Retinoids and Opioids: Factors in the Development of HIV-Related Neurological Disease

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Abstract: Neurological disease occurs frequently in HIV-infected individuals and may occur at even higher rates among infected drug users. Among the potential mechanisms that promote such impairment, retinoid deficiency may have selective effects that could both lead to alterations in immune function and enhanced replication of HIV. Studies are currently underway to examine the possible selective effects of retinoid receptor activation and interactions with opioids on the pathogenesis of neurological disease in the transgenic rat model of HIV infection.

Key words: retinoids, opioids, retinoid receptors, HIV-1, neuro-AIDS; nervous system

INTRODUCTION

HIV-Related Neurological Disease and Drugs of Abuse: Neurological impairment due to HIV-1 (HIV) occurs commonly in infected individuals[1,2]. Evidence from a number of studies suggests that the frequency and severity of neurological disease that occur in the context of HIV infection can also be enhanced by illicit drug use. Recognized early days of the HIV epidemic as a risk factor for infection, the use of opioids (e.g., heroin), methamphetamine, and cocaine accounts for a disproportionately high percentage of AIDS cases overall. Despite this and the fact that neurological abnormalities can be commonly observed among illicit drug users [3], there remain significant gaps in our understanding of the pathogenesis of neuro-AIDS in illicit drug users. In the case of opioids, studies suggest that these agents can modulate both immune function and infection efficiency through direct cellular effects. For example, morphine has been demonstrated to inhibit NF-κB binding in human monocytes and neutrophils activated with lipopolysacchride [4] and to suppress proliferative responses to HIV antigens by lymphocytes while suppressing interferon responses and inducing apoptosis in these cells [5]. There are also a number of examples where morphine has been demonstrated to increase replication of HIV infection, including studies in which morphine enhanced production of virus by infected peripheral blood mononuclear cells following infection and in co-cultures of HIV-infected promonocytic leukemia cells and human brain cells [6,7].

In vivo, neuropathological studies have revealed evidence of HIV encephalitis more frequently in brains from HIV-infected opioid users as compared to infected gay males [8], which also points to the modulatory effects of opioids on immune function and suggests that drug users may be at greater risk for developing HIV dementia. Clinically, HIV-infected individuals with a history of primarily opioid use may be demonstrated to have evidence of cognitive impairment more frequently than non-users [9]. Despite this difference, most studies have shown no increase in HIV disease progression among opioid users as compared to HIV-infected gay men [10,11, [3]. However, findings from a cohort of drug users in Edinburgh, Scotland demonstrate that the underlying factors that are associated with disease progression may differ for drug users and gay men, with drug users more often developing HIV encephalitis and central nervous system opportunistic processes occurring more frequently in gay men [8,12]. The specific mechanisms by which opioids change the natural history of CNS disease in infected individuals are not well understood and have been the focus of intense study.

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Retinoids and Retinoid Receptors: The retinoids are a large family of biologically active agents that are chemically related to vitamin A and have a diverse range of effects on cell function. Retinol is the major form of vitamin A that is detectable in blood. Circulating retinol is largely derived from retinyl esters stored in hepatic stellate cells within cytoplasmic lipid droplets, which normally contain about 50-80% of total body vitamin A [13,14]. The retinyl esters are hydrolyzed and then secreted bound to retinol-binding protein (RBP) [15], and the retinol-RBP complex then binds transthyretin (TTR) for transport to cells where it enters unmodified or after being first converted to all-trans retinoic acid [16,17]. The retinol that enters a cell is converted to retinal and then to all-trans retinoic acid (ATRA). ATRA, especially at higher concentrations, can then be converted into either 9-cis retinoic acid (9-cis RA) or, to a lesser degree, 13-cis retinoic acid. ATRA and 9-cis RA, the major metabolically active products, are then bound by retinoid receptors, which, as a result of this interaction, become activated to bind specific elements in the promoter region of retinoid-responsive genes and/or members of the gene transcriptional complex to modulate gene expression [18]. These retinoid receptors, identified as retinoic acid receptor (RAR) and retinoic X receptor (RXR) [19,20,21,22], can exist as RAR-RXR heterodimers or RXR-RXR homodimers. The retinoid receptors are synthesized as α, β, and γ subtypes and exist in cells in heterodimer combinations that are cell type specific [23]. The primary ligand for RAR is ATRA whereas 9-cis RA can bind either RAR or RXR; 13-cis retinoic acid has been reported to also bind either RAR or RXR.

