PHARMACOLOGY

DOCTOR 2019 | MEDICINE | JU

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Antiviral Agents

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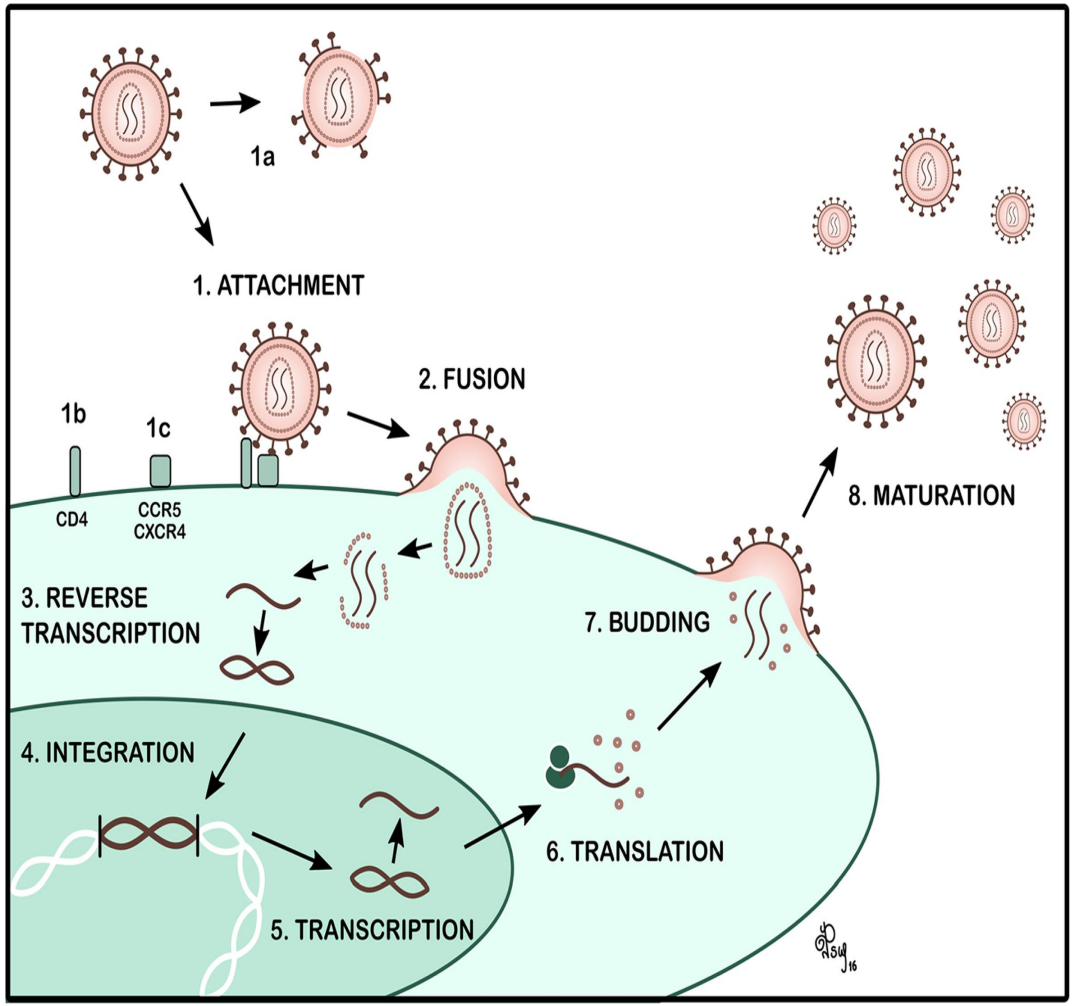
- Viruses are obligate intracellular microbes وهي كائنات انتهازية
- use many of the host cell's biochemical mechanisms and products to sustain their viability

- A mature virus(virion) can exist outside a host cell (they lay dormant outside the cell) and still retain its infective properties (meaning that it would gain back its infective ability once it enters the host cell) .

