the portal vein and hepatic artery is mixed in the penetrating vessels, enters the sinusoids,and percolates along the cords of parenchymal cells (hepatocytes),eventually flows into terminal hepatic venules, and exits the liver via the hepatic vein. The lobule is divided into three regions known as centrolobular, midzonal, and periportal. The acinus is the preferred concept for a functional hepatic unit. The terminal branches of the portal vein and hepatic artery, which extend out from the portal tracts, form the base of the acinus. The acinus has three zones: zone 1 is closest to the entry of blood, zone 3 abuts the terminal hepatic vein, and zone 2 is intermediate. The strategic location of the liver between the intestinal tract and the rest of the body facilitates the performance of its enormous task of maintaining metabolic homeostasis of the body. Venous blood from the stomach and intestines flows into the portal vein and then through the liver before entering the systemic circulation. The liver is the first organ to encounter ingested nutrients, vitamins, metals, drugs, and environmental toxicants as well as waste products of bacteria that enter portal blood. Hepatic sinusoids are the channels between cords of hepatocytes where blood percolates on its way to the terminal hepatic

vein.Sinusoids are larger and more irregular than normal capillaries. The three major types of cells in the sinusoids are endothelial cells,Kupffer cells, and stellate cells.

All the major functions of the liver can be altered detrimentally by acute or chronic exposure to toxicants. When toxicants inhibit or otherwise impede hepatic transport and synthetic processes, dysfunction can occur without appreciable cell damage . Loss of function also occurs when toxicants kill an appreciable number of cells and when chronic insult leads to the replacement of cell mass by nonfunctional scar tissue.

In the pharmaceutical industry, adverse effects on the liver are one of the most frequently cited reasons for discontinuing the development of drug candidates In addition, hepatotoxicity recognized during the postmarketing phase is one of the main causes for withdrawing drugs from the market like Troglitazone . the increasing popularity of herbal medicines, which are generally plant extracts, enhances the incidence of drug-induced liver injury and liver failure.

Bile Formation

Bile is a yellow fl uid containing bile acids, GSH, phospholipids, cholesterol, bilirubin and other organic anions, proteins, metals, ions, and xenobiotics. Adequate bile formation is essential for uptake of lipid nutrients from the small intestine, for protection of the small intestine from oxidative insults , and for excretion of endogenous and xenobiotic compounds. The canaliculi are separated from the intercellular space between hepatocytes by tight junctions, which form a barrier permeable only to water, electrolytes, and to some degree to small organic cations. Under physiological conditions, tight junctions are impermeable to organic anions allowing the high concentrations of bile acids, GSH, bilirubin diglucuronide, and other organic anions in bile. The

structure of the biliary tract is analogous to the roots and trunk of a tree, where the tips of the roots equate to the canalicular lumens. Canaliculi form channels between hepatocytes that connect to a series of larger and larger channels or ducts within the liver. The large extrahepatic bile ducts merge into the common bile duct. Bile can be stored and concentrated in the gallbladder before its release into the duodenum.

Secretion into biliary ducts is usually but not always a prelude to toxicant clearance by excretion in feces or urine. Exceptions occur when compounds such as arsenic are repeatedly delivered into the intestinal lumen via bile, efficiently absorbed from the intestinal lumen, and then redirected to the liver via portal blood, a process known as *enterohepatic cycling*. A few compounds, such as methyl mercury, are absorbed from the biliary tract; the extensive reabsorption of methyl mercury from the gallbladder is thought to contribute to the long biological half-life and toxicity of this toxicant. Alternatively, secretion into bile of toxicant metabolites can be a critical prelude to the development of injury in extrahepatic tissues. A

clinically relevant example of bile as an important delivery route for a proximate toxicant is that of diclofenac, a widely prescribed nonsteroidal anti-inflammatory drug (NSAID) that causes small intestinal ulceration.

Toxicant-related impairments of bile formation are more likely to have detrimental consequences in populations with other conditions where biliary secretion is marginal. For example, neonates exhibit delayed development of multiple aspects of bile formation, including synthesis of bile acids and the expression of sinusoidal and canalicular transporters .Neonates are more prone to develop jaundice when treated with drugs that compete with bilirubin for biliary clearance. Individuals with genetic defi ciency of certain transporters are not only at risk for chronic liver injury and fibrosis, but may also be more susceptible to drugs and hepatotoxicants.

