Al-Rasheed University/ Collage of Pharmacy

Toxicology Lec. #4

Liver toxicity

by:

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TOXIC RESPONSES OF THE LIVER

Introduction

- The liver is the main organ where exogenous chemicals are metabolized and eventually excreted.

- Liver cells are exposed to significant concentrations of these chemicals, which can result in liver dysfunction, cell injury, and even organ failure.

- If an industrial chemical is identified as a hepatotoxant, the use of the chemical may be restricted, the exposure may be minimized by using protective clothing and respirators, and attempts are made to replace it with a safer alternative.

LIVER PHYSIOLOGY

Hepatic Functions

Venous blood, from the stomach and intestine, 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.

Efficient scavenging or uptake processes extract these absorbed materials from the blood for catabolism, storage, and/or excretion into bile.

LIVER PHYSIOLOGY

Hepatic Functions

- Alcohol abuse is the major cause of liver disease in most western countries thus ethanol provides a highly relevant example of a toxicant with multiple functional consequences.

- Early stages of ethanol abuse are characterized by lipid accumulation (fatty liver) due to:
  - diminished use of lipids as fuels
  - impaired ability to synthesize the lipoproteins that transport lipids out of the liver.

- People with hepatic cirrhosis due to chronic alcohol abuse frequently become deficient at detoxifying both the ammonia formed by catabolism of amino acids and the bilirubin derived from breakdown of hemoglobin.

LIVER PHYSIOLOGY

Bile Formation

- Bile is a yellow fluid containing bile acids, glutathione, phospholipids, cholesterol, bilirubin and other organic anions, proteins, metals, ions, and xenobiotics.

- Formation of this fluid is a specialized function of the liver.

- Adequate bile formation is essential for:

➢ uptake of lipid nutrients from the small intestine, for protection of the small intestine from oxidative insults

➢ for excretion of endogenous and xenobiotic compounds.

Major Functions of Liver and Consequences of Impaired Hepatic Functions

TYPE OF FUNCTION	EXAMPLES	CONSEQUENCES OF IMPAIRED FUNCTIONS
Nutrient homeostasis	Glucose storage and synthesis	Hypoglycemia, confusion
	Cholesterol uptake	Hypercholesterolemia
Filtration of particulates	Products of intestinal bacteria (e.g., endotoxin)	Endotoxemia
Protein synthesis	Clotting factors	Excess bleeding
	Albumin	Hypoalbuminemia, ascites
	Transport proteins (e.g., very low density lipoproteins)	Fatty liver
Bioactivation and detoxification	Bilirubin and ammonia	Jaundice, hyperammonemia-related coma
	Steroid hormones	Loss of secondary male sex characteristics
	Xenobiotics	Diminished drug metabolism
		Inadequate detoxification
Formation of bile and biliary secretion	Bile acid–dependent uptake of dietary lipids and vitamins	Fatty diarrhea, malnutrition, Vitamin E deficiency
	Bilirubin and cholesterol	Jaundice, gallstones, hypercholesterolemia
	Metals (e.g., Cu and Mn)	Mn-induced neurotoxicity
	Xenobiotics	Delayed drug clearance

LIVER PATHOPHYSIOLOGY

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
  - the duration of the chemical exposure (acute vs. chronic).

Types of Hepatobiliary Injury

TYPE OF INJURY OR DAMAGE	REPRESENTATIVE TOXINS
Fatty liver	Amiodarone, CCl_4, ethanol, fialuridine, tamoxifen, valproic acid
Hepatocyte death	Acetaminophen, allyl alcohol, Cu, dimethylformamide, ethanol
Immune-mediated response	Diclofenac, ethanol, halothane, tienilic acid
Canalicular cholestasis	Chlorpromazine, cyclosporin A, 1,1-dichloroethylene, estrogens, Mn, phalloidin
Bile duct damage	Alpha-naphthylisothiocyanate, amoxicillin, methylene dianiline, sporidesmin
Sinusoidal disorders	Anabolic steroids, cyclophosphamide, microcystin, pyrrolizidine alkaloids
Fibrosis and cirrhosis	CCl_4, ethanol, thioacetamide, vitamin A, vinyl chloride
Tumors	Aflatoxin, androgens, arsenic, thorium dioxide, vinyl chloride

Mechanisms and Types of Toxin-induced Liver Injury

Cell Death

Based on morphology, liver cells can die by two different modes, necrosis or apoptosis.