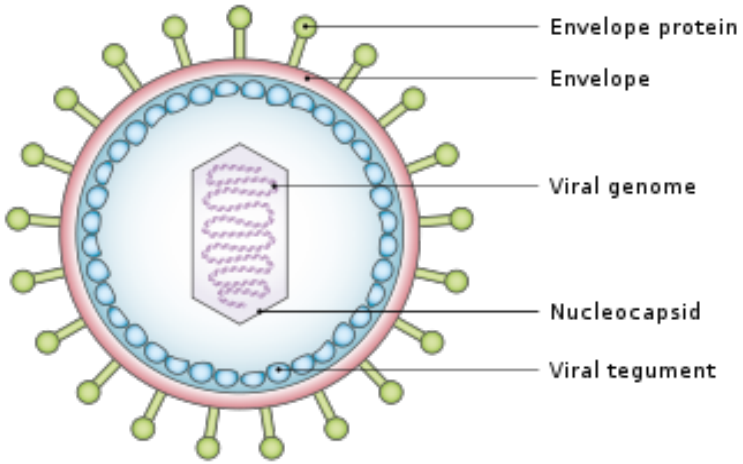
- For a virus to be infectious, it **must** enter the host cell, take over the host cell's mechanisms for nucleic acid and protein synthesis, and direct the host cell to make new viral particles.

1) The virus **attaches** to the host cell via specific proteins present on the surface of the cell.
2) It **fuses** with the cell membrane and enters the cell.
3) (Recall that we have two types of viruses, those are DNA and RNA viruses), RNA viruses would undergo **reverse transcription** to synthesize DNA out of RNA.
4) The synthesized DNA would fuse with the host's DNA (it becomes **integrated** with it).
5) **Transcription** of the integrated DNA occurs.
6) **Translation** of RNA produces host cell proteins AND viral proteins.
7) **Budding**.
8) **Maturation**.



Classification of Viruses.

- Viruses are composed of one or more strands of a nucleic acid (core) either DNA **OR** RNA which we use to classify them, and they're enclosed by a protein coat (capsid).
- Many viruses possess an outer envelope of protein or lipoprotein. (these envelopes makes it easier for the virus to enter the host cell).
- Viral cores can contain either DNA or RNA



- viruses may be classified as DNA viruses or RNA viruses. (most common way of classification).

- Further classification is usually based on morphology, cellular site of viral multiplication inside the host cell, or other characteristics.

DNA viruses, some examples:

- adenoviruses (colds, conjunctivitis) التهاب ملتحمة العين
- hepadnaviruses (hepatitis B);
- herpesviruses (cytomegalovirus chickenpox)
- papillomaviruses (warts)

RNA viruses, some examples:

- arborviruses (yellow fever) الحمى الصفراء
- arenaviruses (meningitis);
- orthomyxoviruses(influenza);
- paramyxoviruses (measles, Mumps النكاف);
- picornaviruses (meningitis, colds);
- rubella virus (German measles)
- retroviruses (AIDS).

Note: Retroviruses (specifically their genomes) are used in gene therapy after modifying them to remove the pathogenic parts.
So, we use their plasmids to transmit specific genes.

Antiviral Agents

Viruses live intracellular, so drugs should be able to enter the human cells.

ANTIHERPESVIRUS AGENTS

Used primarily in the treatment of herpesviruses.

Acyclovir

- **Wide spectrum antiviral agent.** (works on a variety of viruses).
- **Herpes virus.** (especially efficient with this virus).
- **Available as oral tablets, IV injections**(in hospitalized cases) **, eye drops and ointment** (when the infection is localized in certain areas) **, or as a cream.**
- **In Varicella= Chicken Pox, use is restricted to immunocompromised patients** (such as HIV/AIDs patients and those who've had organ transplantation because part of their treatment is taking immunosuppressants) **,** however, immunocompetent patients don't need to take it (they'd get better in 5-7 days without it).
- **Side Effects:** nausea**,** vomiting**, Skin rashes.** (but not in all cases of course)

Acyclovir mimics a specific nucleic acid called **dGTP (deoxy-guanosine triphosphate),**
First, ***acyclovir*** gets incorporated into the host cell. **Then,** it gets converted into ***Acyclovir-MP*** by **viral thymidine kinase**. After that it's converted into ***Acyclovir-DP*** using **cellular kinases**. Then it's converted into ***Acyclovir-TP*** which is *specifically* the molecule that mimics dGTP but affect the virus negatively.

So this Acyclovir-TP gets incorporated in the viral DNA making it dysfunctional and affecting the production of viral proteins.

