Naturally Occurring Toxicants as Etiologic Agents of Foodborne Disease

Food Toxicology
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Learning Objectives

- Examine the etiology (causation) of human disease related to naturally-occurring foodborne toxicants.
- Understand the chemical complexity of foods.
- Explore goiter, tropical ataxia neuropathy (TAN), tropical amblyopia, lathyrism, and their linkage to foodborne toxicants.
- Review a range of natural food toxicants that are involved in human disease.

Complexity of Food

Nutrients

- Carbohydrates
- Proteins
- Lipids
- Minerals
- Vitamins

Non-nutrients

- Food Additives
- Naturally Occurring Secondary Chemicals
- Contaminants
- Processing Chemicals

Non-nutrient Chemicals in Different Foods

• Cheddar Cheese	160
• Orange juice	250
• Banana	325
• Tomato	350
• Wine	475

- Coffee 625
- Cooked beef 625

Natural Toxicants and Human Disease

- Goitrogens
- Cyanogenic glycosides
- Lathyrism
- Lectins
- Alkaloids
- Protease inhibitors
- Vasoactive amines

Goitrogens

- Contribute to growth of goiters
- Compounds in Cruciferae
  - *Brassica* species (cabbage, kale, turnips)
  - Seeds only - not leaves
- Combined w/ iodine deficiency

Cruciferae → Glucosinolates

- A class of about 100 naturally occurring thioglucosides that are characteristic of
  the Cruciferae and related families.
- Diets of people in many parts of the world include considerable amounts of Cruciferous crops and plants.
  - Processed radish and wasabi in the Far East
  - Cabbage and traditional root vegetables in Europe and North America.
  - Rapeseed, kale, swede and turnip may also contribute since they are extensively used as animal feed stuffs.
  - Glucosinolates in crops, such as oilseed rape (Brassica napus) and Brassica vegetables, is undesirable because of the toxicological effects of their breakdown products.
  - Breakdown products include nitriles, isothiocyanates, thiocyanates, epithionitriles and vinyl oxazolidinethiones.

Goitrogens

- Goitrogenic compounds (goitrin) are formed from breakdown of glucosinolates by thioglucosidase
- Goitrogenic metabolites
  - Nitriles; Thiocyanates; Oxazolidine

Goitrogens

- Thyroid gland secretes thyroxine (TY), triiodothyronine (TII), thyroglobulin(TH)
- Controlled by hypothalamus and pituitary
- Hypothalamus produces thyrotropin-releasing hormone (TRH)

- Stimulates pituitary to release thyroid-stimulating hormone (TSH)

Goitrogens

- TSH promotes uptake of iodine, synthesis of TH and release of TY and TII which feed back to reduce TSH
- TY and TII hormones also affect
  - Oxygen consumption, cardiovascular function, neuromuscular activity, cholesterol metabolism, cerebral function
  - Growth and development

Goitrogens

- Goitrin and thiourea inhibit TY synthesis
- Thiocyanates, oxazolidine and nitriles inhibit uptake of iodine by thyroid
- Lack of iodine causes thyroid to enlarge and hypervascularate to trap more iodine = goiter

Goitrogens - Testing

- Weight and histology of thyroid
- Growth rate of patient/animal
- Iodine content of blood and thyroid
- Feed compound - measure uptake of radioactive iodine

Cyanogenic Glycosides

<u>Plant</u>

- Bitter almond
- Cassava root
- Sorghum
- Lima bean

<u>Glycoside</u>

- Amygdalin
- Linamarin
- Dhurrin
- Linamarin

Cassava Root

- The cassava (manioc, yucca; *Manihot esculenta*) is a woody shrub of the Euphorbiaceae (spurge family) that is extensively cultivated as an annual crop in tropical and subtropical regions for its edible starchy tuberous root, a major source of carbohydrate.

  - Cultivars contain varying amounts of CGs
  - Cultivar, drought, and food preparation significant for CGs

Cyanogenic Glycosides

- Toxic chemical = hydrogen cyanide
- HCN released when plant is chewed or chopped
- Releases 2 enzymes normally separate
  - Beta-glucuronidase
  - Hydroxynitrile lyase
- Act synergistically to release HCN

Cyanogenic Glycosides

- Can reduce CN by chopping or grinding in water
- Cassava flour is made from boiled or fermented root
- Intestinal bacteria may also be able to break down cyanogenic glycosides to HCN

Cyanogenic Glycosides

Amygdaline (Laetrile)

- Anticancer compound
- Apricot pits
- Not approved in US
- Several deaths in foreign countries

