How toxins & poisons cause disease

Mammalian Pathobiology
PATB 4130/5130

Don Montgomery, DVM, PhD, Dipl ACVP
766-9929
1174 Snowy Range Road, Rm 101A

Poison – Any substance which (when ingested, inhaled, absorbed, applied to, injected, or developed within the body (in small quantities), by its chemical action, may cause damage to structure or function.

Toxin – typically used interchangeably with ‘poison’. More specifically, this term refers to proteins produced by plants, certain animals and bacteria that are highly toxic for other living organisms. Are differed from simple chemical poisons and plant alkaloids by their high molecular weight and antigenicity.

How do poisons / toxins cause cellular injury, clinical disease, and/or death? – Possible Mechanisms

• Direct physical or chemical injury to cells / tissues / organs through various mechanisms
• Interference with normal metabolic or biochemical pathways
• Interference with normal gene expression or transcriptional pathways
• DNA damage (mutagenicity, teratogenicity, carcinogenicity)
Brown recluse spider bite
(an example of direct toxic action)

Brown recluse spiders have only six pairs of eyes in contrast to most others that have 4

FYI

‘Chick pea’
*Lathyrus odorata*

Toxin interferes with function of lysyl oxidase

(an example of interference with normal biochemical pathways)
Teratogenicity – *Veratrum californicum*

*Cyclops Lamb* – ingestion of the plant on the 14th day of gestation (an example of teratogenic effects)

---

Thalidomide – a historical perspective on a teratogenic drug

- Developed by a German pharmaceutical company and marketed 1957-1961 to treat morning sickness.
- Approx 10,000 children were born with severe birth defects including phocomelia in Africa & Europe.
- Dr. Frances Kelsey refused FDA approval; as a result, only 17 ‘thalidomide babies’ were born in the U.S.
- In 1962, the U.S. Congress enacted laws requiring drug testing for safety during pregnancy.
- Thalidomide is now showing promise in a variety of conditions ranging from cancer to immune-mediated disease

---

Outcomes of poisoning

- Detoxification and elimination after exposure – no or minimal residual structural/functional injury
- Tissue damage with repair/restoration of function following exposure
- Chronic long-term injury – persistent morbidity and carcinogenesis
- Death can occur at any of these stages depending on the poison
Biotransformation

Some poisons are not in themselves inherently dangerous.

Chemical reactions in the body can transform some innocuous compounds that are not inherently dangerous in themselves into poisonous substances.

Examples of Intoxications

Ethylene glycol poisoning

Antifreeze
Ethylene glycol – a major component of antifreeze

- Rapidly absorbed from the gut
- The majority of ethylene glycol is excreted in the urine
- In the liver, the enzyme alcohol dehydrogenase converts to glycoaldehyde:

\[
\text{Ethylene glycol} \xrightarrow{\text{H}_2\text{O}} \text{Glycoaldehyde} \xrightarrow{} \text{Glycolic acid} \xrightarrow{} \text{Glyoxylate} \xrightarrow{} \text{Glyoxylate}
\]
- Glycoaldehyde and glyoxylate deplete ATP stores, damage cell membranes, and inactivate enzymes
- Other metabolic end-products include lactic acid, hippuric acid, and CO\(_2\) → metabolic acidosis

Oxalic acid also binds to Ca\(^{2+}\)
- Hypocalcemia
- Deposited in renal tubules leading to renal failure

Lung Damage

Tryptophan and 3-methylindole
Lesions of AIP

Lungs fail to collapse when chest opened

Early stages, hyaline alveolar membranes

Later stages, pneumocyte proliferation

Lesions of AIP

Lungs fail to collapse when chest opened

Early stages, hyaline alveolar membranes

Later stages, pneumocyte proliferation

Lesions of AIP

Lungs fail to collapse when chest opened

Early stages, hyaline alveolar membranes

Later stages, pneumocyte proliferation

Lesions of AIP

Lungs fail to collapse when chest opened

Early stages, hyaline alveolar membranes

Later stages, pneumocyte proliferation

Lesions of AIP

Lungs fail to collapse when chest opened

Early stages, hyaline alveolar membranes

Later stages, pneumocyte proliferation

Lesions of AIP

Lungs fail to collapse when chest opened

Early stages, hyaline alveolar membranes

Later stages, pneumocyte proliferation
Renal (kidney) injury
Analgesic Nephropathy

Analgesics – what they do

Many NSAIDS have analgesic properties and anti-inflammatory effects exerted through inhibition of cyclooxygenase (COX) enzyme.

