Antiviral therapy
Parasites

Bio 139
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Antiviral Drugs

Fundamental problem:
How can a drug be selectively toxic against viruses, which are acellular life forms which depend on healthy cells to reproduce?

Answer:
It’s not easy.
Not many antiviral drugs exist.
They have problems with efficacy & safety.

Antiviral drugs:
#1. Nucleoside analogs

• Many viruses have their own polymerase enzymes to synthesize viral DNA or RNA
• These polymerases are slightly different from cellular polymerases
• May be slightly less discriminating than cellular polymerases when they pick up nucleotides

Antiviral drugs:
★Nucleoside analogs

• Chemically similar to normal nucleoside bases, the building blocks of DNA & RNA
  – Similar enough that viral polymerases use them
  ★Different enough to cause problems with nucleic acid synthesis
    – Inhibition of synthesis
    – Introduction of mutations

Nucleoside = nucleotide (ATP, TTP, GTP, CTP, UTP) without the phosphate groups (base + sugar only). Phosphorylated in vivo

Antiviral Drugs:
Nucleoside analogs

★ Not shown: AZT (first drug for HIV/AIDS)

Antiviral Drugs:
#2. Neuraminidase inhibitors

Two classes of drugs specifically target influenza viruses:
(Amantadine:
  – inhibits virus uncoating inside the cell
  – can be used for prophylaxis (prevention before exposure to virus) or treatment
  – Resistance emerges quickly; H5N1 is already resistant)

★Neuraminidase inhibitors (Tamiflu):
  – Interfere with the release of new virus from infected cells
  – Can be used to stop spread of infection if given early enough
  – Countries are trying to stockpile this drug in anticipation of a pandemic
Antiviral drugs:
#3. Interferons

- Cells infected by virus naturally produce a variety of chemicals (cytokines) called **interferons**
- Interferons stimulate a range of antiviral activities by the **immune system**
- Interferons can sometimes be used as antiviral drugs

Human Immunodeficiency Virus (HIV) causes the disease **AIDS** (acquired immunodeficiency syndrome)

**HIV is a retrovirus**
- RNA genome
- After entering a cell, gets converted into DNA
- DNA inserts into host chromosome
- RNA → DNA by viral enzyme **reverse transcriptase** (RNA-dependent DNA polymerase)

Antiviral drugs:
Anti-retroviral drugs

**Human Immunodeficiency Virus (HIV)** causes the disease **AIDS** (acquired immunodeficiency syndrome)

- **Interferons**
- **Antiretroviral drugs**

**Antiretroviral drugs**

1. **Entry inhibitors**
   These drugs bind either to the surface of HIV, or to the CD4 target cell surface, to block adsorption & entry of the virus into the cell

2. **Nucleoside analogs**
   Like you heard about before. Reverse transcriptase mistakenly uses them.
   Example: **AZT**

**Categories of Anti-retroviral drugs**

3. **Non-nucleoside reverse transcriptase inhibitors (NNRTI's)**
   Like nucleoside analogs, these drugs affect RT. However, they do NOT act like nucleotides and act directly on HIV's unique RT enzyme.

4. **Protease inhibitors**
   HIV's proteins are initially made as one giant polypeptide that has to be cut into the individual proteins.
   A **protease** does this.
   These drugs block the protease. New viruses are not formed inside an infected cell.

**HIV Protease Inhibitors**

[Image: HIV Protease Inhibitors]
Done with viruses…on to **Prions**

- Certain slow, progressive dementias are **infectious**
- The infectious agent appears to be a **protein**, now named a **prion**
  - NO DNA or RNA is associated with the prion
  - The gene for the prion protein is actually in the genome of the affected individual!
- In humans:
  - Kuru in cannibals of New Guinea
  - Creutzfeldt-Jakob disease
- In animals:
  - Mad cow disease (bovine spongiform encephalopathy BSE)
  - Scrapie in sheep

**Prions**

- Much is **not** known about prions
- Can be transmitted by contact with infected brains, blood
- **May** be transmitted by eating affected beef
  - 1990’s huge British beef scare; massive slaughter
  - Rules regarding what can go into animal feed have been changed to stop transmission of BSE

Intrigued? Find out more:
Gajdusek, D. did the work on kuru
Prusiner, S. won a Nobel prize for his work on prions

**Protozoal infections**

★ Protozoa are single-celled eukaryotes
  - Amoeba, Paramecium

- Some are human pathogens
  - Giardia, Toxoplasma, Plasmodium

**Protozoa: Giardia**

- Very primitive, ancient protozoan
- Causes giardiasis (diarrhea, weight loss)

Two forms: **trophozoite** (feeding form, at right) which lives in small intestine.
★ The **infectious** form of Giardia is called a **cyst**. Cysts can survive in water for months.

