Mechanism of Detoxification

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Objectives:

1. To list the detoxification pathways

2. To describe detoxification pathways and phases in the liver,
Detoxification Pathways

**Toxins**
(fat soluble)

**STEP 1**

**Required Nutrients**
- B Vitamins
- Folic Acid
- Glutathione
- Antioxidants
  - eg. Milk Thistle
  - Carotenoids
- Vitamin E
- Vitamin C

**STEP 2**

**Waste Products**
(water soluble)

**Required Nutrients**
- Amino Acids:
  - Glutamine
  - Glycine
  - Taurine
  - Cysteine
- Sulphurated phytochemicals eg.
  - found in garlic & cruciferous vegetables

**Eliminated from the body via:**
- Gall Bladder
- Kidneys
- Bile
- Bowel actions
- Urine

**Toxin List**
- metabolic end products, micro-organisms, contaminants / pollutants, insecticides, pesticides, food additives, drugs, alcohol

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**THE LIVER DETOXIFICATION PATHWAYS**

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FAT-SOLUBLE TOXINS

PHASE I
[Cytochrome P450 Enzymes]
- Oxidation
- Reduction
- Hydrolysis
- Hydration
- Dehalogenation

PHASE II
[Conjugation Pathways]
- Sulfation
- Glucorondiation
- Glutathione Conjugation
- Acetylation
- Amino Acid Conjugation
- Methylation

WASTE
Eliminated via:
- Gall Bladder
- and Kidneys
Xenobiotics are compounds that have no nutrient value (cannot be used by the body for energy requirements) and are potentially toxic. They are present as natural components of foods or they may be introduced into foods as additives or through processing. Pharmacologic and recreational drugs are also xenobiotic compounds. The liver is the principal site in the body for the degradation of these compounds. Because many of these substances are lipophilic, they are oxidized, hydroxylated, or hydrolyzed by enzymes in **phase I** reactions. **Phase I** reactions introduce or expose hydroxyl groups or other reactive sites that can be used for conjugation reactions (the **phase II** reactions).
Xenobiotic or waste metabolite in the diet or peripheral circulation → Phase I reactions → Primary metabolite → Phase II reactions → Secondary metabolite, suitable for excretion

- Reduction
- Oxidation
- Hydroxylation
- Hydrolysis
- Conjugation
- Sulfation
- Methylation
- Glucuronidation
Monooxygenase (mixed function oxidases) incorporate one atom from molecular oxygen into a substrate (creating a hydroxyl group), with the other atom being reduced to water. The overall reaction catalyzed by a cytochrome P450 enzyme is:

\[
R-H + O_2 + NADPH + H^+ \rightarrow R-OH + H_2O + NADP^+
\]
The cytochrome P450 enzyme family contains at least 100 to 150 different isozymes. The human enzymes are generally divided into six major subfamilies, and each of these is further subdivided. For example, in the naming of the principal enzyme involved in the oxidation of ethanol to acetaldehyde, CYP2E1, the CYP denotes the cytochrome P450 family, the 2 denotes the subfamily, the E denotes ethanol, and the 1 denotes the specific isozyme.
Transforming a toxin to a more chemically reactive form makes it more easily metabolized by the phase II enzymes.

If the phase II detoxification systems are not working adequately, these intermediates can cause substantial damage, including the initiation of carcinogenic processes. Each enzyme works best in detoxifying certain types of chemicals, but with considerable overlap in activity among the enzymes.
A significant side-effect of phase I detoxification is the production of *free radicals* as the toxins are transformed--for each molecule of toxin metabolized by phase I, one molecule of free radical is generated. Without adequate free radical defenses, every time the liver neutralizes a toxin exposure, it is damaged by the free radicals produced.
The most important antioxidant for neutralizing the free radicals produced in phase I is *glutathione*. In the process of neutralizing free radicals, however, *glutathione* (GSH) is oxidized to *glutathione disulfide* (GSSG). Glutathione is required for one of the key phase II detoxification processes.
This is called the *conjugation pathway*, whereby the liver cells add another substance (e.g. cysteine, glycine or a sulphur molecule) to a toxic chemical or drug.

