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Research Article

Obvious Considerations in Antiviral Design. From Human Poxvirus to SARS-CoV-2

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Abstract

Viruses exist for many years, even much is known about their biology, their physicochemical characteristics, their structural characteristics and how to combat them through the development or design of antivirals, which are nothing like antimicrobials. Not at all, since an antimicrobial is designed or has as its target action mechanism some bacterial structure that does not exist in viruses. Therefore, the design of an antiviral predisposes to know the structure and the viral cycle.

Today, this issue takes on an important role due to the existence of the SARS-CoV-2 virus and monkeypox, like human smallpox that is supposed to have been eradicated from the planet since 1980, according to the WHO.

Keywords: *Antivirals; Viral Structure; Design; Considerations*

Introduction

One of the paradoxes of medicine today is that the simplest of organisms is the most difficult to control, because while great advances were made in controlling complex organisms such as bacteria, with hundreds of different antibiotics, currently there are only a few proven antiviral drugs. The main barrier in the development of antivirals is the difficulty of distinguishing between viral replicative mechanisms and host replicative processes. However, in the past two decades progress has been made in discovering the molecules necessary for viral replication, including characterizing the mechanisms involved and developing antiviral agents that inhibit them. On the other hand, on more than one occasion and due to a vaccination campaign we have heard the phrase: "...remember, it is a viral condition, do not fight it with antibiotics..." or perhaps just "it is viral". This handy phrase is applied even in cases where the etiology of a disease is not fully known. It is a wide umbrella, a comfortable bodyguard.

However, these phrases are spontaneously related to the inability of antibiotics to deal with something against which they were not designed, since in general, for their design, the structural unit of bacteria is used as the basis: the cell, which is far from of the structural unit of viruses: the virion (Table 1).

Characteristic	Bacteria	Viruses
Structural unity	Cell	Virion
Nucleic Acid	DNA and RNA	DNA or RNA
Proteins	Abundant	Scarce
Lipids and carbohydrates	Abundant	Scarce
Enzymes	Abundant	Scarce
ATP generating capacity	Yes	No
Ribosomes	Present	Absent
Binary fission	Yes	No

Table 1: *Main differences between bacteria and viruses.*

Material and Methods

In a brief trip to the interior of the viral structure, we would find ourselves in the case of enveloped viruses, with an external envelope consisting mainly of glycoproteins and lipids, then and always we would find a protein structure the capsid that protects the viral genome. found inside, which consists of a single type of nucleic acid, that is, only RNA or only DNA (never both), which can be associated with proteins (constituting the nucleocapsid), therefore the design of the Antiviral agents should make use of this characteristic as a starting point, since dealing with an RNA virus (Ribovirus; HIV and SARS-CoV-2 virus) is not the same as dealing with a DNA virus (Deoxyribovirus; Herpes and Poxviruses) [1,2].

Knowing this characteristic necessarily leads to knowing about the infective cycle of the virus and therefore about vulnerable sites, possible targets of action in the design of antivirals.

In general, it is possible to visualize at least 6 stages in the infective cycle of viruses: Adsorption of the virus to the host cell, penetration of the virus into the cell. Stripping or exposure of the viral genome. Viral Replication or synthesis of new copies of the viral genome. Viral progeny formation: which involves the assembly. Exit of virions: for example, by cell lysis [2,3].

These are the key points in the development of therapies that include the use of antivirals and the proposed agents have been proposed for their ability to interfere with the viral replication stage in cell cultures. These tests should include controls for cell toxicity, to choose an antiviral that inhibits viral replication directly and not only due to its toxic effects on host cells. The best targets for antiviral inhibtion are those molecules with a unique function of the virus, without a counterpart in the host cell [4].

Results and Discussion

Thus, in the case of herpes simplex virus, the antiviral acyclovir has been used, which is an analog of guanosine (one of the nucleosides used in DNA synthesis by the enzyme DNA polymerase, where this analog is incorporated efficiently into viral DNA only in infected cells The incorporated base that lacks ribose (unlike its normal counterpart) thus prevents DNA chain elongation This action is at two levels: it prevents DNA elongation and also it is a better substrate for viral enzymes than for cellular ones.

