Virology

Lec (4)

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Teaching Objectives:
1. To classify types of drug according to each family.
2. To recognize the mechanism of action of each drug.
3. To
interferon's induced mechanisms

Antiviral chemotherapy: Drugs active against viruses used when vaccines are not available or not highly effective.

Why anti-viral drugs are needed.

1-To reduce morbidity and mortality of viral infection.

2-To decrease economic loss due to viral infection like mad cow and avian flu.

3-To treat increasing numbers of immunosuppressed patients who are increased risk of infection.

The number of Anti-viral drugs is very small compared with the number of drugs available to treat bacteria and parasite.

Difficulty in obtaining selective toxicity against viruses, because viruses are obligate intracellular parasite as well as other reasons like poor absorption, rapid metabolism and rapid excretion.

Antiviral agent must be

1-Capable of selectively inhibiting viral infection without damaging the host cells.

2-Reduce disease symptoms without modifying the immune response in the host.

Types of antiviral agents:

Inhibitors of Orthomyxoviruses

A-Inhibitors of early events:

1-Amantadine: this drug blocks the replication of influenza virus by inhibiting uncoating of the virus.

2-Rimantidine is one of derivative of amantadine have the same mode of action with fewer side effects.

B-Inhibitors of late events:

1- Zanamivir (Relenza).
2- Oseltamivir (Tamiflu).

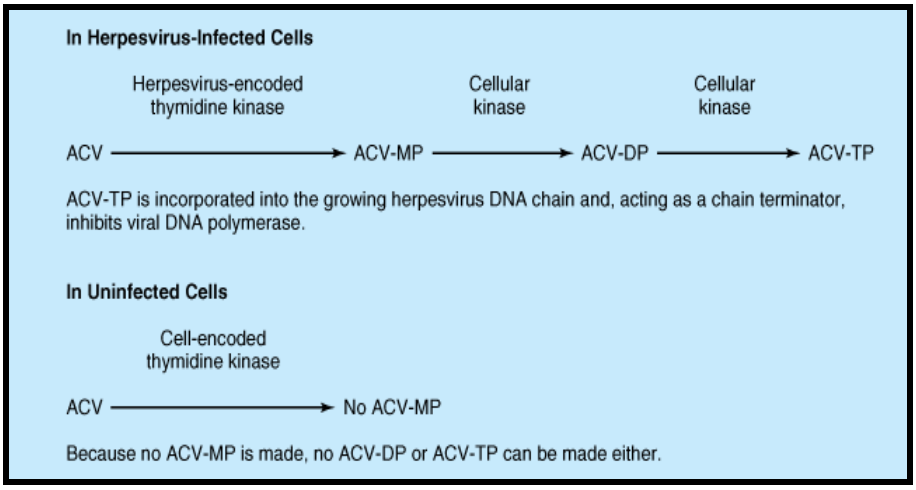
These types of drugs inhibit the neuraminidase of influenza virus and prevent release of viruses.

Inhibitors of herpesviruses.

A-Nucleoside inhibitors:

Nucleoside analogs: They inhibit nucleic acid replication by inhibition of enzymes of the metabolic pathways for purines or pyrimidines or inhibition of polymerase's for nucleic acid replication.

1- **Acyclovi**r (Zovirax). Is active primarily against HSV-1, HSV-2 and Varicella-Zoster virus (VZV). It is relatively non-toxic, because it is activated preferentially within virus infected cells. This is due to the virus-encoded thymidine kinase, which phosphorylates acyclovir much more effectively than does the cellular thymidine kinase. Only HSV-1, HSV-2 and VZV encode kinase that efficiently phosphorylates acyclovir.



2- Ganciclovir: [dihydroxypropoxymethyl guanine (DHPG)] It is structurally similar to acyclovir but is more active against HCMV. The ganciclovir is activated by a HCMV-encoded phosphokinase in a process similar to that by which HSV activates acyclovir

3- Vidarabine: Is an antiviral drug which is active against herpes simplex and varicella zoster viruses. It is phosphorylated by cellular kinase to the triphosphate. Which inhibits the HSV-encoded DNA polymerase more effectively than the cellular DNA polymerase.

4-Idodeoxyuridine (IDU): The drug is phosphorylated to the triphosphate by cellular kinase and incorporated in to DNA use to treat HSV.

5-Triflurothymidine (trifluridine, viroptic): It is a mechanism of action is probably similar to IDU.

6-Cidofovir: It is useful in treatment CMV, HSV and Molluscum contagiosum.

B-Non-nucleoside inhibitors:

Foscarnet: This drug inhibit the DNA polymerase of herpesvirus by mechanisms distinct from the nucleoside analogues described above, usually binds to DNA polymerase at the pyrophosphate

cleavage site and prevents removal of the phosphates from nucleoside triphosphates (dNTP) use to treat patients with HSV ,HCMV.

Inhibitors of Retroviruses.

A-Nucleoside inhibitors:

1-Azidothymidine (AZT, Zidovudine) this drug causes chain termination during DNA synthesies. It is particularly effective against DNA synthesis by reverse transcriptase of HIV and inhibits growth of the virus in the cell culture. Other drugs that have a similar mode of action and used to treat patients with AIDS who are intolerant or resistant to AZT.