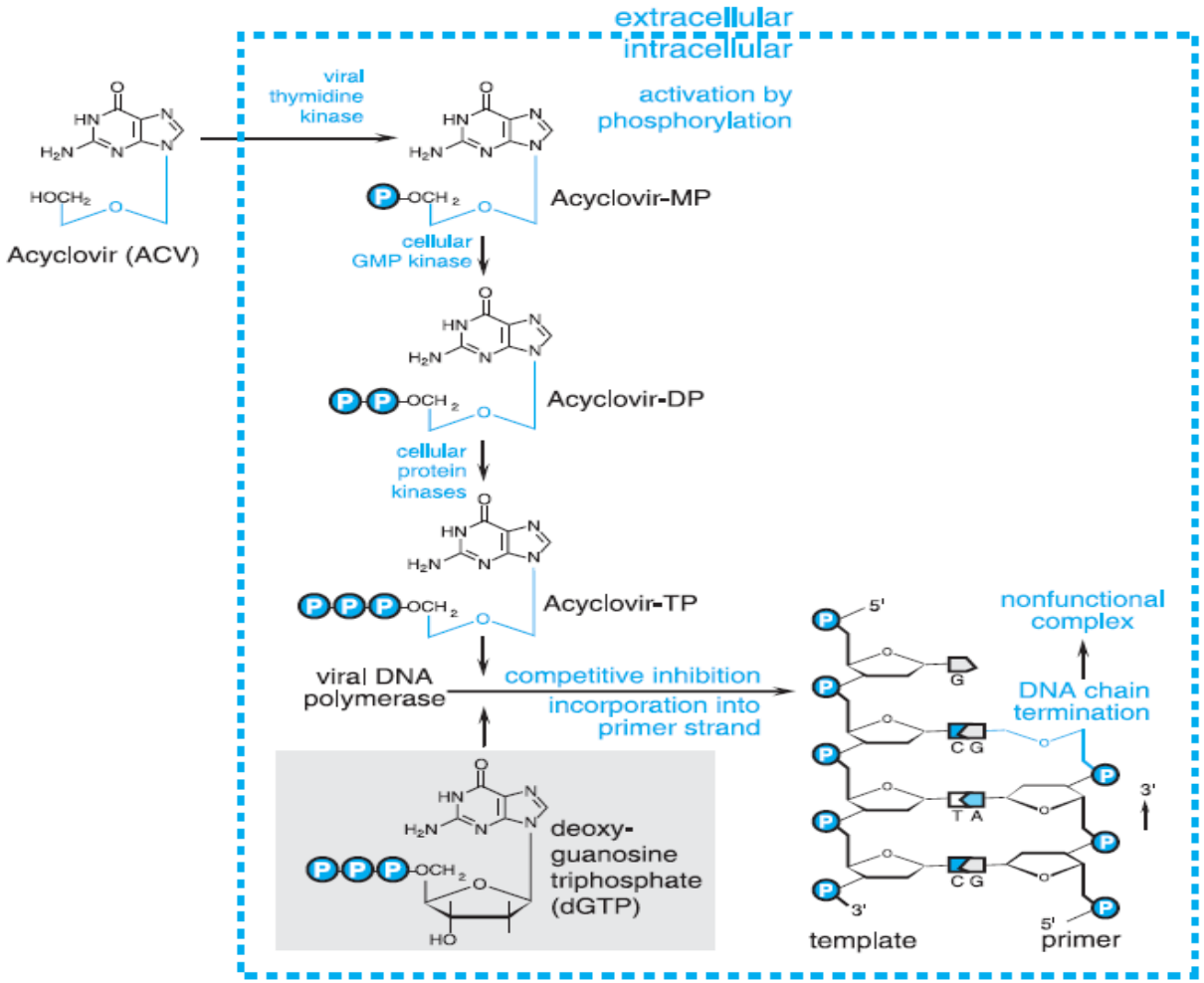


Figure 49–2. ***Conversion of acyclovir to acyclovir triphosphate leading to DNA chain termination.*** Acyclovir is converted to the monophosphate (MP) derivative by a herpesvirus thymidine kinase. Acyclovir-MP is then phosphorylated to acyclovir-DP and acyclovir-TP by cellular enzymes. Uninfected cells convert very little or no drug to the phosphorylated derivatives. Thus, acyclovir is selectively activated in cells infected with herpesviruses that code for appropriate thymidine kinases. Incorporation of acyclovir-MP from acyclovir-TP into the primer strand during viral DNA replication leads to chain termination and formation of an inactive complex with the viral DNA polymerase. (Adapted from Elion, 1986, with permission.)

ANTIINFLUENZA AGENTS ,examples are:

- *Amantadine ,Rimantadine, Oseltamivir, Zanamivir*

- Amantadine (*Symmetrel*) is a synthetic tricyclic amine,
- rimantadine (*Flumadine*) is its -methyl derivative.