1. Necrosis is characterized by:

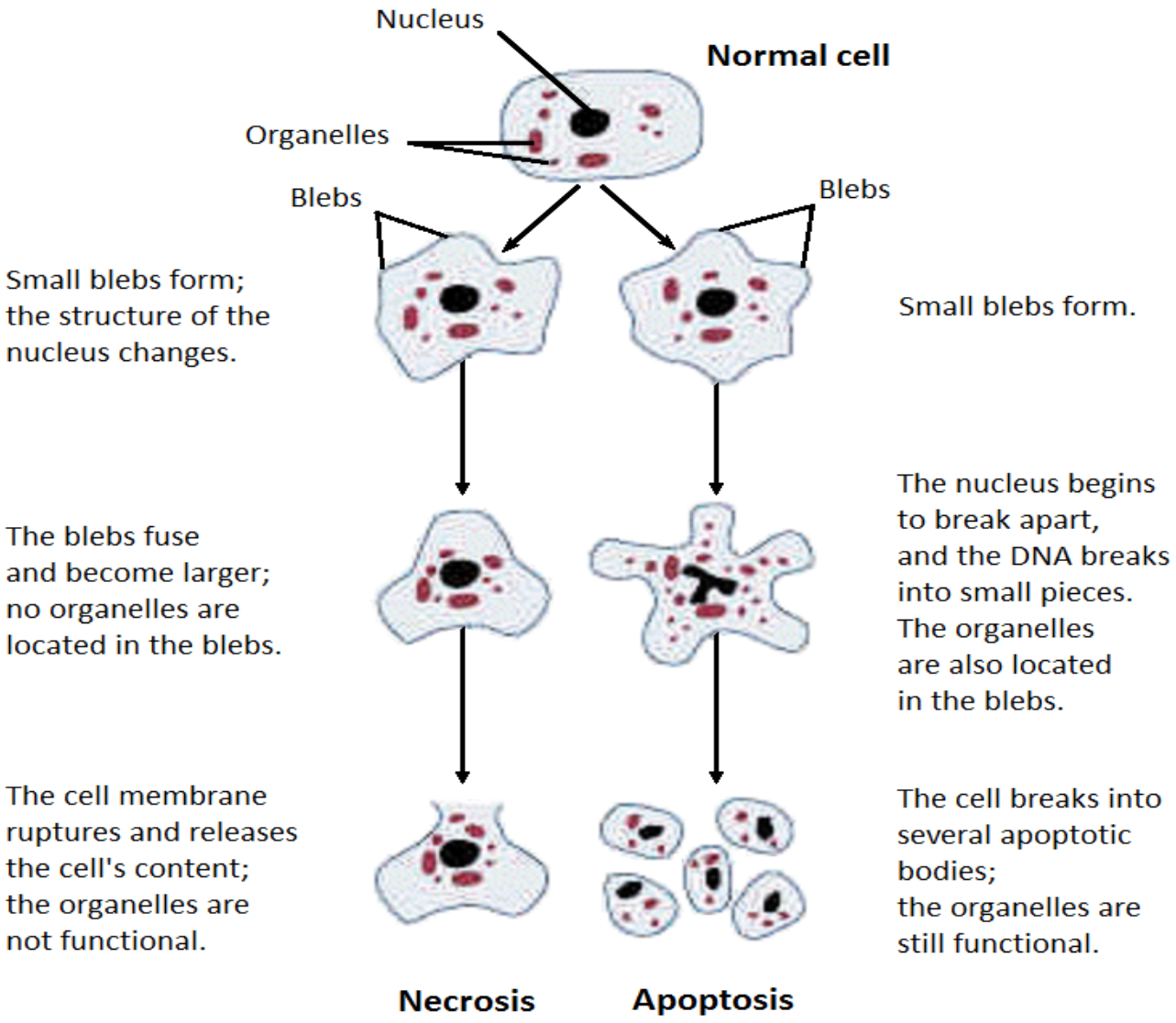
- cell swelling
- leakage of cellular contents
- nuclear disintegration
- influx of inflammatory cells.

- Because necrosis is generally the result of an exposure to a toxic chemical or other traumatic conditions, large numbers of contiguous hepatocytes and nonparenchymal cells may be affected.

2. Apoptosis is characterized by:

- cell shrinkage
- chromatin condensation
- nuclear fragmentation
- formation of apoptotic bodies, and generally, lack of inflammation.

Apoptosis vs. Necrosis



Apoptosis pathways

- Two major molecular pathways mediate the apoptosis process.

1. One pathway is mediated by members of the death-receptor such as Fas/CD95/TNF-R1. Binding of a death-ligand (such as CD95 ligand or TNFα) to its death-receptor induces activation of the caspase cascade (initiator caspases e.g., caspases 8 or 10, and executioner caspases 3, 6 or 7) which leads to DNA fragmentation.
2. The second pathway can be induced by various stimuli such as ionizing radiation causing DNA damage, heat, osmotic shock or growth factor starvation. These stimuli alter the mitochondrial membrane permeabilization, which subsequently results in the release of pro-apoptotic mitochondrial proteins into the cytosol. These pro-apoptotic factors ultimately lead to caspases activation (initiator caspase 9, and executioner caspases 3, 6 or 7) and cell death.

Apoptosis pathways