2- Dideoxyinosine

3- Dideoxycytidine (Zalcitabine, DDC)

4-Stavudine (zerit, d4T)

5-Lamivudine

6- Tenfovir

B-Non-nucleoside inhibitors:

These drugs are not cause chain termination but binding with reverse transcriptase and inducing a conformational change that inhibits the synthesis of viral DNA

1-Nevirapine (viramune) is usually used in combination with AZT and didnosine

2-Delavirdine

3-Efavirenz

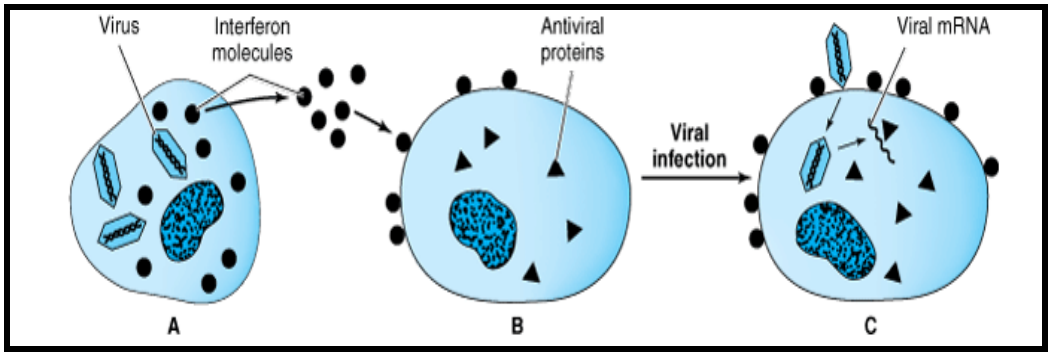
Inhibitors of other viruses.

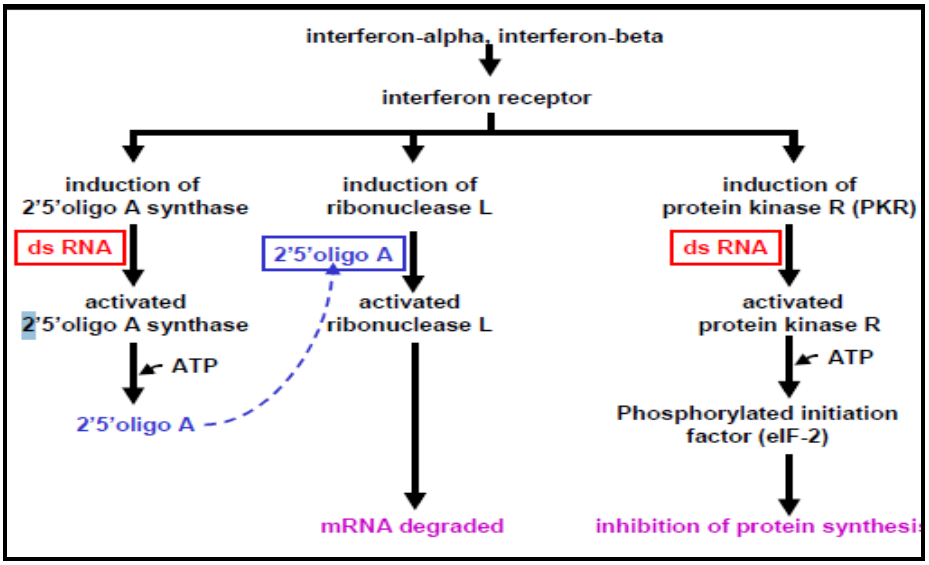
-Ribavirin: It inhibits nucleic acid synthesis of several DNA and RNA viruses.

Inhibitors of viral protein synthesis

1-Interferon are a heterogenous group of glycoprotein's produced by human and other animal cells after viral infection or after exposure to other inducers, they inhibit the growth of viruses by blocking the translation of viral proteins.

Interferon's are divided into three groups based on the cell of origin, namely leukocyte, fibroblast and lymphocyte, they are also know as alph, beta and gamma-Interferon's, respectively alph and beta interferon's are induced by viruses.





Interferons play a crucial role in human disease. The importance of type I IFNs in inflammation, immunoregulation, and T-cell responses has been recognized, and various cell types, including fibroblasts and epithelial cells as well as cells of hematopoietic origin, is known sources of IFNs. Type I IFNs are multifunctional
immunomodulatory cytokines with profound effects on the cytokine cascade, including various antiinflammatory properties. The antiviral effects of these proteins were among the first properties identified. These proteins are produced by virus-infected cells and upon their release act on neighboring cells where they establish an antiviral state. Type II IFN is produced by T cells, NK cells, and macrophages upon activation. Interferon-□ has an immunopotentiating effect and further stimulates macrophage activation. It also induces the enhanced expression of MHC class I and II molecules in macrophages, dendritic cells, and B cells. Interestingly, this effect is also mediated in nonimmune cells. This effect on the expression of MHC molecules has implications on processes associated with antigen presentation to T cells.

2- Fomivirsen is an antisense DNA blocks the replication of CMV by binding with mRNA within infected cell and prevents the translated.

3- Methisazone inhibits the protein synthesis of poxviruses by blocking the translation of late mRNA.