Metabolism: friend and foe? (De)Toxification processes in the liver

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Liver

• located in right upper quadrant of abdomen
• heaviest internal organ (1.5 kg)
• functions:
  ▫ bile production and excretion
  ▫ metabolism of fats, proteins and carbohydrates
  ▫ detoxification of xenobiotics
  ▫ storage of glycogen, vitamins and minerals
  ▫ blood detoxification and purification
Liver

- made up of hepatic lobules which consist of hepatocytes
- portal triad:
  - hepatic artery, portal vein and bile duct as well as lymphatic vessels and branch of vagus nerve
- xenobiotics reach liver via portal vein (from gastrointestinal tract) or via hepatic artery (from systemic circulation)
Drug Metabolism

- biotransformation of a drug or toxin in the body
  - aim: detoxification of xenobiotic
- pathways of drug metabolism can be divided into
  - phase I (modification)
  - phase II (conjugation)
  - phase III (excretion)
- drugs can undergo one of four potential biotransformations:
  - active drug to inactive metabolite
  - active drug to active metabolite
  - inactive drug to active metabolite (prodrug)
  - active drug to toxic metabolite (biotoxification)
Phase I

- Phase I
  - oxidation, reduction or hydrolysis of xenobiotics
  - aim: modification/functionlization
  - drug becomes inactive
  - **BUT** also creating active compounds (e.g. mutagens)
  - only metabolites are pharmacologically active
    - original substance is called prodrug
- important enzyme family: **cytochrome P450**
CYP450

- heme proteins located in ER
  - P450 from the spectrophotometric peak
- major enzyme involved in drug metabolism
  - 90-95% of all CYP are located in the liver
- drugs can also increase or decrease activity of various CYP enzymes
- grapefruit juice inhibits CYP 3A4-mediated metabolism
  - increased bioavailability
  - overdosing

CYP Polymorphism

• CYP polymorphism: primary cause of interindividual differences in therapeutic effects and adverse reactions to drugs

• CYP 2D6 (e.g. codein into morphine)
  ▫ poor metabolizer – little or no CYP 2D6 function
  ▫ intermediate metabolizer – slow CYP 2D6 function
  ▫ extensive metabolizer – normal CYP 2D6 function
  ▫ ultrarapid metabolizer – multiple copies of CYP 2D6 gene expressed

• CYP 2C19 (e.g. diazepam into nordazepam)
  ▫ 3-5 % no or poor CYP 2C19 function
Phase II

• Phase II (conjugation reaction)
  ▫ aim: conjugation of water-soluble groups onto the molecule -> excretion
  ▫ unlikely to be pharmacologically active
• important enzymes:
  ▫ Glutathione-S-transferase (GST)
  ▫ UDP-glucuronosyltransferase (UGT)
  ▫ Sulfotransferase (ST)
  ▫ N-acetyltransferase (NAT)

Fast vs. Slow Acetylators

- rate of acetylation is genetically determined
  - 40-70% of Americans and Caucasians are slow acetylaters
- slow acetylation may lead to higher blood levels of the drug
  -> increase in toxic reactions
- isoniazid
  - different elimination half-life (0.5-1.6 h vs. 2-5 h)
- slow acetylaters: higher risk of bladder cancer
  - amino group is hydroxylated
    -> mutagenic nitrenium ion in bladder
- fast acetylaters: higher risk of colon cancer
First-Pass Effect

- concentration of a drug is greatly reduced before it reaches the systemic circulation
  - example: morphine (oral), propranolol (oral)
  - -> low bioavailability

- **BUT**: some drugs are enhanced in potency
  - example: THC (active metabolite is 11-hydroxy-THC)

  - Morphine is metabolized into morphine-6-glucuronide (phase II) which is more potent than morphine

  [https://de.wikipedia.org/wiki/Morphin](https://de.wikipedia.org/wiki/Morphin)
  [https://www.n-tv.de/wissen/THC-synthetisch-hergestellt/article1307781.html](https://www.n-tv.de/wissen/THC-synthetisch-hergestellt/article1307781.html)
Enterohepatic Circulation

- circulation of drugs from the liver to the bile followed by entry into the small intestine, absorption by the enterocyte and transport back to the liver
  - longer half-time of drugs
  - extension of intoxication
- example: α-Amanitin (inhibits RNA polymerase II)

A. phalloides
Examples for Toxification
Paracetamol

- converted into hepatotoxic metabolite NAPQI
  - CYP 2E1
- detoxification by glutathion (GSH)
- in case of overdose:
  - GSH storage ↓
  - NAPQI binds to hepatic proteins resulting in acute liver injury
- antidote: N-acetylcysteine

Lewis et al., Goldfrank's toxicologic emergencies, 2009
**Methanol**

- Methanol shows low toxicity
  - damage optic nerve, CNS depression
- Formate and formaldehyde significantly more toxic
  - hypoxia, metabolic acidosis
- Treatment: ethanol
  - Competitive inhibitor of alcohol dehydrogenase

![Chemical Diagram](https://www.fotocommunity.de/photo/methanol-alkohol-florianm/915449y)

![Chemical Diagram](https://www.anaesthesiamcq.com/AcidBaseBook/ab8_6a.php)
N-Nitrosamine

- nicotine-derived nitrosamine ketone (NNK)
  - tobacco-specific nitrosamines
- procarcinogen that needs activation to exert its effects
  - dimethylnitrosamine -> carbenium ion
  - ultimate carcinogen

Gzman et al., Diagn Path, 2012
https://www.modernmom.com/...
Aromatic Amines

- 2-naphthylamine
  - found in cigarette smoke and roasted/grilled meat
  - glucuronidation (detoxification) or N-hydroxylation by CYP450 (toxification)
  - bladder cancer due to formation of nitrenium ion which can react with proteins, DNA and RNA

Lin & Lu, Pharm Review, 1997
Benzo[a]pyren

- polycyclic aromatic hydrocarbon
- found in automobile exhaust fumes, tobacco smoke and many foods (roasted/grilled meat)
- metabolites are mutagenic and carcinogenic

https://en.wikipedia.org/wiki/Benzo(a)pyrene
Aflatoxin

- aflatoxins are produced by certain molds
  - found e.g. in nuts, rice, spices
- metabolic activation of Aflatoxin B1 to epoxide and binding to guanine but also proteins

How to test for mutagens?

**Ames Test**
- identification of mutagens
- *Salmonella typhimurium*
  - carry mutations in genes involved in histidine synthesis
  - capability of tested substance to create mutation so that bacteria can grow on histidine-free medium
- mimic metabolic conditions
  - use of S9 mix
    (product of rat liver homogenate)

https://en.wikipedia.org/wiki/Ames_test
Take Home Message

• liver is one of the main organs for metabolism
  ▫ phase I and phase II
• processes in the liver that have an effect on drug
  ▫ CYP polymorphism
  ▫ first-pass effect
  ▫ enterohepatic circulation
• examples for toxification processes:
  ▫ Paracetamol
  ▫ Methanol
  ▫ N-Nitrosamine
  ▫ Aromatic amines
  ▫ Benzo[a]pyren
  ▫ Aflatoxin B1
• metabolism: friend AND foe

Metabolic Activation!
Thank You For Your Attention!

Questions?
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CYP Polymorphism

- if CYP converts a drug that has a strong effect into a substance that has a weaker effect
  → poor metabolizers will have an exaggerated response to the drug and stronger side-effects
- if CYP converts a drug into a substance that has a greater effect
  → ultrarapid metabolizers will have an exaggerated response to the drug and stronger side-effects