Toxic Responses Of The Liver

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INTRODUCTION TO THE LIVER

- Major target organ of many toxins
- Understanding of hepatotoxicity:
  1. MAJOR FUNCTIONS OF THE LIVER
  2. ITS STRUCTURAL ORGANISATION
  3. BILE FORMATION
(1) LIVER FUNCTIONS

• Complex organ – many vital functions:
  – Carbohydrate/Fat/Protein metabolism
  – Drugs & hormone metabolism
  – Immunologic function
  – Bilirubin formation and excretion
(2) STRUCTURAL ORGANISATION

KEY ROLE IN INTERMEDIARY METABOLISM

Heart
Hepatic Artery
Hepatic Vein
Portal Vein
Intestines
Bile Duct
LIVER
The lobule

Anatomical view from periphery to central vein

A. Oxygenated blood arrives in branch of hepatic artery

B. Branch of hepatic portal vein brings blood from intestine

D. Bile duct takes bile to gall bladder.

C. Central veins take away processed blood.
The acinus

Figure 13-2. Schematic of liver operational units, the classic acinus.

The lobule is centered around the terminal hepatic vein (central vein). The acinus has as its base the penetrating vessels, where blood flows down the acinus past the cords of hepatocytes. Zones 1, 2, and 3 are regions that are increasingly distant from the blood supply.
Sinusoids
Fenestrated endothelium
Separated from hepatocytes by Space of Disse
Semipermeable membrane – materials exchange
Lipoprotein metabolism – process LDL, HDL, VLDLs
Antigen presentation
Ito Cells

Stellate cells
Differentiate into myofibroblasts
Cytokine secretion
Secrete ECM proteins
Kupffer Cells

- Non-specific host defence
- Inflammation/Phagocytosis
- Antigen presentation
- Cytokine secretion
- Senescent and damaged RBCs
- Tumour cell surveillance
(3) BILE FORMATION

- Composed of bile salts, glutathione, phospholipids, cholesterol, bilirubin, organic anions, proteins, metals, ions, xenobiotics

- Bile formation essential for:
  - Lipid uptake from small intestines
  - Protection of small intestine from oxidative injury
  - Excretion of endogenous and xenobiotic compounds
Bile Excretion

- Driving Force of Bile Formation -
  - Active Transport of Bile Salts

- ATP-dependent exporters
  - MDR (multiple-drug resistance)
  - cMOAT (canalicular multiple organic ion transporter)
Bile Excretion

- Metals Added
  - Diffusion v receptor
  - Excretion by lysosomes
- Cu, Mn, Cd, Se, Au, Ag, As
Bile Excretion

Canaliculi → Channels → Bile Ducts → Common Bile Duct → Small Intestine → Enterohpatic Cycling
FACTORS INVOLVED IN LIVER INJURY

Susceptible because of:

- **ANATOMY:**
  - Considerable cardiac output
  - Unusual sinusoidal architecture

- **LOCATION:**
  - 1st organ perfused by things absorbed from GIT

- **FUNCTION:**
  - Primary organ involved in biotransformation
**BIOACTIVATION & DETOXIFICATION**

**PHASE I**
- Cyt P450 (centrilobular)
- Oxidation/reduction/hydrolysis
- Xenobiotic $\rightarrow$ Reactive intermediate

**PHASE II**
- Glutathione/transaminases (periportal)
- Conjugations
- $\rightarrow$ Stable metabolite

**Balance**
- Cell Injury $\rightarrow$ Detoxification
Bioactivation

- **Ethanol**
  - \( \text{EtOH} \rightarrow \text{acetaldehyde} \)  
    (rapidly by alcohol dehydrogenase)
  - \( \text{Acetaldehyde} \rightarrow \text{acetate} \)  
    (slowly by aldehyde dehydrogenase)
  - Polymorphisms in Asian people
    - More “fast” & less “slow” \( \rightarrow \) Build-up of acetaldehyde
Bioactivation

Cytochrome P450 is a Haem-containing protein

The basic reaction that it catalyses is monooxygenation:
- one atom of $O_2$ is incorporated into a substrate (RH)
- the other is reduced to water using NADPH:

\[
\text{SUBSTRATE (RH)} \quad \text{O}_2 \quad \text{H}_2\text{O} \quad \text{PRODUCT (ROH)}
\]

\[
\text{NADPH} + \text{H}^+ \quad \text{NAD} \quad \text{P}^+
\]
Cytochrome P450 Enzymes

A superfamily of enzymes in the SER with wide substrate specificity – a major group responsible for drug metabolism

**Important Points to Remember:**

- Each isozyme can metabolise MANY different drugs
- Many drugs can be metabolised by more than one isozyme

- Few compounds are conjugated directly, so PHASE I metabolism is a very important line of defence

- Unfortunately Cyt p450 can → reactive oxygen compounds that are hepatotoxic (esp CYP2E1 & CYP3A)
Bioactivation

