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RESEARCH ARTICLE

ANTIVIRAL CHEMOTHERAPY

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ABSTRACT

Aside for their importance in treating viral diseases, Antiviral drugs make excellent laboratory tools. These can block the functions of specific viral proteins and thus specific stages in viral infection. Antiviral drugs, in conjunction with viral mutations that confer drug resistance, can help to identify the roles of viral proteins and dissect the details of how these proteins do their jobs. Drug resistance mutations can provide selectable markers for engineering interesting mutant viruses and performing a great role in viral genetics.

INTRODUCTION

Both bacteria and viruses were first shown to cause diseases in the late 19thcentury. Antibiotics active against bacterial diseases began to be widely used in 1940s. However, the clinical use of drugs to treat viral diseases in human lagged behind and the first Antiviral drugs were introduced only in the 1960s. A major factor accounting for this delay is that viruses replicate within host cell, using many elements of the host cell machinery. Therefore, there are fewer obvious targets for chemotherapy against bacteria. (Wagnor, Heweron 2003)

How Antiviral drugs work:

Antiviral drugs attack the following stages of the life cycle of a virus.

- Attachment
- Uncoating
- Nucleoside analogies,
- Non-nucleoside inhibitors of reverse transcriptase & polymerase
- RNA synthesis
- RNA cleavage
- Protein synthesis
- Protein processing
- Release of viruses
- Using viruses against other viruses (5&2).

Capsid binding drug prevent uncoating

Picornaviruses bind to their cellar receptor via a 'canyon' in the surface of the capsid. Beneath the canyon floor is a drug-binding side – a pocket. This pocket is lined with hydrophobic amino acid side chain, is occupied by a lipid molecule. Binding of a capsid-binding drug to the pocket displaces the lipid molecules. The presence of the drug can alter the structure to the canyon floor, thereby preventing proper interaction with the cellular receptor and preventing attachment. Pleconaril (img.1) is asuch kind of drug which prevents the attachment of Picornavirus. It is also used against HIV. (3&4).

Some drugs block ion channels and prevent uncoating

Influenza virus enters ion-mediated endocytosis. As a result, the virions find themselves in endosome with low pH. This

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permits fusion of the influenza envelope with the endosome membrane, mediated by low pH conformation of the viral hemagglutinin. Viral M2 protein produces a channel to enter H+ ion and the low pH changes the conformation of matrix protein. This result the liberation of the viral nucleocapsid from the envelope. Amantadine (img.2) block the entry of H+ ions, thereby preventing the uncoating. (Acheron, 2001).

Nucleoside analogue

There are some example like Acyclovir (img.3) and Gancyclovir, (img.4) both active against Herpesvirus, and Azidothymidine (img.5) active against HIV-1. Upon entering cells, nucleoside analogues must first be activated by phosphorylation so that they mimic the natural substrate of DNA-polymerases, deoxynucleoside 5'-triphosphatase. These phosphorylated analogues can inhibits viral DNA-polymerases in two ways. They can act as a competitive inhibitor, blocking binding of natural nucleotide triphosphate to the active site of the enzyme. Alternatively, analogue can incorporated into the growing DNA chain and terminate it's elongation (Balvfour, 1999).

Non nucleoside inhibitor

In monotherapy, **Nevirapine (**img.6) drug cause an initial in the number of HIV virions but resistance set in and virus titer rise. It is an inhibitor of reverse transcriptase.

Foscarnet (img.7) is a competitive inhibitor of viral DNA-polymerase. It binds to pyrophosphate site. It is used against HIV. It is useful when the infecting virus has gained resistance to other drug such as Acyclovir (Flexner, 1998).

RNA synthesis inhibitor:

Ribavirin (img.8) acts as a guanosine analogue and inhibits 5' cap formation on mRNA. It can inhibits the Polioviruses with have not a methyl guanine cap; so there must be alternative mechanism for Ribavirin action. It is likely that this drug introduce multiple mutation into viral RNA rendering it incapable of a new round of cell infection. (5&6).

RNA cleavage inhibitor:

Heptazyme is a ribozyme that cleaves Hepatitis-C RNA at highly conserved region.

Protein synthesis inhibitor:

Formiversen (img.9) is an antisense oligonucleotide made of 21 nucleoside that are phosphorothioate stabilized. It can be administered as an intra-ocular injection for CMV-retinitis. It specifically hybridises to the mRNA for CMV early2 protein, blocking it's translation (Richard).