- *Their mechanism of action involves inhibition of the viral M2 protein, an integral membrane protein that acts as a H channel* (used to increase the acidity).

- Blockade of the M2 protein **prevents** the acid-mediated dissociation of the ribonucleoprotein complex

- **Ribonucleoprotein** an association that combines a RNA and an RNA-binding protein together.

- the pH changes that result from M2 inhibition inhibit viral assembly.

During the replication of many **viruses**, hundreds to thousands of proteins assemble around the **viral** nucleic acid to form a protein shell called a capsid.

OTHER ANTIVIRAL AGENTS

Used in the treatment of

HBV
hepatitis C virus (HCV)
respiratory syncytial virus (RSV)
some human papilloma virus (HPV)
HIV infection

Anti HIV Agents

1st example: Zidovudine

- Inhibits viral DNA production.
- Expensive. (its disadvantage)
- Causes nausea, vomiting,, muscle pain, and bone marrow suppression (decreasing the immunity of an already immunocompromised patient).

2nd example: Indinavir

- Protease inhibitor.
- block the part of HIV called protease. HIV-1 protease is an enzyme required for the proteolytic cleavage of the viral polyprotein precursors into the individual functional proteins found in infectious HIV-1. Indinavir binds to the protease active site and inhibits the activity of the enzyme preventing the production of functional proteins
- Expensive. (most HIV agents are, and they have lots of bad effects)
- Causes Nausea, Vomiting, Diarrhea, Renal stone formation.
- indinavir wears off quickly after dosing, so requires very precise dosing every eight hours to prevent HIV from forming drug-resistant mutations, including resistances to other protease inhibitors

Interferones

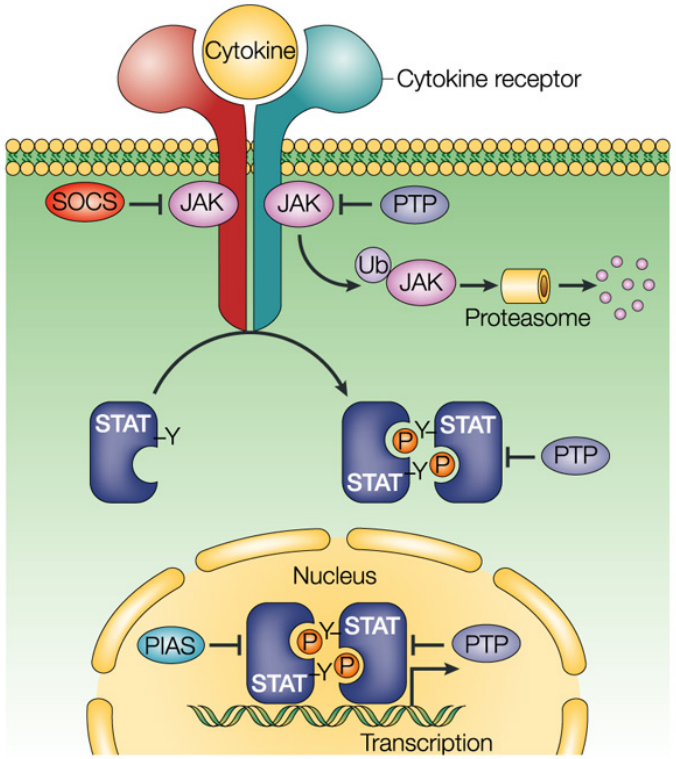
- Interferons (IFNs) are potent cytokines that possess antiviral,immunomodulating (so that the body would recognize the virus and respond to it), and anti-proliferative activities.
- Natural substances produced by virally infected cells. (Artificial drugs which mimic the effect of these naturally produced substances have been made).
- Viral infection gives immunity for variable duration.
- Modify the immune response to increase resistance to viral infection, and control growth of the virus using anti-proliferative activity.

- Obtained in small amounts from donor's WBCs. (the donor should be a patient who had got infected and then treated from it.)
- Nowadays, obtained commercially by recombinant DNA technology.
- **Used in Hepatitis C, and some leukemias.**
- Can cause nausea, fever, and malaise (flu-like symptoms).

Mechanisms of Action.

Following binding to specific cellular receptors, IFNs activate the JAK-STAT signal transduction pathway.

This, in turn, leads to synthesis of over two dozen proteins that contribute to viral resistance mediated at different stages of viral penetration. (remember how viruses enter host cells by binding to certain proteins at the surface of these host cells).



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