Carbon Tetrachloride

\[ \text{P450} \quad \text{CYP2E1} \]

\[ \text{CCl}_4 \xrightarrow{\text{P450} \quad \text{CYP2E1}} \text{•CCl}_3 \xrightarrow{} \text{CCl}_3\text{OO•} \]

Lipid peroxidation of fatty acid
Bioactivation

- **Acetaminophen**
  - 1st introduced into clinical medicine late 1900s – "back door" - no formal preclinical animal toxicity studies
  - Attracted little attention and was soon forgotten
  - Potential hepatotoxicity was not suspected until the first clinical reports of severe and fatal liver damage following OD in 1960s
  - Species differences in its metabolic activation
  - Paracetamol is involved in 15 to 30% of deliberate self-poisonings in UK
Acetaminophen

- Glutathione-S-transferase is important
- Uses glutathione as a cofactor
- Acetaminophen metabolite conjugated by Glutathione
- Toxicity only revealed when GSH levels depleted to a certain level due to:
  - Overdose
  - Fasting
Acetaminophen

Overdose

P450

NAPQI
(N-acetyl-p-benzoquinoneimine)

Sulphate/Glucuronide
Saturated

Glutathione

Covalent Binding to
Macromolecules

Cell Death
(Zone 3)

Glutathione Conjugate

No Glutathione Conjugate
Sinusoidal Cells in Liver Toxicity

- Kupffer cells/Ito cells become activated after exposure to toxins
- Kupffer cells can be activated by Vit A
  - This then enhances acute toxicity of CCl₄
- Activated Kupffer cells produce reactive oxygen species & reactive nitrogen species
Mechanisms of Liver Damage

- **Cell skeleton**
  - Microcystin:
    - Covalently binds to cytoskeletal proteins
    - Leads to hyperphosphorylation reactions
    - Microtubular scaffolding collapses, resulting in deformation of hepatocyte
Mechanisms Of Liver Damage

• **Cholestasis**
  • Toxins can inhibit bile formation by various mechanisms
    • Transporter/Export function
    • Tight junction leakage
    • Concentration of reactive substances
Mechanisms

- **Mitochondrial Damage**
  - Toxins can:
    - Inhibit mitochondrial DNA synthesis
    - Lead to free radical production by effects on electron transport chain
Response To Damage

- In general, tissues respond similarly:
  - Inflammation
  - Degeneration / Necrosis
  - Recovery/Proliferation/Malignancy
Types Of Liver Injury

- **Response of liver to injury relates to:**
  - Degree & duration of the insult
  - Cell population affected

- **Types of injury include:**
  - Fatty change
  - Hepatocellular death
  - Canalicular cholestasis
  - Bile duct damage
  - Sinusoidal damage
  - Cirrhosis
  - Neoplasia
Fatty Change

- Increased lipid in hepatocyte cytoplasm
- Due to altered lipid metabolism
- Common with acute toxins
- Potentially reversible
- Most common cause is alcohol
Fatty Change
Cell Death

- Necrosis (Eg/ due to acetaminophen)
  - Cell swells
  - Leakage of cytoplasm
  - Nuclear disintegration
Apoptosis

- Features
  - Cell shrinkage
  - Nuclear fragmentation
  - Formation of apoptotic bodies
  - Usually no/minimal inflammation
Cholestasis

- Reduced formation/secretion of bile
  - Leads to accumulation of things like bilirubin that are normally excreted in bile
  - Results in icterus

- Offending drugs:
  - Cyclosporin
  - Oestrogens
Bile Duct Damage

- Cholangiodestructive cholestasis
- Increased serum activity of gamma glutamyltransferase (GGT)
- Bile duct epithelial damage →
  - Necrosis, Inflammation, Fibrosis
  - Bile duct hyperplasia
  - Bile duct loss (Vanishing bile duct syndrome)
Biliary Inflammation & Fibrosis
Cirrhosis

- Progressive liver injury – chronic action
- Necrotic areas replaced by fibrous tissue
- Result of repetitive injury of liver cells
- Associated with alcohol abuse
Cirrhosis
Neoplasia

- Primary neoplasms arise from cells in the liver
  - Hepatocytes
  - Bile duct epithelium

- Secondary neoplasms arise from cells outside the liver
  - Invasion
  - Metastasis

- Aflatoxins
  - Result in hepatocellular carcinoma
Hepatocellular adenoma
Hepatocellular carcinoma
Bile Duct Adenoma
Bile Duct Carcinoma
In Summary

- The liver is a metabolically important organ
  - Biosynthesis
  - Nutrient metabolism
  - Detoxification & biotransformation

- But remember its Achilles heel effect
  - High cardiac output & optimum anatomic location
  - Biotransformation can produce toxic substances
  - Enterohepatic circulation leads to re-exposure
Thank You!

WHAT Am I, CHOPPED LIVER?

Soon.

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