Protein processing inhibitor:

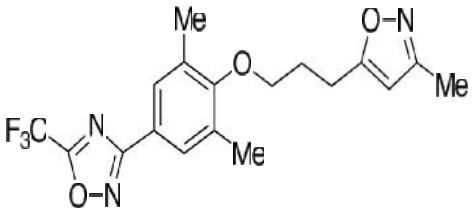
Ritonavir (img.10) is used against HIV-1. It cleaves the Gag precursor of viral capsid protein within the assembled virion. Without this cleavage, the progeny virions are unable to infect cells. HIV protease is also a good target because it has an unusual substrate specificity; it cleaves between phenylalanine and proline, a site that is rarely if ever cleaved by human protease. Ritonavir is a peptidomimetic drug. It's design began with one of the Gag-Pol polyprotein that is cleaved to release reverse transcriptase.(5&7).

Inhibition of viral release

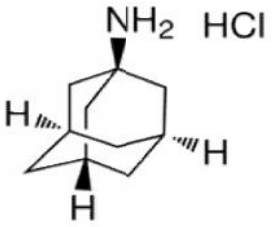
Most viruses do not require any special mechanism to be replaced from the cells surface but Influenza virus does. It initially attaches to cells by interaction between the virionhemagglutinin protein and cellular sialic acid, also known as N-acetylneuramimic acid, which is present on many membrane glycoproteins and gangliosides. This greatly facilitates viral entry. However, at the end of viral replication cycle binding of hemagglutinin protein on virions to sialic acid on the cell surface inhibits release of newly formed viral particles. To overcome this problem, Influenza virus encodes another envelope protein, the enzyme neuraminidase. It cleaves sialic acid from the membrane glycoproteins, permitting release of the virus without the enzyme, the virus remains stuck and can not spread to other cells. Two neuraminidase inhibitors presently available, zananavir (img. 11) and oseltanavir (img.12).(8&9).

Using viruses against other viruses

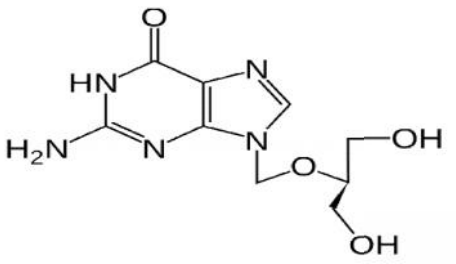
The latent stage of infection with adeno associated virus (AAV) requires a helper virus for replication, but can integrate and maintain a latent stage in cells that it infects without a helper virus. Then when these cells are interred with an adenovirus, the reactivation of AAV can lead to reduce yield of the infecting pathogen. Another approach toward using viruses to combat other viruses is to make advantage of the fact that HIV requires a "biochemical handshake" between the CD4 receptor on the surface of the cell it infects and a second co-receptor such as CXCR4. An 'HIV missile' being is based on a recombinant vesicular stomatitis virus(VSV)(img-13) that contains genes for both the CD4 and CXCR4 proteins but lacks it's own surface protein that interacts with VSV receptors. Thus, this engineered virus can attach to any membrane that contains the HIV envelope glycoprotein, since it interacts with CD4 and CXCR4. This will include HIV, but significantly, also cells infected with HIV that express envelope glycoprotein (gp120) on their surface. (Acheron, 2001).



