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Review article

Polypharmacology in HIV inhibition: can a drug with simultaneous action against two relevant targets be an alternative to combination therapy?☆

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ABSTRACT

HIV infection still has a serious health and socio-economical impact and is one of the primary causes of morbidity and mortality all over the world. HIV infection and the AIDS pandemic are still matters of great concern, especially in less developed countries where the access to highly active antiretroviral therapy (HAART) is limited. Patient compliance is another serious drawback. Nowadays, HAART is the treatment of choice although it is not the panacea. Despite the fact that it suppresses viral replication at undetectable viral loads and prevents progression of HIV infection into AIDS HAART has several pitfalls, namely, long-term side-effects, drug resistance development, emergence of drug-resistant viruses, low compliance and the intolerance of some patients to these drugs. Moreover, another serious health concern is the event of co-infection with more than one pathogen at the same time (e.g. HIV and HCV, HBV, herpes viruses, etc). Currently, the multi-target drug approach has become an exciting strategy to address complex diseases and overcome drug resistance development. Such multifunctional molecules combine in their structure pharmacophores that may simultaneously interfere with multiple targets and their use may eventually be more safe and efficacious than that involving a mixture of separate molecules because of avoidance or delay of drug resistance, lower incidence of unwanted drug-drug interactions and improved compliance. In this review we focus on multifunctional molecules with dual activity against different targets of the HIV life cycle or able to block replication, not only of HIV but also of other viruses that are often co-pathogens of HIV. The different approaches are documented by selected examples.

Contents

☆ Dedicated to Professor Jan Balzarini on the occasion of his retirement and in recognition to many years of fruitful collaboration

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1. Introduction

Infections by human immunodeficiency virus (HIV) and several other viruses (e.g. herpes viruses, hepatitis B and C, influenza, etc) are the main cause of morbidity and mortality worldwide. These viral infections represent a continuous serious concern and a global threat to human health in the twenty first century. In particular, HIV infection and the AIDS pandemic not only constitute a serious health problem but also have important social and economic consequences all over the world. HIV still causes approximately 3 million deaths annually [1]. Despite the outstanding advances in the treatment of HIV infection, AIDS still remains an incurable disease and represents one of the most important challenges for chemotherapy in this century and possibly one of the most common chronic infectious diseases in the near future. HIV is an unprecedented and fearful pathogen which rapidly mutates to escape the immune system. Moreover, HIV targets the $CD4^+$ T lymphocyte cells and causes immunodeficiency, which often leads to a high susceptibility to opportunistic infections by several other pathogens including viruses, bacteria and protozoa.

Although there is no cure for HIV/AIDS, there are currently 24–27 approved drugs for the management of HIV infection that are used in combination in highly active antiretroviral therapy (HAART). It is generally accepted that antiretroviral monotherapy is not a good option to treat the HIV infection. The reason is that an incomplete inhibitory activity against HIV is associated with emergence of antiviral drug resistance, which has been observed with all antiretroviral agents discovered to date. HAART chemotherapy turned out to be useful to better suppress viral replication leading to undetectable viral loads, suppression of prominent drug resistance and to block progression of HIV infection into AIDS. However, long-term chemotherapy of AIDS and HIV infection suffers from several pitfalls, such as side effects and eventual development of drug resistance (which compromises the long-term viral suppression), low compliance and the intolerance of many patients to drugs. Therefore, it can be assumed that drug resistance is probably the most important factor of the failure of treatment and eradication of HIV infection. There is indeed an increasing number of infected people who harbour HIV strains resistant to multiple drugs. Moreover, the transmission of HIV variants resistant to at least one of the drug classes used in HAART has been reported in the literature [2-4]. Even more importantly, the presence of HIV mutations associated with drug resistance has been detected in treatment-naïve patients, that is, individuals who had never received any prior antiretroviral therapy.

Due to the difficulty of achieving viral eradication, combination antiretroviral therapy is nowadays a realistic modality for the prolonged reduction of the viral burden. Antiretroviral drugs acting on different viral targets and/or on the same target but with different mechanisms of action have proved successful in HAART. Indeed, the combination of currently available antiretroviral agents exploits drug interactions of compounds that are synergistic or have additive activity. When those drugs are combined, the virus needs to mutate simultaneously at multiple positions in the genome to circumvent the drug-directed blockade.

Another serious health concern is the event of co-infection of patients with more than one pathogen at the same time. Several cases of HIV patients co-infected with other pathogens, such as hepatitis B virus (HBV), hepatitis C virus (HBC), herpes simplex virus (HSV), enteroviruses, tuberculosis, *Leishmania*, etc., have indeed been reported and also require combination therapy.

One alternative to combination therapy, which may help to increase the antiretroviral armamentarium and to address the devastating impact of HIV infection, is the use of hybrid (conjugated, multifunctional) molecules that combine pharmacophores in their structure that can simultaneously interfere with multiple targets [5]. These agents may eventually be more safe and efficacious than combination of single molecules, may delay the emergence of drug resistance or may prevent compromising drug-drug interactions. Multi-target drugs therefore represent an exciting strategy in the fight against complex infections and drug resistance.

This review will focus on multi-target molecules with dual activity against different targets of HIV or with dual concomitant activity against the replication of HIV and other co-pathogenic viruses. The different approaches will be illustrated with selected examples.

2. Multi-target drugs

A multi-target or hybrid drug can be defined as a chemical entity that combines the pharmacophores of two or more drugs with different mechanisms of action in a single molecule which is capable to interact simultaneously with two or more molecular targets [6]. Drugs of this kind are usually classified, according to the degree of framework merging, as “conjugated”, “fused” or “merged” hybrids [6]. Thus, in “conjugated” drugs both parent molecules are separated by a linker (cleavable or non-cleavable). “Fused” drugs are those in which both frameworks are directly coupled without a linker in between, and finally in “merged” drugs the frameworks integrate into a single scaffold that shares common structural features of the parent drugs to generate smaller and simpler molecular entities. On the other hand, hybrid drugs can also be classified according to the mode of action. Thus, the hybrid drug may act as a single molecule (non-cleavable hybrids) or be cleaved inside the cell releasing both parent drugs (co-drugs). Although most of the co-drugs use a linker to connect both parent drugs, there are examples in the literature of fused hybrids that release both intact compounds inside the cell. Finally, the classification can also be based on the targeted binding sites. For example, the sites can be (i) pockets of a single protein that are adjacent in space, (ii) pockets located on different proteins but recognizing similar endogenous ligands, or (iii) pockets of different proteins that recognize different ligands [7]. In order to simplify this scenario, this review follows the mode of action classification of the compounds.