Immunological Effects of Retinoids: Retinoid have been demonstrated to have significant effects on immune function. In animals, retinoids have been generally shown to suppress proinflammatory responses in activated immune cells [24,25,26,27,28,29,30]. In contrast, vitamin A deficiency in experimental animals is characteristically associated with enhanced proinflammatory immune responses, effects that can be reversed by vitamin A supplementation [31,32,33,29,34]. In contrast, studies of vitamin A deficiency in humans can show a mixed picture, with findings that can be seen as due to enhanced or suppressed immune response. This may be due to the fact that, in contrast to what is observed in animals with experimental deficiency,

chronic depletion of vitamin A in humans may be associated with a chronic illness, such as HIV infection or liver or renal disease, and with deficiency of other nutrients that are important for the maintenance of a normal immune function, such as zinc and selenium. For example, vitamin A deficient children were found to have lower naive and higher memory T cell percentages in blood, and these numbers were reversed by treatment with vitamin A [35]. In other human studies, vitamin A deficiency resulted in decreased cell-mediated immune function [36,37] and antibody responses [36] and in lower numbers of CD4+ lymphocytes, all which also normalized following vitamin A administration [30,35,38].

RESULTS

Retinoids and HIV Infection: In vitro studies have demonstrated that retinoids can either enhance or suppress replication of HIV in infected cultures. Factors that appear to influence which effect is observed include the specific retinoid utilized, when infection is initiated relative to exposure to the retinoid, and whether the cells have been exposed to another activating stimulus [39,40,41,42,43] [42,44,45,46] [39,45,44,47]. In clinical studies involving patients with HIV infection, 13-cis retinoic acid induced regression of oral leukoplakia [48], and AIDS-related Kaposi's sarcoma lesions have been shown resolve with treatment with topical preparations of either 9-cis RA or the synthetic RXR-specific retinoid agonist bexarotene [49,50]. A candidate target for these effects is the viral LTR, which contains the promoter elements that are required for expression of the HIV genome [39,51]. Notably, a retinoic acid response element has been demonstrated in the HIV long terminal repeat (LTR) which can be inhibited by ATRA and 9-cis RA acid through activation of RAR-α and RXR-α [39].

In the setting of HIV infection, vitamin A deficiency has been associated with more frequent mother to child transmission of HIV by pregnant women, both in Malawi and in the United States [52,53]. Independent of the HIV status of the mother, deficiency is also associated with retardation of growth and development of the child following birth [54]. In recent studies it was shown that both periodic supplementation and a single high dose of vitamin A given during the post-partum period can improve survival among HIV

infected children who are supplemented at, respectively, 6 months and 6 weeks of age [55,56]. For children supplemented at age 6 weeks, however, benefit was seen only for those who were negative for HIV infection at baseline but were positive at 6 weeks of age [56]. These findings not only demonstrate the potential beneficial effects of retinoid repletion in this setting, but also the selective nature of these effects. In studies of injection drug users, vitamin A deficiency was associated with low CD4+ T cell counts, more rapid progression to AIDS, and an increased mortality [57,58]. Low serum retinol levels did not correlate with plasma HIV load, however [59,] and viral load and CD4 counts were not affected by vitamin A supplementation (60 mg of oral retinol equivalent) [59]. This may reflect the fact that these individuals were likely to be also deficient in other micronutrients. However, these findings, again, reflect the complex mechanisms that underlie these effects.