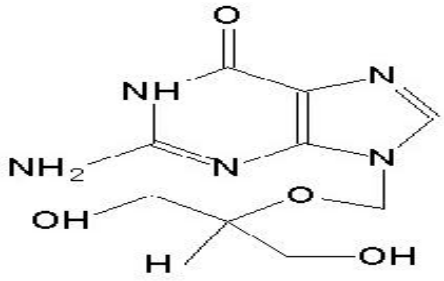
1. Pleconaril



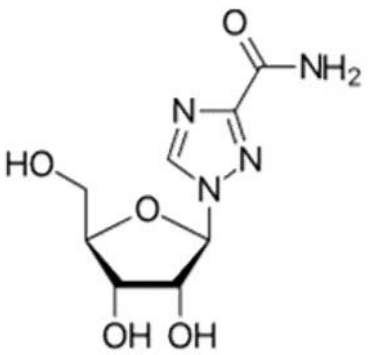
2. Amantadine



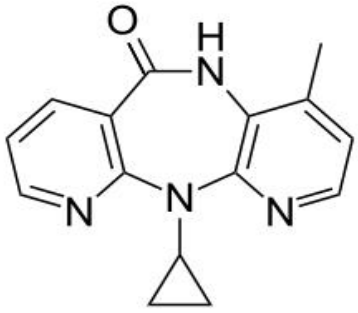
3. Acyclovir



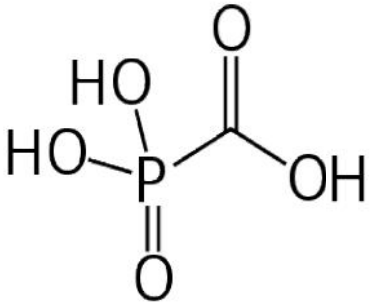
4. Ganciclovir



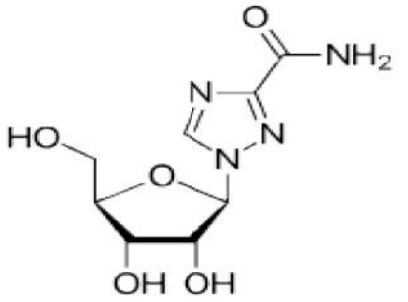
5. Azidothymidine



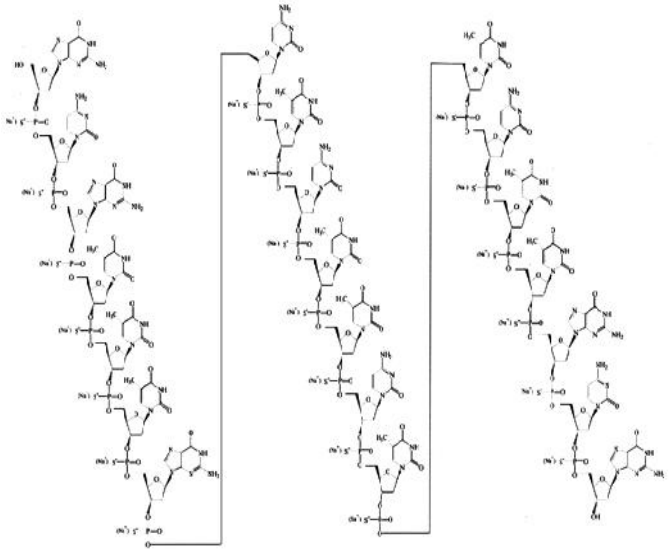
6. Nevirapine



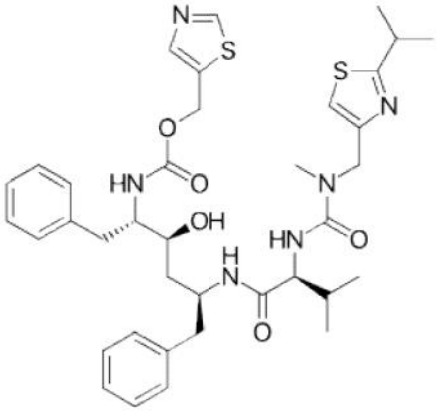
7. Foscarnet



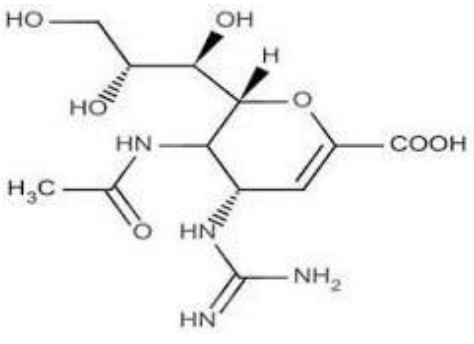
8. Ribavirin



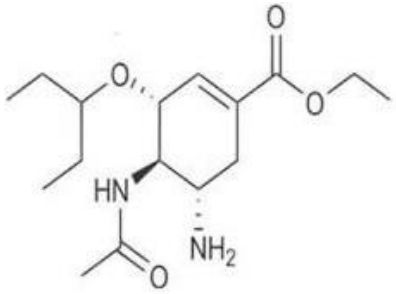
9. Formivirsen



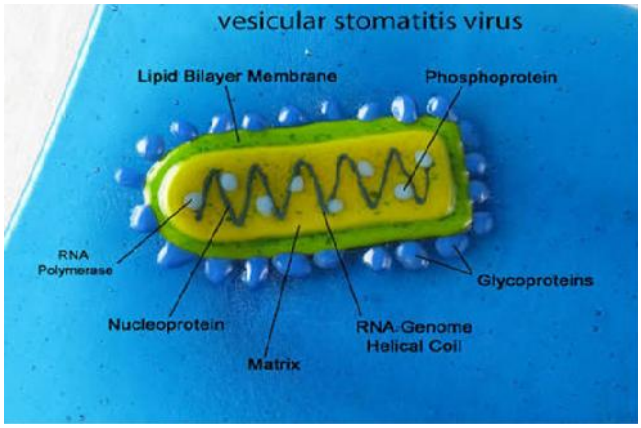
10. Ritonavir



11. Zananavir



12. Oseltanavir



13. Vesicular stomatitis virus (VSV)

DISCUSSION

In summary, the field of Antiviral chemotherapy is a very active area. Part of excitement is that we are taking the knowledge, we have gained over many years about viruses and are putting it to work to treat viral diseases. The success against Influenza virus, HIV-1, Herpesvirus etc. lead to optimism that other viral diseases will be susceptible to Antiviral chemotherapy in future. Furthermore, Antiviral drugs provide a avenue for learning more about viruses.

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