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Nanotechnology applications for improved delivery of antiretroviral drugs to the brain ☆

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ABSTRACT

Human immunodeficiency virus (HIV) can gain access to the central nervous system during the early course of primary infection. Once in the brain compartment the virus actively replicates to form an independent viral reservoir, resulting in debilitating neurological complications, latent infection and drug resistance. Current antiretroviral drugs (ARVs) often fail to effectively reduce the HIV viral load in the brain. This, in part, is due to the poor transport of many ARVs, in particular protease inhibitors, across the blood-brain barrier (BBB) and blood-cerebrospinal fluid barrier (BCSBF). Studies have shown that nanocarriers including polymeric nanoparticles, liposomes, solid lipid nanoparticles (SLN) and micelles can increase the local drug concentration gradients, facilitate drug transport into the brain via endocytotic pathways and inhibit the ATP-binding cassette (ABC) transporters expressed at the barrier sites. By delivering ARVs with nanocarriers, significant increase in the drug bioavailability to the brain is expected to be achieved. Recent studies show that the specificity and efficiency of ARVs delivery can be further enhanced by using nanocarriers with specific brain targeting, cell penetrating ligands or ABC-transporters inhibitors. Future research should focus on achieving brain delivery of ARVs in a safe, efficient, and yet cost-effective manner.

Contents

Abbreviations: ABC transporter, ATP-binding cassette membrane transporter; AIDS, acquired immunodeficiency syndrome; apoE, apolipoprotein E; ARVs, antiretroviral drugs; BBB, blood-brain barrier; BCSFB, blood-cerebro spinal fluid barrier; CD4, cluster of differentiation 4; CNS, central nervous system; CSF, cerebrospinal fluid; HAART, highly active antiretroviral therapy; HAD, human immunodeficiency virus-associated dementia; hCMEC/D3, human brain microvessel endothelial cell line; HIV, human immunodeficiency virus; HIVE, human immunodeficiency virus encephalitis; LDL, low-density lipoprotein; MCMD, minor cognitive/motor disorder; MMA-SPM, methylmethacrylate-sulfopropylmethacrylate; MRP, multidrug resistance-associated proteins; NNRT, non-nucleoside reverse transcriptase inhibitors; NRTI, nucleoside reverse transcriptase inhibitor; PBCA, poly(butyl cyanoacryalate); PEG, polyethylene glycol; PIs, HIV protease inhibitors; PIL, PEGylated immunoliposomes; P-gp, P-glycoprotein; PLA, polylactide; PLGA, poly(D,L-lactide-co-glycolide); SLN, solid lipid nanoparticles; Tat, transcriptional activator; Vpr, viral protein R.

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1. HIV infection and CNS illnesses

1.1. Human immunodeficiency virus (HIV)

Human immunodeficiency virus (HIV) is a lentivirus from the *Retroviridae* family responsible for the acquired immunodeficiency syndrome (AIDS). At present, there are two known types of HIV, HIV-1 and HIV-2, with HIV-1 being much more virulent, transmittable and prevalent, and the cause of the majority of HIV infections in the world [1]. HIV infection results in compromised immune defense by causing extensive destruction of T-helper cells, macrophages, dendritic cells and other cellular components associated with cell-mediated immunity [2,3]. As a result, HIV-infected patients are substantially more vulnerable to opportunistic infections. The abnormal immune responses triggered by HIV infection can also result in other complications such as neurological illnesses.

1.2. HIV epidemiology

According to the 2007 update by the Joint United Nations Program on HIV/AIDS and World Health Organization [4], every day over 6800 individuals become newly infected and over 5700 patients die from AIDS. It is estimated that 33.2 million persons worldwide are infected with HIV-1, and the developing nations continue to be its primary victims. Although signs of a decline in the cases of new infection have been observed due to better prevention efforts, the sub-Saharan African region remains as the epicenter of the pandemic. An estimated 22.5 million people in these countries, equivalent to 5% prevalence, are living with HIV-1 infection. The prevalence is also alarmingly high in the Caribbean Islands (1.0%), Latin America (0.5%), Eastern Europe and Central Asia (0.9%). In East Asia, 92,000 adults and children were found newly infected with HIV-1 in 2007, representing almost a 20% increase from 2001. Even though the numbers of new HIV-1 infections have been relatively stable in the developed nations, this disease is still an unresolved health issue. In North America only, 1.3 million people are living with HIV-1, equivalent to 0.6% prevalence. These data indicate that the current treatment of HIV-1 still needs significant improvement.

1.3. Complications associated with HIV infection of the central nervous system

1.3.1. Pathophysiology

HIV and other lentiviruses are unique from other viruses due to their ability to infect and replicate in non dividing cells including those of the monocyte/macrophage lineage. In particular, HIV targets the cluster of differentiation 4 positive (CD4+) T lymphocytes and cells of the monocyte-macrophage lineage [5]. CD4− negative cells may also be targeted, but these viral strains are highly sensitive to neutralization by host antibodies and are present only at sites where circulating antibody levels are low (e.g. in brain) [6,7]. Once the virus fuses with the host cell, DNA is produced from its RNA genome via the enzyme reverse transcriptase, and then DNA is incorporated into the host's genome by an integrase enzyme and replicates as a part of the host DNA [1,8].

HIV is known to invade the central nervous system (CNS) early in the course of the infection and primarily targets brain mononuclear macrophages, perivascular macrophages and microglia. [7,9]. The virus can enter the CNS compartment from the systemic circulation via two routes: i) through the blood-cerebro spinal fluid barrier (BCSFB) at the choroid plexus as cell-free viral particles [10], and/or ii) through the blood-brain barrier (BBB) in form of infected monocytes [11]. The second route is known as the "Trojan horse approach". In brief, monocytes infected by HIV-1 are able to cross the BBB between the capillary endothelial cells in a complex process regulated by the secretion of chemokines (e.g. MIP-1a/b, MCP-1, RANTES) from glial cells [12]. The brain macrophages and microglial cells, upon infection are responsible for further production of HIV-1 virus, and can also release viral proteins such as glycoprotein 120 (gp120), Tat (transcriptional activator) and Vpr (viral protein R) [13–16]. These viral proteins have been shown to be neurotoxic *in vitro* and trigger various harmful events such as activation of apoptotic pathways, cell-cycle arrest of neuronal cells and stimulation of the production of reactive oxidative species, glutamate, cytokines and other inflammatory factors from uninfected astrocytes [17–19], which further accelerate the neurodegeneration process. Additionally, gp120 and Tat can render the BBB leakier which further promotes the permeability of HIV-infected monocytes [20–22]. Other CNS cell types can also be infected by HIV. Low-grade production of provirus has been