

Role of Cytochrome P450 Systems in Substance of Abuse Mediated HIV-1 Pathogenesis and NeuroAIDS

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Abstract

The impact of HIV-1 pathogenesis, substance of abuse, and AIDS development and progression in neurons (neuroAIDS) on neurodegeneration has been discussed in the recent edition of "The neurology of AIDS" [1]. This book also covers the perspectives of HIV-infected patients who suffer from neurodegeneration. Their perspectives are intriguing and an eye-opener for the researchers in the field of substance of abuse and neuroAIDS. Further, the book highlights several unresolved issues that need to be addressed in order to rescue/decrease AIDS and neuroAIDS development, especially in the populations who regularly consume substances of abuse. Thus, there is a critical need to investigate alternate pathway that is responsible for neuroAIDS associated neurodegeneration among HIV-infected substance of abusers. This would help discover novel interventions as well as drug dose adjustments for these individuals. This editorial article highlights: 1) Problems associated with HIV-1 and substance of abuse; 2) Possible role of alternate cytochrome P450 pathway in substance of abuse associated HIV-1 pathogenesis: Brief review of the literatures; 3) Proposed alternate cytochrome P450 pathway in substance of abuse associated HIV-1 pathogenesis: Author's perspectives; 4) Conclusion.

Problems Associated with HIV-1 and Substance of Abuse

HIV-1 and neuroAIDS

In the past decade numerous preventive and treatment strategies initiated by World Health Organization, Communicable Disease Center, and private organizations, e.g. Gate Foundation have steered not only to steady decline in HIV-1 infections, but has also reduced the development and progression of AIDS. The introduction of highly active antiretroviral therapy (HAART) has led to a significant decrease in AIDS development [2]. The HAART medication increased the life span of AIDS patients from 5-10 years to >25 years. Thus, AIDS can be classified as chronic manageable disease in the countries where HAART is easily accessible. Since AIDS patients live longer, HIV-1 packaged in monocyte-derived macrophages (secondary target of HIV-1 and major viral reservoirs) can infiltrate into CNS and infect the brain causing neuroAIDS. In spite of the success of HAART medication, the prevalence of neuroAIDS has led to a steady increase in the development of HIV-associated neurocognitive dysfunction (HAND) [3]. HAND lead to reduced concentration and memory and slowness of physical movements, which significantly compromises the life style of HIV-1 patients and increases social and financial burdens. Further, AIDS patients with HAND have to be treated with other medications, which leads to further increase in drug-drug interactions [4]. Drug-drug interactions mediated drug toxicity is one of the major concerns in treating HIV-infected individuals, and they decrease the adherence of HAART and other medications.

Substance of abuse in HIV-1

The prevalence of mild-to-moderate alcohol consumption and tobacco use is >2.5-fold higher in HIV-infected population (50-60%) than the general population (15-20%), and the co-abuse of alcohol and tobacco among HIV+ population is extremely worrisome [5]. Similarly, the consumption of other substances of abuse, such as methamphetamine and cocaine are significantly higher in HIV-infected population than the general population. The increase in the

consumption of substances of abuse in HIV-infected population significantly impacted the adherence of HAART medication and compromised the treatment of HIV-infected individuals. Individuals who are addicted with these substances of abuse rarely take one drug, and therefore the neurotoxic effects of consuming multiple drugs may not only be additive, but synergistic. As a result, these substances of abuse cause severe neurological and psychological impairments, which further exacerbate the neurological impairments caused by HIV-1 infection and neuroAIDS [6].

The use of alcohol, tobacco, methamphetamine, and cocaine poses serious concerns to HIV-infected individuals in terms of HIV-1 infection, AIDS progression, neuroAIDS development, and HAND severity. The interaction of these drugs with HIV-1 is very complex, and occurs at many levels, e.g. biological, behavior, and personality. Methamphetamine and cocaine are known to increase HIV-1 infection through common injection used to administer these drugs. These drugs also drive the individuals with unsafe and inappropriate sex leading to increased HIV-1 infection. Alcohol, tobacco, methamphetamine, and cocaine have been shown to increase HIV-1 replication leading to further immune suppression and AIDS progression [7]. Alcohol and tobacco are also known to disrupt blood-brain barrier and infiltrate HIV-1-infected macrophages into the brain leading to neuroAIDS, HAND, neuroinflammation, brain damage, and neuropsychological impairment [8]. However, the mechanism by which these substances

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of abuse, especially alcohol and tobacco increase HIV-1 replication, especially in macrophages is not known. Oxidative stress generated either directly by these substances or upon metabolism is believed to be responsible for increased HIV-1 replication [9]. These substances or their metabolites can generate oxidative stress by binding to their respective receptors and mediating signaling cascade leading to expression of inflammatory cytokines and chemokines [10]. In addition to their role in inflammatory pathway, the author proposes alternate cytochrome P450 (CYP) pathway, in which CYP enzymes metabolize these substances of abuse in HIV-infected cells and generate reactive oxygen species (ROS) and reactive metabolites, which increase HIV-1 replication in macrophages, microglia, and astrocytes.

Possible Role of Alternate Cytochrome P450 Pathway in Substance of Abuse Associated HIV-1 Pathogenesis: Brief Review of the Literatures

CYP and substance of abuse

CYP is a super family of heme enzymes that are responsible to metabolize majority of marketed drugs and several substances of abuse, including alcohol and tobacco's [11]. The metabolism of these drugs by CYP enzymes is known to generate ROS and/or toxic metabolites causing oxidative stress and cell toxicity [12]. CYP2E1 is known to metabolize alcohol and cause oxidative stress-mediated liver damage [13]. Similarly, CYP2A6 metabolizes tobacco major constituent, nicotine, leading to oxidative stress-mediated lung cancer and liver damage [14]. In addition, CYP2A6 and CYP2A13 are known to activate/metabolize several nicotine-derived nitrosamine ketones (NNK) and generate procarcinogens, which are known to cause lung and esophagus cancers, as well as liver damage. CYP3A4 metabolizes methamphetamine and cocaine, however, the implication of these metabolites on toxicity is unknown [15]. The role of CYP2E1 and CYP2A6 in oxidative stress and HIV-1 replication in HIV-infected cells by alcohol and tobacco, respectively, is unknown.