**Protozoal infections**

- Unlike bacteria, protozoal infections involve **complex life cycles**
  - More than one host organism may be needed to complete life cycle
- Gaining access to a new host is difficult & dangerous for the protozoa
  - Multiple forms/life stages to survive different conditions
  - **Trophozoite**: motile, feeding form
  - **Cyst**: reproductive form that finds a new host

**Protozoa: Giardia**

- Fecal-oral transmission
- Humans are not the only hosts
  - Bane of hikers: "pure" mountain streams often contain Giardia cysts from wild animals
  - Filter your water!
Protozoa: Toxoplasma

- **Definitive host is the domestic cat**
  - Can infect many other animals but sexual reproduction occurs only in cats
- Trophozoite form lives in cat intestines; reproductive cysts are passed in (cat) urine & feces
- Cats get infected by hunting infected prey (esp. rodents)
- In animals other than cats, Toxo trophozoites form protected cysts in various tissues
  - Carnivores eating the cysts become infected too
- Humans acquire Toxo by:
  - Contact with cat waste
  - Eating cysts in meat not cooked to well-done
    - Primarily pork, mutton, lamb (but also beef, chicken)
- Toxoplasmosis usually is not a real bad disease in otherwise healthy people
  - though immunocompromised people (such as AIDS patients) will die of toxoplasmosis

Protozoa: Plasmodium (malaria)

- **500 million cases per year**
  - 1 to 3 million deaths
- Endemic in tropical areas
- An association with swamps has long been recognized: “bad air”
- Plasmodium has a complex life cycle with multiple forms/stages
  - **Mosquito** is crucial insect vector
    - this was not recognized until almost 1900
    - Sexual reproduction occurs only in Anopheles mosquitoes
- Life cycle:
  1. Infected mosquito bites human
  2. “Sporozoite” form migrates to the liver
    - Asexual reproduction occurs in hepatocytes (liver cells)
  3. “Merozoite” form released from liver
  4. Merozoites infect red blood cells (erythrocytes)
    - Inside RBCs, called the “trophozoite” form
    - Asexual reproduction again, by trophozoites
  5. Huge numbers of RBC’s lyse in synchronized waves, releasing more merozoites to infect more RBC
    - High fever spikes with each round of red cell lysis
  6. Some sexual forms (gametocytes) are released; mosquito biting human picks up malaria gametocytes to complete the cycle

# Significance:
Toxoplasma infection of **unborn babies** (congenital toxoplasmosis) is catastrophic (fetal death, severe malformations in live-born children)

- Pregnant women should avoid contact with cat waste (Dad should change the litter box) and should eat all meats well-done

- Global extent of malaria in last 50 years
- High risk of malaria 1994, 2016, 2046
- Tropic of Cancer
- Tropic of Capricorn
- Mosquito eradication efforts with DDT
- Now many malaria-carrying mosquitoes are resistant to DDT
- Best control now: insecticide-soaked bednets
- Mosquito biting human picks up malaria gametocytes to complete the cycle
Mosquito → Blood → Liver → RBCs → RBCs → Blood → Mosquito

**Protozoa: Plasmodium (malaria)**

- Drug resistance to anti-malaria drugs is now widespread
- Attempts continue to produce some kind of vaccine
- In the meantime, distribution of insecticide-soaked bed nets is a cheap & effective way to significantly decrease disease & death, especially in children
- American travelers to endemic areas often take anti-malarial drugs to prevent infection
  - 100% DEET insect repellant
  - Long sleeves & pants

- Ch. 13 p. 375-376 (antivirals)
- Ch. 10 291-292 prions
- Ch. 11 305-308 protozoa (animal-like protists); malaria
- Ch. 22 p. 667-668 Giardia
- Ch. 23 p. 713-714 Toxoplasmosis
- Ch. 23 p. 710-713 malaria