Mechanisms and Types of Toxin-induced Liver Injury

The response of the liver to chemical exposure depends on the intensity of the insults, the cell population affected, and the durationof the chemical exposure (acute vs. chronic). Milder stresses may just cause reversible cellular dysfunction, e.g., temporary cholestasis after exposure to estrogens. However, acute poisoning with acetaminophen or carbon tetrachloride triggers parenchymal cell necrosis. Exposure to ethanol induces steatosis, which may enhance the susceptiblity to subsequent inflammatory insults.

Cell Death

Based on morphology, liver cells can die by two different modes, necrosis or apoptosis. Necrosis is characterized by cell swelling, leakage of cellular contents, nuclear disintegration and an influx of inflammatory cells. Because necrosis is generally the result of an exposure to a toxic chemical or other traumatic conditions, e.g., ischemia, large numbers of contiguous hepatocytes and nonparenchymal cells may be affected. Necrotic process can be identified by the release of liver-specific enzymes such as alanine (ALT) or aspartate (AST) aminotransferase into the plasma. In contrast, apoptosis is characterized by cell shrinkage, chromatin condensation, nuclear fragmentation, formation of apoptotic bodies, and, generally a lack of inflammation. There are two pathways for apoptosis In the **extrinsic pathway** of apoptosis, ligands (e.g., Fas ligand, TNF-α) bind to their respective death receptor (Fas receptor, TNF receptor type I), which triggers the trimerization of the receptor followed by recruitment of various adapter molecules and procaspases to the cytoplasmic tail of the receptor. The assembly of this death-inducing signaling complex (DISC) leads to the activation of initiator caspases (caspase-8 or -10). In hepatocytes, the active initiator caspase cleaves Bid, a member of the Bcl-2 family of proteins, then translocates together with other Bcl-2 family members such as Bax to the mitochondria. These proteins form pores in the outer membrane of the mitochondria and cause the release of intermembrane proteins such as cytochrome *c* and other apoptotic inducing factors. **The intrinsic pathway** is generally triggered by a cytotoxic stress or DNA damage, which activates the tumor suppressor p53 .This protein acts as transcription factor to promote the formation of pro-apoptotic Bcl-2 family members, e.g., Bax. The increased Bax translocation to the mitochondria induces the release of mitochondrial intermembrane proteins including cytochrome *c, Smac, endonuclease G, and* apoptosis-inducing factor (AIF) .

The characteristic morphological features of apoptosis are caused by the activation of caspases, which trigger the activation of enzymes such as caspase-activated DNase (CAD) responsible for inter nucleosomal DNA fragmentation if the rate of apoptosis is substantially increased, the apoptotic process cannot be completed. In this case, cells undergo secondary necrosis with breakdown of membrane potential, cell swelling, and cell contents release. Mechanisms of toxin-induced injury to liver cells include lipid peroxidation, binding to cell macromolecules, mitochondrial damage, disruption of the cytoskeleton, and massive calcium influx.

Canalicular Cholestasis

Defined physiologically as a decrease in the volume of bile formed or an impaired secretion of specific solutes into bile, cholestasis is characterized biochemically by elevated serum levels of compounds that normally are concentrated in bile, particularly bile salts and bilirubin. When biliary excretion of the yellowish bilirubin pigment is impaired, this pigment accumulates in the skin and eyes, producing jaundice, and spills into urine, which becomes bright yellow or dark brown. Many different types of chemicals cause cholestasis The molecular mechanisms of cholestasis are related to expression and function of transporter systems in the basolateral and canalicular lead to increased hepatic uptake, decreased biliary excretion, and increased biliary reabsorption of a drug may contribute to its accumulation in the liver. Furthermore, there is a growing list of drugs including rifampicin, bosentan, and troglitazone, which are known to directly inhibit BSEP (bile salt export pump). However, estrogen and progesterone metabolites inhibit BSEP from the canalicular side after excretion by MRP2 . A substantial inhibition of bile salt excretion can lead to accumulation of these compounds in hepatocytes and may directly cause cell injury. Bile acids are substrates for the nuclear receptor farnesoid X receptor (FXR). FXR activation stimulates the small heterodimeric partner 1 (SHP1), which downregulates NTCP and limits bile acid uptake .In addition, FXR activation causes the increased expression of BSEP and MDR3, which enhances the transport capacity for bile acids and phospholipids, respectively, at the canalicular membrane. Recent findings indicate that agonists of the nuclear xenobiotic receptors constitutive androstane receptor (CAR) and pregnane X receptor (PXR) can not only induce MRP3 and -4 expression but also induce bile acid hydroxylation by Cyp3a11 and Cyp2b10 resulting in improved export and detoxification of bile acids during cholestasis, Thus, the pharmacological modulation of transporter expression may counteract some of the detrimental effects of cholestasis with various etiologies