Acute Cyanide Poisoning: Mechanism

- Shuts down cellular respiration - energy metabolism in mitochondria
- Binds ferric ion on cytochrome oxidase in Krebs cycle
- Min lethal dose 0.5-3.5 mg HCN/kg bw

Acute Cyanide Poisoning

Symptoms

- Muscular paralysis
- Mental confusion
- Respiratory distress
- Rapid onset

Acute Cyanide Poisoning

Treatment

- Nitrite or amyl nitrite

- Converts hemoglobin (Fe^{+2}) to methemoglobin (Fe^{+3})
  - Draws CN^- away from cytochrome oxidase
- Add thiosulfate to form thiocyanate

Chronic Cyanide Poisoning

- Occurs in areas of cassava in diet
- Not well understood
- Two disorders
  - Tropical Ataxia Neuropathy (TAN)
  - Tropical Amblyopia

Chronic Cyanide Poisoning

Tropical Ataxia Neuropathy (Konzo)

- Atrophy of optic nerve, ataxia, mental disorders
- More prevalent - West Africa
- High prevalence of goiter
- Low levels of S-containing aa
- Elevated plasma thiocyanate (goitrogen)

Chronic Cyanide Poisoning

Dietary Modifiers

- No goiter with adequate iodine
- Malnutrition increases neural effects
- Protein-deficient diets
  - Lack S-containing amino acid to convert CN^- to thiocyanate

Chronic Cyanide Poisoning

Tropical Amblyopia

- Atrophy of optic nerve
  - Blurred vision, blindness
- Africa and South America where cassava is staple in diet
- Reproducible in lab animals

Lathyrism

- Consumption of peas – esp. *Lathyrus sativus*
  - *Grass pea*, *blue sweet pea*, *chickling vetch*, *Indian pea*, *Indian vetch*, *white vetch*, *almorta* or *alverjón* (Spain), *guaya* (Ethiopia), and *khesari* (India).
  - Primarily restricted to areas in Asia/Africa
- Well-known neurodegenerative disease
  - Enzyme inhibitor (BAPN)
  - Neurotoxic amino acid (ODAP)

- Hardy plant, drought resistant

Lathyrism

Two forms disease

- Osteolathyrism - animals
- Neurolathyrism - humans

Osteolathyrism

Animals

- Bone deformations
- Weakness in artery wall and connective tissues
- Beta-L-glutamylaminoproprionitrile (BAPN)

Osteolathyrism

Mechanism

- BAPN inhibits lysyl oxidase enzyme
- Lysyl oxidase is needed to crosslink collagen strands for strength
- Collagen is main component of connective tissue and bones

Neurolathyrism

Humans

- Chronic consumption of *L. sativus*
- Paralysis of legs followed by general weakness and muscle rigidity
- Young man disease
- Sudden onset
  - Calf muscle spasms
- No animal model

Neurolathyrism

Humans

- *B-N*-oxalyl-*L-alpha,B*-diaminoproprionic acid (ODAP)

Neurolathyrism

Humans

- Etiologic agent may be ODAP
- Only found with *L. sativus* species
- OPAP interferes with normal function of nerve synapse
  - Inhibits uptake of glutamic acid
- No animal model to study

Cholinesterase Inhibitors

- Found in a variety of plants - potato, tomato, eggplant
- Western African calibar bean (prototype)
  - Physostigmine
  - Natural carbamate

Cholinesterase Inhibitors

- Solanine - most studied - potato
- Glycoalkyloid - 20-100 mg/kg wet wt
- >200 mg/kg banned by FDA
- Lenape potato variety incident
  - > 300 mg/kg

Cholinesterase Inhibitors

Solanine

- Greatest concentrations
  - Peel, around sprouts
- Natural/artificial light increases levels
  - Russet Burbank - 250-700 mg/kg – 5 days
  - Green due to chlorophyll
    - Ttoxicity marker

Cholinesterase Inhibitors

Solanine

- Documented human toxicity and death
- Potato sprouts, sprouted potatoes, greened potatoes
- Gastric pain, nausea, vomiting, hyperesthesia, increased & accelerated respiration
  - 2/6 deaths
- Concentration unknown

Cholinesterase Inhibitors

Solanine - Case Study

- 420 mg/kg total alkaloid content
- Approx 50% solanine = 200 mg/kg
- Need to consume 1 kg potato for toxicity due to only solanine
- May act with other glycoalkyloids
  - Chaconine
- Animal LD_{50} 500-1000 mg/kg