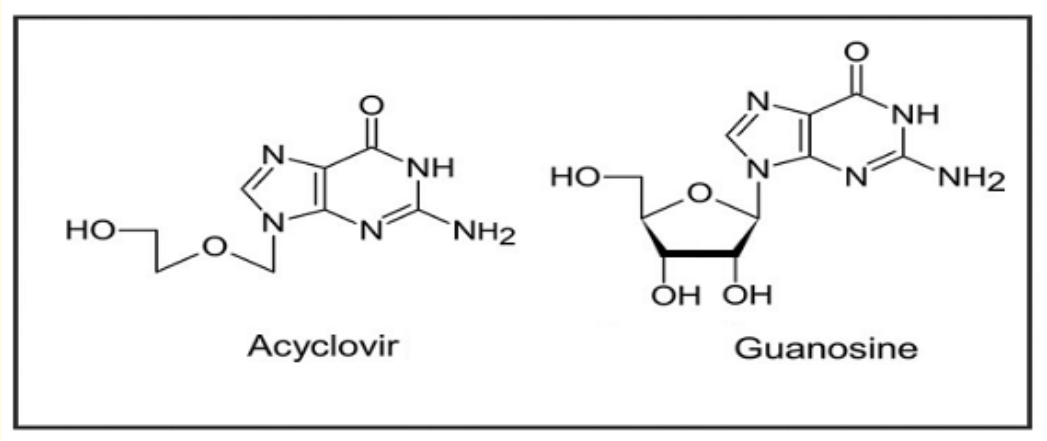

Figure 1: *Acyclovir and guanosine structure.*

Another case that deserves mention in humans is the infection by the human immunodeficiency virus: HIV, where AZT (zidovudine) has been used, which is a synthetic analog of deoxythymidine, another nucleoside used in DNA synthesis (Figure 2) and inhibits the replication of retroviruses. AZT is converted to triphosphate (TP) by cellular enzymes, and thus the AZT TP is incorporated into the new strand of DNA much more efficiently by viral reverse transcriptase than by cellular DNA polymerase. Thus, the elongation stage is inhibited, since the AZT TP does not contain the -OH group in position 3 necessary to continue adding nucleosides.

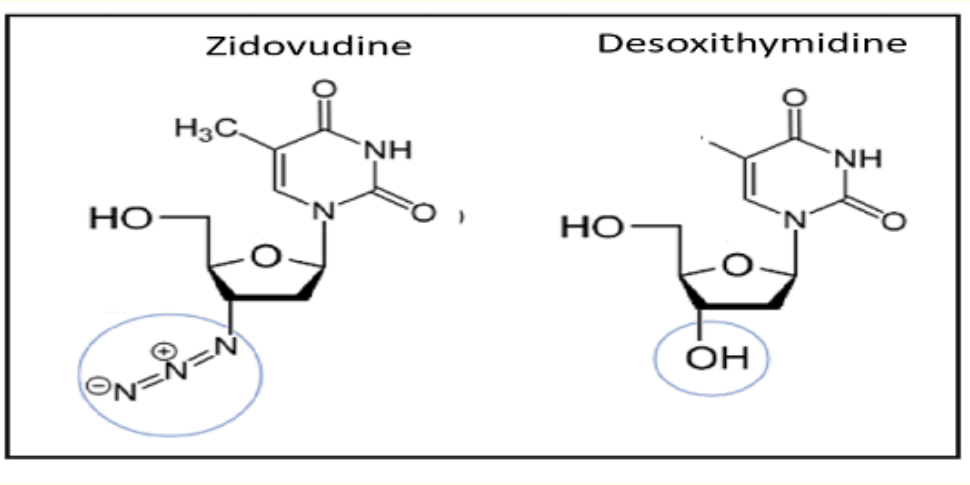

Figure 2: *Zidovudine and deoxythymidine structures.*

An honorable mention goes to the strategy called antisense therapy, which is related to the use of DNA sequences, which will give rise to an RNA complementary to the messenger RNA, thus preventing the next phase: the synthesis of viral proteins.

Let us remember that for a protein to be synthesized, the DNA sequence (deoxyribonucleic acid) that specifies its composition must be transcribed that is, copied that is, the corresponding gene into an RNA molecule called messenger. This messenger RNA must then be read by the ribosomes a process called translation to give rise to the sequence of amino acids that will form said protein.

Since the nucleotide sequence of messenger RNA determines the amino acid ordering of the protein, that RNA sequence is said to "make sense". By contrast, an RNA sequence that is the mirror image of messenger RNA that is, a complementary chain will be a nonsense molecule or, perhaps more appropriately, antisense since it does not carry the correct information for the synthesis of the protein. To design these antisense molecules, the ability of the bases to pair specifically: an A joins a U and a G joins C. Thus, if the `sense' sequence is, for example, AACGGUCU, the antisense sequence will be UUGCCAGA. messenger, forms a duplex and prevents its reading by the ribosomes and, therefore, the synthesis of the protein, since the RNA must be single-stranded or single-stranded to be 'translated'.

Conclusion

An antiviral strategy not yet addressed in antiviral therapy and that also targets the viral replication stage, but not the elongation phase-like all those mentioned but rather to achieve the inhibition of the initiation phase of the synthesis of the viral DNA. I am referring to the use of oligonucleotides with a sequence analogous to the viral origin of replication (ORI). In theory, there would be a competition kinetics between the authentic on site and the added synthetic on, by the protein (UL9 or similar) that binds early to the DNA to initiate the duplication of the genomic material of the virus.

Although there are other strategies based on the stages of the infection cycle that have also been explored, until now viruses have successfully faced all attempts made by man except for the smallpox virus to achieve their eradication from the planet, which It will undoubtedly lead researchers to develop new strategies to deal with this small but remarkable adversary.

Acknowledgments

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