Lesions in the kidney reflect acute coagulative necrosis (infarction) of renal papillae or crest.

Equine kidney (above) following butazolidone. Human kidney (right). White areas are zones of necrosis.
Feline kidney with analgesic nephropathy.

The homogeneous pink areas are zones of coagulative necrosis – the type of injury when tissue is deprived of its blood supply.

The mechanism of necrosis is possibly related to inhibition of prostglandin synthesis leading to ischemia in the more dependent portions of the kidney.

- Indomethacin (a COX-inhibitor) reduces blood flow in the renal medulla 20% in some studies.
- Dehydration likely also plays a role in many cases.

Liver injury – Mycotoxins:
Acute & chronic injury and carcinogenicity
Aflatoxin B₁

Aflatoxin B₁ is one of the primary toxins produced by the fungus Aspergillus flavus that can contaminate feedstuffs (rice, peanuts, corn)

The liver is one of the primary targets for aflatoxin

- Aflatoxins can cause or be associated with:
  - Acute liver injury with necrosis of hepatocytes
  - With survival, acute liver injury can become chronic with scarring and cirrhosis
  - Liver cancer (hepatocellular carcinoma)

Liver of a pig with chronic injury due to aflatoxin exposure. The upper right photo is normal liver.
Hepatocellular carcinoma

Events in Hepatic Injury and Carcinogenesis

- AFB₁ is metabolized to a toxic intermediate by hepatic Cytochrome P₄₅₀ enzymes
- The toxic epoxide preferentially binds to guanine residues on many genes causing a GC → TA transversion in DNA
- This point mutation has been observed at codon 249 of the p53 tumor suppressor gene.

Mechanism of Chemical Carcinogenesis

NER = nucleotide excision repair
Functions of the p53 suppressor gene

- Regulation of:
  - The cell cycle
  - Apoptosis
  - DNA repair

P21, CDK = cyclin dependent kinase
GADD45 = growth arrest and DNA damage
BAX = BCL2-associated X protein

Evidence linking hepatocellular carcinoma (HCC) to AFB₁
- This specific mutation in the p53 gene occurs in >50% of HCCs in areas of the world where the incidence of aflatoxicosis is high
- The incidence of this mutation in HCCs in parts of the world with low aflatoxicosis is about 1%
- Patients with positive urine AFB₁-guanine excretion are 3 times more likely to develop HCC

Aflatoxin B₁ and hepatitis B virus infection
- Patients with hepatitis B surface antigen (HBsAg) are 4-7 times more likely to develop HCC
- Patients with BOTH HBsAg and AFB₁ are 60 times more likely to develop HCC
- There is a synergism between HBV infection and exposure to AFB₁
Synergistic Mechanisms

- HB x protein, a gene product of HBV, inhibits nucleotide excision repair
- One study indicates HBx inactivates p53
- Another study indicates HBx inhibits p53-induced apoptosis
- HBx promotes apoptosis following DNA damage when p53 is functional but promotes a growth advantage to cells with the AFB1 mutation in the p53 gene

Sample Question #1

Which of the following is not an example of biotransformation? Briefly give two reasons for your answer.

1. Ethylene glycol
2. Brown recluse spider bite
3. Aflatoxicosis
4. 3-methylindole induced lung disease

Sample Question #2

Exposure to aflatoxin B1 and infection with hepatitis B virus infection greatly increases the risk of liver cancer. In this scenario, which would be more likely as the initiator and which would be the promoter? Briefly defend your answer.