Vasoactive Amines

- Highest in cheese (aged), beer, wine
- Lower levels in banana, tomato, avocado, spinach, orange
- Spoiled meat (see food allergy)
- “Pressor Amines” (catecholamines)
  - Cause vasoconstriction, hypertension

Vasoactive Amines

- Meat/fish - bacterial action
  - Putrescine, cadaverine
- Banana/avocado
  - Dopamine, tyramine
- Catecholamine neurotransmitters
  - Norepinephrine, dopamine, serotonin

Vasoactive Amines: Problems

- Monoamine oxidase (MAO)
  - Widely distributed in body
  - Breaks down vasopressive amines
- MAO inhibitors - treat clinical depression
- Co-exposure to vasopressive amines in food
  - Mostly tyramine

Vasoactive Amines: Tyramine Mechanisms

- Indirect action
- Displaces normal catecholamines from granules in nerves
- Leads to hypertension
- Can be severe in presence of MAO inhibitors

Vasoactive Amines

Levels in Food - mg/kg

- Tyramine*****
  - Cheese 20-2000
  - Avocado 25
- Seratonin
  - Banana pulp 30

  - Avocado 10
- All others < 10, all sources

Vasoactive Amines

Symptoms

- Hypertension
  - Mild to severe
- Migraine headache
- Rare - intracranial bleeding/death

Pyrrolizidine Alkaloids

- A problem in food animal forage and human subpopulations exposed acutely in a toxic incident or chronically via cultural foods.
- High levels in some plants >5% dry wt
- 100 different compounds

Pyrrolizidine Alkaloids

- Most human exposure from herbal tea or crop contamination
  - Low level exposure from milk/meat
  - Bush tea in Jamaica
- Decreased use as herbal medicine
  - Comfrey - wound dressing (+other)
- Carcinogenic and liver toxin in animals
  - Epoxidation

PA Hepatotoxicity: Veno-Occlusive Disease

- Occlusive lesions are produced in the centrolobular hepatic veins (obliterating endophlebitis).
- Subendothelial edema, narrowing and occlusion of the lumina, atrophy, and necrosis of liver cells with portal hypertension are the results.

Tajikistan, 1992

- Due to a military blockade there was a late wheat harvest.
- Weeds were able to thrive in wheat fields.
- The harvest contained large amounts of the seed of *Heliotropium lasocarpium*.
  - The first cases occurred 6 weeks after contaminated bread was consumed.
- By the spring of 1993 there had already been more than 3900 cases.

- Patients at Stage I had abdominal pain, nausea, vomiting and asthenia.
- In Stage II hepatomegaly followed.
- Stage III was characterized by ascites.
- In the final stage there is hepatic encephalopathy.
- Case fatality ratio was 1.3% and increased with age.

Protease Inhibitors

- Anti-nutritional compounds
  - Legumes, grains, potatoes, eggplant, onion
- Inhibit gastric enzymes that break down proteins
  - e.g. trypsin (protease)
- All toxicity studies in animals
  - Human relevance unclear

Protease Inhibitors

- Pancreatic hypertrophy
  - Pancreatic hypersecretion of amino acid-rich proteins
    - aa deficiency
    - Growth retardation
- Similar mechanism of lathryism

Other Possible Natural Toxicants

- Caffeine
- Spices
- Licorice, nutmeg, sassafras
- Phytoalexins

Vicine and Convicine

- Fava bean alkaloids
- Causes favism in people who have an inherited absence of the enzyme glucose-6-phosphate dehydrogenase (G6PD) in their red blood cells
  - Headaches, dizziness, nausea, yawning, then
  - Vomiting, abdominal pain, and fever.
  - At this point, symptoms either spontaneously subside,
  - Or acute hemolytic anemia via oxidative stress occurs

Vicine and Convicine
Lectins

- Proteins or glycoproteins that bind carbohydrates
- Cause cells to agglutinate
- Basis for blood-type assays (hemagglutination)
- Decrease nutrient absorption from intestinal cells

Lectins: Sources

- Plant (800 species) and animal tissues
- Black beans, soybeans, lima beans, kidney beans, peas, lentils

Lectins: Problem

- Cause growth retardation from consumption of raw product
- Some very toxic (legume-specific)
  - Ricin - castor bean - rat LD50 0.05 mg/kg
  - Kidney bean - 0.5% rat diet two wks
- Growth retardation
  - 0.5-1% of diet black bean and soybean
- Heating destroys toxicity

Lectins: Mechanism of Action

- Unknown; complex
- Prevents nutrient uptake
- Gut flora involved
  - Germ-free animals show less effects
- Immune component?