Immunomodulatory Effects of Retinoids and Opioids on Activated Immune Cells: In studies that showed increased HIV progression in vitamin A-deficient drug users, it was also possible that the observed clinical outcomes might have resulted from impaired interactions between the opioid and retinoid systems in cells, resulting in deleterious effects on the immune status of these individuals. Therefore, such potential interactions in vitro using U937 cells, a human mononuclear cell (myelomonocytic) cell line were studied [60]. The cells were incubated with retinoid agonist and/or antagonist then activated with PHA alone or in the presence of morphine. The effects of these treatments on proinflammatory cytokine responses in these cells was examined by measuring TNF-α gene expression by PCR, the percentage of cells that were positive for this cytokine using flow cytometry, and protein secretion by ELISA. These studies revealed that, in the absence of morphine, TNF-α production was increased by PHA activation and this effect was suppressed by the retinoid agonists but not by the antagonists and suppressed following incubation with both retinoid agonist and antagonists. Interestingly, in the context of activating RXR or inhibiting RAR with, respectively, a selective agonist or antagonist, the suppressive retinoid effect was inhibited by morphine through morphine binding to mu opioid receptor (MOR). Furthermore, RXR agonists and RAR antagonists increased activation of the MOR gene promoter and intracytoplasmic and surface protein expression. Therefore, these studies demonstrate a specific modulatory effects of morphine on retinoid-induced suppression of TNF-α production activated U937 cells.

The Transgenic Rat Model of HIV Infection: The HIV-1 transgenic rat was produced using fertilized eggs that were microinjected with pNL4-3 proviral DNA rendered non-infectious by the removal of a fragment that encompasses the 3' region of gag and the 5' region of pol [61]. The transgene, however, remains under control of the HIV-1 LTR and, therefore, can encode mRNA for env, vif, tat, and nef [62]. Replication of the incorporated viral genes occurs in circulating immune cells, spleen, lymph nodes, skin, and in the nervous system of the transgenic rat, and the animals develop abnormalities in all of the systems that express virus, including pathological features of HIV encephalitis [61]. The rats also develop clinical immunodeficiency with impaired delayed-type hypersensitivity and antigen-specific antibody responses [61]. The transgenic rats also over time develop T cell abnormalities with increased percentages of naïve CD4+ and CD8+ T cell subsets and decreased percentages of effector/memory subsets, impaired generation of Th1 (pro-inflammatory) cytokine responses with a reduction in T cells expressing IFN-γ and decreased IFN-γ secretion, increased activation-induced apoptosis of T lymphocytes, and increased splenic T cell proliferative responses to mitogen stimulation [63,61]. In studies of vitamin A deficiency using the transgenic rat, T cells from deficient animals produced higher levels of IFN-γ and secreted increased amounts of TNF-α than what was observed for non-deficient rats [64]. In addition, transgenic rats with vitamin A deficiency produced higher levels of MOR mRNA than non-deficient rats and wild type rats on either diet. Finally, expression of levels of HIV env and nef mRNA was higher for the transgenic rats with vitamin A deficiency than for rats in the other groups. These data demonstrate that both immune and viral effects can be observed in an in vivo model of HIV infection and vitamin A deficiency. Studies in this model could greatly contribute to our understanding of the mechanisms that underlie the development of neurological impairment in humans with a history of HIV infection and drug use.

DISCUSSION

Retinoids induce immunomodulatory and virologic effects that appear to be clinically beneficial to patients with HIV infection. The mechanisms that underlie these effects remain to be fully defined, but likely include effects from activation of specific retinoid receptor subtypes in immune cells as well as other cells that may be infected by the virus. The HIV-1 transgenic rat provides an ideal model for studies of factors that might modulate the pathogenic mechanisms that underlie the development of HIV-1 related abnormalities in these animals and, by extrapolation, in humans. Studies utilizing this model will likely shed light on approaches for developing therapeutic strategies for treating patients with HIV-related neurological disease.

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