- This makes the toxin or drug water-soluble, so it can then be excreted from the body via watery fluids such as bile or urine.
- Individual xenobiotics and metabolites usually follow one or two distinct pathways.
There are essentially six phase II detoxification pathways:

- Glutathione conjugation
- Amino acid conjugation
- Methylation
- Sulfation
- Acetylation
- Glucuronidation
1. Glutathione conjugation

- A primary phase II detoxification route is \textit{conjugation} with glutathione: (\(\gamma\)-glutamylcysteinylglycine), (a tripeptide composed of three amino acids--cysteine, glutamic acid, and glycine).

- Glutathione conjugation produces water-soluble mercaptates which are excreted via the kidneys.
The elimination of fat-soluble compounds, especially heavy metals like mercury and lead, is dependent upon adequate levels of glutathione, which in turn is dependent upon adequate levels of methionine and cysteine.
Studies have demonstrated that a deficiency of methionine can, in itself, cause liver cancer without the presence of a carcinogen, and also that the deficiency of methionine can permit a heavy metal to cause toxic effects.
Glutathione is also an important antioxidant.

This combination of detoxification and free radical protection, results in glutathione being one of the most important anticarcinogens and antioxidants in our cells, which means that a deficiency is cause of serious liver dysfunction and damage.
A deficiency can be induced either by:

- diseases that increase the need for glutathione,
- deficiencies of the nutrients needed for synthesis,
- or diseases that inhibit its formation.
Several amino acids: (*glycine, taurine, glutamine, arginine, and ornithine*) are used to combine with and neutralize toxins. Of these, glycine is the most commonly utilized in phase II amino acid detoxification.

Patients suffering from hepatitis, alcoholic liver disorders, carcinomas, chronic arthritis, hypothyroidism, toxemia of pregnancy, and excessive chemical exposure are commonly found to have a poorly functioning amino acid conjugation system.
3. Methylation

- Methylation involves conjugating methyl groups to toxins.
- Most of the methyl groups used for detoxification comes from S-adenosylmethionine (SAM).
4. Sulfation

- Sulfation is the conjugation of toxins with sulfur-containing compounds. The sulfation system is important for detoxifying several drugs, food additives, and, especially, toxins from intestinal bacteria and the environment.
5. Acetylation

- Conjugation of toxins with acetyl-CoA is the primary method by which the body eliminates sulfa drugs. This system appears to be especially sensitive to genetic variation, with those having a poor acetylation system being far more susceptible to sulfa drugs and other antibiotics.

- Acetylation is dependent on thiamine, pantothenic acid, and vitamin C.
6. Glucuronidation

- Glucuronidation, the combining of glucuronic acid with toxins, in Phase II can be reversed by Beta glucuronidase enzymes produced by pathological bacteria and cause toxins to be reabsorbed increasing toxicity.
Sulfoxidation

- Sulfoxidation is the process by which the sulfur-containing molecules in drugs and foods are metabolized.
It is also the process by which the body eliminates the sulfite food additives used to preserve many foods and drugs.

Normally, the enzyme sulfite oxidase (molybdenum dependent enzyme) metabolizes sulfites to safer sulfates, which are then excreted in the urine.
Those with a poorly functioning sulfoxidation system, however, have an increased ratio of sulfite / sulfate in their urine.

Those with a poorly functioning sulfoxidation detoxification pathway are more sensitive to sulfur-containing drugs and foods containing sulfur or sulfite additives.
Conclusions:

- The liver plays several roles in detoxification: it filters the blood to remove large toxins, synthesizes and secretes bile full of cholesterol and other fat-soluble toxins, and enzymatically disassembles unwanted chemicals.
The enzymatic process usually occurs in two steps referred to as: *phase I* and *phase II*.

*Phase I* reactions introduce or expose hydroxyl groups or other reactive sites.

*Phase II* This is called the **conjugation pathway**, whereby the liver cells add another substance (eg. cysteine, glycine or a sulphur molecule) to a toxic chemical or drug.
Any Questions