Bile Duct Damage

Another name for damage to the intrahepatic bile ducts is *cholangiodestructive cholestasis* . A useful biochemical index of bile duct damage is a sharp elevation in serum activities of enzymes localized to bile ducts, particularly alkaline phosphatase. In addition, serum levels of bile acids and bilirubin are elevated, as observed with canalicular cholestasis. Initial lesions following a single dose of cholangiodestructive chemicals include swollen biliary epithelium,debris of damaged cells within ductal lumens, and inflammatory cell infiltration of portal tracts. Chronic administration of toxins that cause bile duct destruction can lead to biliary proliferation and fibrosis resembling primary biliary cirrhosis(PBC). A number of drugs have been implicated to

cause prolonged cholestasis with features of PBC . However, only in rare cases will there be permanent damage or even loss of bile ducts, a condition known as *vanishing bile duct syndrome*. Cases of this persisting problem have been reported in patients receiving antibiotics , anabolic steroids, contraceptive steroids, and carbamazepine.

Sinusoidal Damage

The sinusoid is a specialized capillary with numerous fenestrae for high permeability. The functional integrity of the sinusoid can be compromised by dilation or blockade of its lumen or by progressive destruction of its endothelial cell wall. **Dilation** of the sinusoid will occur whenever efflux of hepatic blood is impeded. The rare condition of primary dilation, known as *peliosis hepatis*, has been associated with exposure to anabolic steroids and the drug danazol. **Blockade** will occur when the fenestrae enlarge to such an extent that red blood cells become caught in them or pass through with entrapment in the interstitial space , Endothelial cell gaps and injury have been shown after exposure to acetaminophen, Microcystin and galactosamine /endotoxin. A consequence of endothelial cell injury is the loss of barrier function with extensive blood accumulation in the liver resulting in hypovolemic shock. **Progressive destruction** of the endothelial wall of the sinusoid will lead to gaps and then ruptures of its barrier integrity, with entrapment of red blood cells. These disruptions of the sinusoid are considered the early structural features of the vascular disorder known as veno-occlusive disease, Well established as a cause of veno-occlusive disease are the pyrrolizidine alkaloids (e.g., monocrotaline, retrorsine, and seneciphylline) found in some plants used for herbal teas and in some seeds that contaminate food grains. Numerous episodes of human and animal poisoning by pyrrolizidine alkaloids have been reported around the world, including massive problems affecting thousands of people in Afghanistan. Veno-occlusive disease is also a serious complication in about 15% of the patients given high doses of chemotherapy (e.g., cyclophosphamide) . Selective depletion of glutathione within sinusoidal endothelial cells and activation of matrix metalloproteinases are critical events in the mechanism of endothelial cell injury in veno-occlusive disease.

Fatty Liver

Fatty liver (steatosis) is defined biochemically as an appreciable increase in the hepatic lipid (mainly triglyceride) content,which is<5% by weight in normal human liver. Currently, the most common cause of hepatic steatosis is insulin resistance due to central obesity and sedentary lifestyle. However, acute exposure to many hepatotoxins, e.g., carbon tetrachloride, and drugs can induce steatosis. Compounds that produce prominent steatosis associated with lethality include the antiepileptic drug valproic acid and the antiviral drug fialuridine , Ethanol is by far the most relevant drug or chemical leading to steatosis in humans and in experimental animals. Often, drug-induced steatosis is reversible and does not lead to death of hepatocytes. The

metabolic inhibitors ethionine, puromycin, and cycloheximide cause fat accumulation without causing cell death. Although steatosis alone may be benign, it can develop into steatohepatitis (alcoholic or nonalcoholic), which is associated with significant liver injury. Steatohepatitis can progress to fibrosis and even hepatocellular carcinoma. Livers with steatosis are more susceptible to additional insults such as hepatotoxins.

Drug-induced steatosis is mainly caused by compounds such amiodarone, tamoxifen, perhexiline, amineptine, doxycycline & tetracycline. which accumulate in mitochondria and inhibit β-oxidation and mitochondrial respiration.

