Advanced Drug Delivery Reviews 103 (2016) 121–143

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/addr

Role and modulation of drug transporters in HIV-1 therapy☆

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ARTICLE INFO

Article history:
Received 12 January 2016
Received in revised form 29 April 2016
Accepted 3 May 2016
Available online 13 May 2016

Keywords:
HIV-1
Antiretroviral drugs
ABC transporter
SLC transporter
Blood–tissue barriers
Nuclear receptors
Drug disposition

ABSTRACT

Current treatment of human immunodeficiency virus type-1 (HIV-1) infection involves a combination of antiretroviral drugs (ARVs) that target different stages of the HIV-1 life cycle. This strategy is commonly referred to as highly active antiretroviral therapy (HAART) or combined antiretroviral therapy (cART). Membrane-associated drug transporters expressed ubiquitously in mammalian systems play a crucial role in modulating ARV disposition during HIV-1 infection. Members of the ATP-binding cassette (ABC) and solute carrier (SLC) transporter superfamilies have been shown to interact with ARVs, including those that are used as part of first-line treatment regimens. As a result, the functional expression of drug transporters can influence the distribution of ARVs at specific sites of infection. In addition, pathological factors related to HIV-1 infection and/or ARV therapy itself can alter transporter expression and activity, thus further contributing to changes in ARV disposition and the effectiveness of HAART. This review summarizes current knowledge on the role of drug transporters in regulating ARV transport in the context of HIV-1 infection.

Contents

Abbreviations: ABC transporter, ATP-binding cassette membrane transporter; AhR, Aryl hydrocarbon receptor; AIDS, Acquired immunodeficiency syndrome; ARV, Antiretroviral drug; BBB, Blood–brain barrier; BCRP, Breast cancer resistance protein; BTB, Blood–testicular barrier; CAR, Constitutive androstane receptor; CCR5, Cysteine–cysteine receptor 5; CD4, Cluster of differentiation-4; CNS, Central nervous system; CNT, Concentrative nucleoside transporter; CPE, CNS penetration effectiveness; CVF, Cervicovaginal fluid; CXCR4, Cysteine-X-cysteine receptor 4; CYP, Cytochrome P450 enzymes; ENT, Equilibrative nucleoside transporter; ER, Estrogen receptor; FXR, Farsenoid X receptor; GI, Gastrointestinal; gp, Glycoprotein; GR, Glucocorticoid receptor; GSH, Glutathione; GSSG, Glutathione disulfide; HAART, Highly active antiretroviral therapy; HIV, Human immunodeficiency virus; HIVE, HIV-1 encephalitis; LXR, Liver X receptor; MDR, Multidrug resistance; MRP, Multidrug resistance-associated protein; NNRTI, Non-nucleoside reverse transcriptase inhibitor; NRTI, Reverse transcriptase inhibitor; OAT, Organic anion transporter; OATP, Organic anion-transporting polypeptide; OCT, Organic cation transporter; OCTN, Organic cation/cartinine transporter; P-gp, P-glycoprotein; PI, Protease inhibitor; PPAR, Peroxisome proliferator-activated receptor; PXR, Pregnane X receptor; SLC transporter, Solute carrier membrane transporter; SULT, Sulfotransferase phase II metabolizers; TDF, Tenofovir disoproxil fumarate; TMD, Transmembrane domain; UGT, UDP-glucuronosyltransferase; UNAIDS, Joint United Nations Program on HIV/AIDS; VDR, Vitamin D receptor; WHO, World Health Organization.

☆ This review is part of the *Advanced Drug Delivery Reviews* theme issue on "HIV/AIDS_dasNeves_Sarmento_Sosnik".

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http://dx.doi.org/10.1016/j.addr.2016.05.001
0169-409X/

1. Introduction

Since the discovery of the human immunodeficiency virus 1 (HIV-1), tremendous progress has been made in the management of HIV-1 infection. HIV-1 pharmacotherapy in the form of highly active antiretroviral therapy (HAART) or combined antiretroviral therapy (cART) has been effective in suppressing plasma viral load, delaying the onset of viral resistance, and significantly reducing HIV-associated mortality [1]. However, the use of HAART does not lead to complete eradication of the virus and treatment can fail due to several contributing factors including: i) adverse effects and non-adherence in patients, ii) drug–drug interactions from multiple drugs undergoing similar pharmacokinetic pathways, iii) viral persistence in latently infected cell reservoirs, and iv) sub-optimal antiretroviral drug (ARV) concentrations in viral sanctuaries, all of which can cause drug resistance and viral rebound [2–4]. The distribution and efficacy of ARVs at specific sites of infection may be influenced not only by drug metabolism and protein binding, but also by the presence and function of members of the ATP-binding cassette (ABC) and solute carrier (SLC) transporter superfamilies [4]. This review will discuss the challenges facing current HIV-1 pharmacotherapy, involvement of ABC and SLC transporters in ARV transport and disposition, and the regulation of these transporters by pathological processes as well as by ARV therapy itself.

