Abstract

The available antiretroviral compounds can effectively suppress the replication of HIV-1 and block the disease progression. However it is impossible to eradicate the virus from the organism as the HIV-1 integrated in the genome is not affected by the existing anti-HIV-1 drugs. Therefore, new latency reversing agents are being actively developed as part of “shock and kill” therapy to reactivate the provirus and clear the reservoir. Normosang (heme arginate; HA) is a human hemin-containing compound used to treat acute porphyria. Heme is physiologically catabolised by heme oxygenases to form iron (Fe^{2+}), carbon monoxide (CO) and biliverdin that is further converted to bilirubin by biliverdin reductase.

In this study, we have demonstrated that HA inhibited HIV-1 replication during the acute infection, which was accompanied by the inhibition of reverse transcription. On the other hand, HA synergised with phorbol myristyl acetate (PMA) and reactivated the HIV-1 provirus in ACH-2 cells and the HIV-1 “mini-virus” in Jurkat cell clones A2 and H12. HIV-1 ‘‘mini-virus’’ was reactivated also by HA-alone. Further, we have studied the effects of heme degradation products on latent HIV-1 reactivation when added individually. We employed addition of ascorbate to generate Fe^{2+}, resulting in an increased expression of both HIV-1 provirus and “mini-virus”. The other two heme degradation products, CO or bilirubin, decreased the provirus expression. Antioxidant N-acetyl cysteine as well as iron chelator desferrioxamine inhibited the reactivation of HIV-1 provirus stimulated by PMA alone and in combination with either HA or ascorbate, suggesting that the effects of HA were mediated by heme- and iron-induced redox stress. Additionally, the effective concentrations of HA did neither affect activation of a T-cell line with PMA nor induce activation of the unstimulated cells. Finally, we demonstrated the synergistic effects of HA and PMA on HIV-1 expression in peripheral blood mononuclear cells of HIV-infected patients effectively controlled by antiretrovirals cultured ex vivo. These results may point towards a new direction in the latent HIV-1 reactivation and therapy.

Key words: HIV-1, latency, reactivation, heme arginate, iron, CO, bilirubin, ascorbate, redox stress, latency reversal, therapeutic reactivation