Fibrosis and Cirrhosis

Hepatic fibrosis (scaring) occurs in response to chronic liver injury and is characterized by the accumulationof excessive amounts of fibrous tissue, specifically fibril forming collagens type I and III, and a decrease in normal plasma membrane collagen type IV. With continuing collagen deposition, the architecture of the liver is disrupted by interconnecting fibrous scars. When the fibrous scars subdivide the remaining liver mass into nodules of regenerating hepatocytes, fibrosis has progressed to cirrhosis and the liver has limited residual capacity to perform its essential functions. The primary cause of hepatic fibrosis/cirrhosis in humans worldwide is viral hepatitis. However, biliary obstruction and in particular alcoholic and nonalcoholic steatohepatitis are of growing importance for the development of hepatic fibrosis. In addition, fibrosis can be induced by chronic exposure to drugs and chemicals including ethanol and by heavy metal. Repeated treatment with carbon tetrachloride,thioacetamide, dimethylnitrosamine, aflatoxin, or other chemicals has been associated with hepatic fibrosis in experimental animals and humans. Central to the development of fibrosis is the activation of hepatic stellate cells (HSC) , which are the main cell type producing extracellular matrix proteins .

Activating of HSC can be reactive oxygen species and lipid peroxidation products generated in injured hepatocytes. In addition, Kupffer cells can release reactive oxygen and proinflammatory cytokines during the phagocytosis of cell debris or apoptotic bodies that can recruiting more inflammatory cells and enhancing the injury and oxidant stress.

Tumors

Chemically induced neoplasia can involve tumors that are derived from hepatocytes, bile duct cells, or the rare, highly malignant angiosarcomas derived from sinusoidal lining cells. Hepatocellular cancer has been linked to chronic abuse of androgens,alcohol, and a high prevalence of aflatoxin-contaminated diets. In addition, viral hepatitis, metabolic diseases such as hemochromatosis and α1-antitrypsin deficiency, and nonalcoholic steatohepatitis are major

risk factors for hepatocellular carcinoma. Angiosarcomas have been associated with occupational exposure to vinyl chloride and arsenic. Exposure to Thorotrast (radioactive thorium dioxide used as contrast medium for radiology) has been linked to tumors derived from hepatocytes, sinusoidal cells, and bile duct cells. The compound accumulates in Kupffer cells and emits radioactivity throughout its extended half-life.

The molecular mechanism of hepatocellular carcinoma is complex and poorly understood. The malignant transformation of hepatocytes occurs as a result of **increased cell turnover** due to chronic liver injury, persistent inflammation, regeneration, and cirrhosis. **Direct DNA** binding of carcinogens or their reactive metabolites (e.g., aflatoxin metabolites) or **indirect DNA** modifications by reactive oxygen species generated during inflammation and cell injury can lead to genetic alterations in hepatocytes resulting in impaired DNA repair, the **activation** of cellular oncogenes, and **inactivation** of tumor suppressor genes. An overall imbalance between stimulation of proliferation and inhibition of apoptosis in the liver leads to the survival and expansion of these preneoplastic cells. The functional inactivation of p53 by mutations prevents the induction of apoptosis.

Critical Factors in Toxicant- Induced Liver Injury

Location and specialized processes for uptake and biliary secretion produce higher exposure levels in the liver than in other tissues of the body, and strikingly high levels within certain types of liver cells. Then, the abundant capacity for bioactivation reactions infl uences the rate of exposure to proximate toxicants. Subsequent events in the pathogenesis appear to be critically infl uenced by responses of sinusoidal cells and the immune system.

Uptake and Concentration

Hepatic “first pass” uptake of ingested chemicals is facilitated by the location of the liver downstream of the portal blood flow from the gastrointestinal tract. Lipophilic compounds, particularly drugs and environmental pollutants, readily diffuse into hepatocytes because the fenestrated epithelium of the sinusoid enables close contact between circulating molecules and hepatocytes. Other toxins are rapidly extracted from blood because they are substrates for transporters located on the sinusoidal membrane of hepatocytes Phalloidin and microcystin are illustrative examples of hepatotoxins that target the liver as a consequence of extensive uptake into hepatocytes by sinusoidal transporters. Ingestion of the mushroom *Amanita phalloides* is a common cause of severe, acute hepatotoxicity in continental Europe and North America.
Because of its dual blood supply from both the portal vein and the hepatic artery, the liver is presented with appreciable amounts of all toxicants in the systemic circulation. Accumulation within liver cells by processes that facilitate uptake and storage is a determining factor in the hepatotoxicity of vitamin A and several metals. Vitamin A hepatotoxicity initially affects stellate cells, which actively extract and store this vitamin. Early responses to high-dose vitamin A therapy are stellate cell engorgement, activation, increase in number, and protrusion into the sinusoid . Cadmium hepatotoxicity becomes manifest when the cells exceed their capacity to sequester cadmium as a complex with the metal-binding protein, metallothionein (MT).
Iron poisoning produces severe liver damage. Hepatocytes contribute to the homeostasis of iron by extracting this essential metal from the sinusoid by a receptor-mediated process and maintaining a reserve of iron within the storage protein ferritin. Acute Fe toxicity is most commonly observed in young children who accidentally ingest iron tablets .The cytotoxicity