2. Human immunodeficiency virus type-1 (HIV-1) infection

2.1. Epidemiology

The Joint United Nations Program on HIV/AIDS (UNAIDS) and World Health Organization (WHO) reported that 36.9 million people globally were living with HIV-1 in 2014, 2 million of which were new infections [5,6]. In that same year, an additional 1.2 million people died from complications related to the acquired immunodeficiency syndrome (AIDS) [5]. Sub-Saharan Africa remains the epicenter of the pandemic with 25.8 million people infected with HIV-1. This region is responsible for 66% of new infections and 790,000 AIDS-related deaths in 2014 alone. The number of people infected by the virus is also considerably high in other regions such as Asia and the Pacific (5.0 million), Latin America (1.7 million), as well as Eastern Europe and Central Asia (1.5 million) [5]. North America and Western and Central Europe account for 2.4 million of the HIV-1 infected population and 85,000 new infections, with more than half of the new infections reported in the region originating from the United States of America [5]. Though the rate of new infections has declined over the past 15 years, the total number of people living with HIV continues to rise, indicating the need for more effective treatment approaches.

2.2. HIV-1 life cycle

HIV is a lentivirus from the *Retroviridae* family that targets the immune system and causes AIDS. Two variants of the virus have been identified to date (HIV-1 and HIV-2), with HIV-1 being the most prevalent and leading cause of HIV infection worldwide, while HIV-2 is predominantly found in West Africa [7]. HIV-1 is a spherical virus with a 9 kb genome encoding nine genes: *gag*, *pol*, *env*, *vif*, *vpu*, *vpr*, *tat*, *rev*, and *nef* [7]. It is known to primarily infect cells expressing the cluster of differentiation-4 (CD4) receptor (i.e., $CD4^+$ T lymphocytes and mononuclear phagocytes), however HIV-1 viral isolates have been identified that do not require CD4 for target cell entry. These non-CD4 using viral strains are highly sensitive to neutralization by host antibodies and may occur at sites such as the central nervous system (CNS), where circulating neutralizing antibodies are low [8,9].

Cellular infection of $CD4^+$ cells by HIV-1 involves a complex series of events that facilitate viral entry, integration of viral DNA into host cell genome, and subsequent release of viral particles from newly infected cells (Fig. 1). HIV-1 entry is initiated by the binding of viral envelope spike, a protein complex comprised of glycoprotein (gp) 120 and 41, to the CD4 receptor that triggers a conformational change and allows the subsequent interaction of gp120 to chemokine co-receptors, cysteine–cysteine receptor 5 (CCR5) or cysteine-X-cysteine receptor 4 (CXCR4) [10,11]. Binding of gp120 to the co-receptor causes the fusion of viral and cell membranes, allowing the insertion of viral RNA into the cytoplasm of the target cell. Immediate reverse transcription of HIV-1 RNA into double-stranded DNA by viral reverse transcriptase, followed by its translocation into the nuclear envelope, enables the integration of viral genetic material into the host cell genome via HIV-1 protein integrase and host DNA repair enzymes [7,10]. Subsequent expression of viral genes by the host cell leads to the production of precursor proteins essential for the assembly of new virions. The final step of HIV-1 infection involves viral maturation and secretion, which is characterized by a viral envelope containing the gp120–gp41 complex, and cleavage of precursor viral proteins by HIV-1 protease to yield a mature virus that can infect other target cells. Inhibition of the HIV-1 protease enzyme can result in the production of non-infectious viral particles that are unable to initiate the replication cycle in susceptible cells. Additionally, gp120–gp41 may also be shed from infected cells as soluble proteins [12].

2.3. HIV-1 persistence: tissue sanctuaries and cellular reservoirs

Exposure to HIV-1 occurs primarily through reproductive or gastrointestinal (GI) mucosal routes, therefore initial replication of the virus occurs within target cells of the mucosal tissue [13]. Viral transmission is facilitated by several potential pathways, including endocytosis, transcytosis, and virus attachment to mannose C-type lectin receptors (i.e., DC-SIGN) located on dendritic cells and macrophages [14]. Initial replication takes place in regional lymph organs, leading to modest primary amplification. Migration of infected T lymphocytes or virions into the bloodstream results in secondary amplification and massive infection of susceptible cells in the GI tract, spleen, and bone marrow [10]. Infection is divided into two phases: acute and chronic. During acute infection, the virus rapidly multiplies in host cells while the immune system is able to respond effectively and decrease viral load [10,13]. The virus can then accumulate to levels high enough to form