of free iron is attributed to its function as an electron donor for the Fenton reaction, where hydrogen peroxide is reductively cleaved to the highly reactive hydroxyl radical, an initiator of lipid peroxidation. Accumulation of excess iron beyond the capacity for its safe storage in ferritin is initially evident in the zone 1 hepatocytes, which are closest to the blood entering the sinusoid.

Bioactivation and Detoxification

One of the vital functions of the liver is to eliminate exogenous chemicals and endogenous intermediates. Therefore, hepatocytes contain high levels of phase-I enzymes, which have the capacity to generate reactive electrophilic metabolites. Hepatocytes also have a wide variety of phase-II enzymes, which enhance the hydrophilicity by adding polar groups to lipophilic compounds and target these conjugates to certain carriers in the canalicular or plasma membrane for excretion.

Although electrophiles may be effectively conjugated and excreted,the intermediate is highly reactive, and some of these compounds can react with proteins and other target molecules before an interaction with a phase-II enzyme ,and if the amount of the reactive metabolite exceeds the capacity of the hepatocyte to detoxify it, covalent binding to cellular macromolecules will occur and potentially result in cell injury. Thus, the balance between phase-I reactions,which generate the electrophile, and conjugating phase-II reactions determines whether a reactive intermediate is safely detoxified or may cause cell dysfunction or injury.

Because the expression of phase-I and -II enzymes and of the hepatic transporters can be influenced by genetics (e.g., polymorphism of drug-metabolizing enzymes) and lifestyle (e.g., diet, consumption of other drugs and alcohol),the susceptibility to potential hepatotoxins can vary markedly between individuals. Several prominent and important examples are discussed.

Acetaminophen(APAP)

One of the most widely used analgesics, acetaminophen is a safe drug when used at therapeutically recommended doses. Typical therapeutic doses of acetaminophen are not hepatotoxic, because most of the acetaminophen gets glucuronidated or sulfated with little drug bioactivation. However, an overdose can cause severe liver injury and even liver failure after an overdose, the formation of large amounts of (*N*-acetyl-*p*-benzoquinone imine) NAPQI leads first to depletion of cellular glutathione (GSH) stores and subsequently causes covalent binding of NAPQI to intracellular proteins, higher levels of P450 enzymes and lower GSH content in centrilobular hepatocytes are the main reasons for the predominant centrilobular necrosis observed after APAP poisoning

Because protein binding can be prevented by conjugation of NAPQI with GSH, any manipulation that reduces hepatic GSH levels, e.g., fasting or protein malnutrition, potentially enhances the toxicity of APAP. In contrast, interventions such as the supply of cysteine, the rate limiting amino acid for GSH synthesis, promote the detoxification of NAPQI and limits cell

injury. A significant factor in APAP hepatotoxicity can be the consumption of alcoholic beverages. In addition to potential malnutrition in alcoholics, ethanol is a potent inducer of CYP2E1, which is the main enzyme responsible for the metabolic activation of APAP in humans.

In bioactivation of acetaminophen the reactive intermediate (NAPQI), which can deplete glutathione or form covalent adducts with hepatic proteins. These will "prime" hepatocytes for cytokines released by activated Kupffer cells. Progression to cell death is thought to involve activation of iNOS and other processes that produce reactive nitrogen species and oxidative stress. In other hand agents that activate Kupffer cells exacerbate the toxicity. Exchange of signals between toxicant-primed and activated Kupffer cells probably is a factor in the acute hepatotoxicity produced by many compounds that damage hepatocytes.

Ethanol

Morbidity and mortality associated with the consumption of alcohol is mainly caused by the toxic effects of ethanol on the liver . This targeted toxicity is due to the fact that>90% of a dose of ethanol is metabolized in the liver. Three principal pathways of ethanol metabolism are known

1-Alcohol dehydrogenase (ADH) oxidizes ethanol to acetaldehyde with the electrons are transferred to NAD+, which leads to the production of NADH. Acetaldehyde is further oxidized to acetate in a NAD-dependent reaction by acetaldehyde dehydrogenase (ALDH). This pathway is mainly regulated by the mitochondrial capacity to utilize NADH and regenerate NAD+ The formation of excess reducing equivalents and acetate stimulates fatty acid synthesis and is a major factor in the development of alcohol-induced steatosis.Both ADH and ALDH exhibit genetic polymorphisms and ethnic variations, which play a role in the development of alcoholism and liver damage

2- The second major pathway involves the alcohol-inducible enzyme CYP2E1, which oxidizes ethanol to acetaldehyde The enzyme is located predominantly in hepatocytes of the centrilobular region and requires oxygen and NADPH, this reaction is most relevant for high doses of ethanol and, due to the enzyme’s inducibility, for chronic alcoholism.

3- The third pathway involves catalase in peroxisomes. In this reaction, ethanol functions as electron donor for the reduction of hydrogen peroxide to water. Thus, the capacity of this pathway is limited due to the low levels of hydrogen peroxide. It is estimated that <2% of an ethanol dose is metabolized through this pathway.

The increased levels of acetaldehyde present in individuals that carry this polymorphism is thought to cause the “flushing” syndrome after ethanol exposure.

The mechanisms of alcohol-induced liver disease are complex

1- Steatosis is a common feature of chronic alcohol consumption. It is caused by the excessive supply of acetate and NADH, which promotes fatty acid synthesis.

2-ethanol and acetaldehyde inhibit the DNA binding of peroxisome proliferator-activated receptor-α (PPAR-α), which regulates constitutive and inducible expression of mitochondrial and peroxisomal fatty acid metabolizing enzymes.

3-enhanced synthesis and reduced consumption of fatty acids, Where ethanol exposure inhibits the transfer of triglycerides from liver to adipose tissue where Acetaldehyde inhibits the microsomal triglyceride transfer protein, which incorporates triglycerides into VLDL, and disrupts the export mechanism of VLDL by interfering with microtubular function

Carbon Tetrachloride(CCL4)

Cytochrome P450-dependent conversion of CCl4 to •CCl3 and then to CCl3OO• is the classic example of xenobiotic bioactivation to a free radical that initiates lipid peroxidation by abstracting a hydrogen atom from the polyunsaturated fatty acid of a phospholipid ,CCl4-induced lipid peroxidation increases the permeability of the plasma membrane to Ca2+, leading to severe disturbances of the calcium homeostasis and necrotic cell death In addition, the •CCl3 radical can directly bind to tissue macromolecules and some of the lipid peroxidation products are reactive aldehydes, e.g., 4-hydroxynonenal, which can form adducts with proteins also Kupffer cells may enhance the injury by oxidant stress or TNF-α generation, which may lead to apoptosis.

In support of these different components of the mechanism of CCl4-mediated cell and organ damage,beneficial effects were shown with inhibition of CYPs, preservation of Ca2+ homeostasis, antioxidants, and anoxia . In contrast, treatments with chemicals that induce CYP2E1,e.g., ethanol or acetone, enhance the injury. This was confirmed in humans.

Regeneration The liver has a high capacity to restore lost tissue and function by regeneration. Loss of hepatocytes due to or cell injury triggers proliferation of all mature liver cells. This process is capable of restoring the original liver mass.

Hepatocytes are normally quiescent, i.e., are in G0 phase of the cell cycle. In order to proliferate, they need to enter the cell cycle. The process is initiated by cytokines (TNF-α, IL-6), which prime hepatocytes to respond to essential growth factors such as hepatocyte growth factor (HGF) and transforming growth factor-α (TGF-α). Both cytokines and growth factors are involved in the activation of transcription factors and ultimately expression of cell cycle-regulating proteins, i.e., cyclins, the activators of cyclin-dependent kinases (CDK), and p18, p21, and p27,inhibitors of CDKs.

regeneration is not just a response to cell death but is a process that actively determines the final injury after exposure to hepatotoxic chemicals such as thioacetamide,

APAP,chloroform, CCl4, galactosamine, and allyl alcohol . Inhibition of mitosis with colchicine prevented tissue repair and aggravated hepatectomy liver injury after thioacetamide.