CYP and HAART

Individuals with drug addictions are less likely to comply with HAART therapy, and therefore, these individuals are likely to have increased HIV-1 replication and AIDS progression. Although chronic alcohol and tobacco consumptions are known to decrease response to HAART, current practice guidelines for HAART regimen do not exclude patients who regularly consume mild-to-moderate levels of alcohol or smoke. Further, there is emerging evidence that HAART drugs, especially non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) cause neurotoxicity as a result of accumulation of these drugs or their metabolites in the brain [3]. Thus, substances of abuse may exacerbate the neurotoxicity caused by HAART drugs. Liver CYP3A4 is known to metabolize all the NNRTIs and PIs, which are dominantly present in HAART regimens [16]. Further, NNRTIs and PIs are inducers as well as inhibitors of CYP3A4, which can alter the metabolism and therefore efficacy of these drugs [15]. For example, protease inhibitor ritonavir is a strong inhibitor of CYP3A4 and therefore is generally given with other NNRTI or PI regimen to increase the plasma concentrations of these drugs. Darunavir/ritonavir and lopinavir/ritonavir are commonly used HAART regimens, which also have the capability to cross the blood-brain barrier.

There is nothing known about the role of CYP pathway in alcohol, tobacco, methamphetamine, NNRTI, and PI mediated increased HIV-1

replication, decreased response to HAART regimes, and neurotoxicity. Thus, there is a critical need to investigate the role of CYP pathway in substance abuse and HAART mediated oxidative damage, HIV-1 replication, neurotoxicity, and response to HAART in HIV-infected individuals. The knowledge obtained from this study is expected to increase treatment outcomes in HIV-infected individuals who are addicted to these drugs.

Proposed Alternate Cytochrome P450 Pathway in Substance of Abuse Associated HIV-1 Pathogenesis: Author's Perspectives

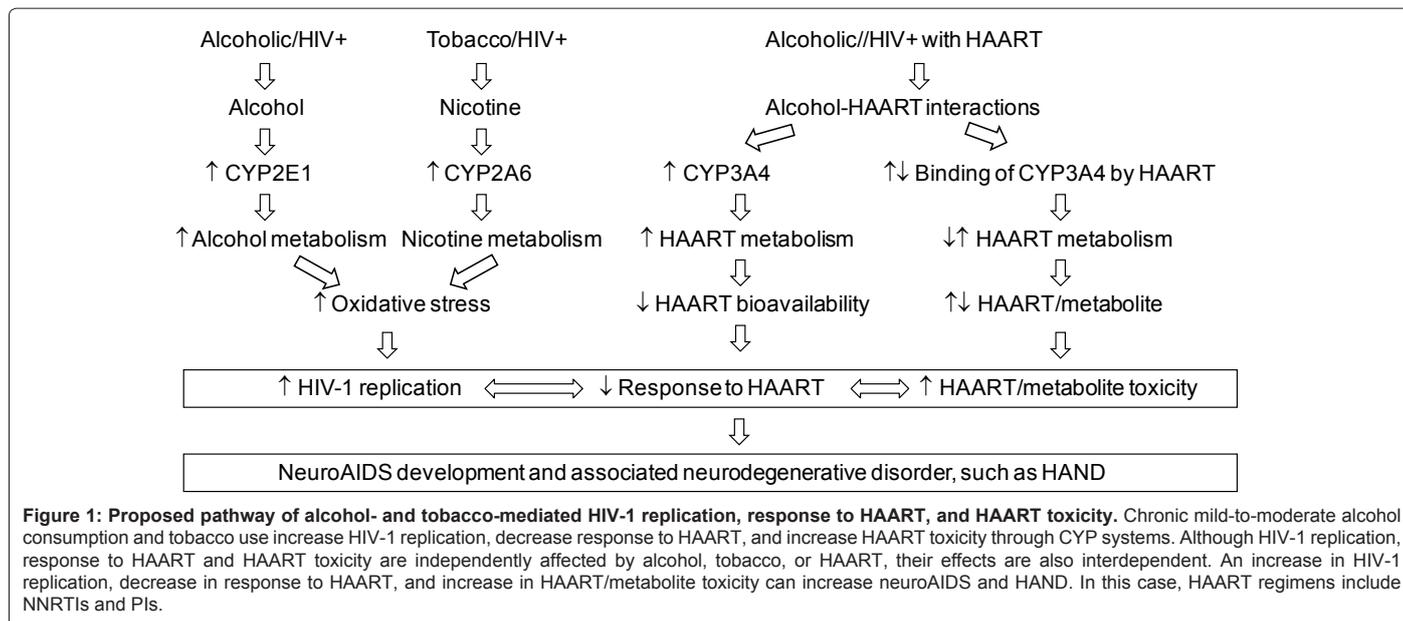
Proposed pathway

The author hypothesizes that CYP2E1 plays a critical role in alcohol-mediated, while CYP2A6 plays an important role in tobacco-mediated oxidative stress and HIV-1 replication in macrophages, astrocytes, and neurons (Figure 1). Further, the author hypothesizes that the enzyme level and activity of CYP3A4 are altered by alcohol and/or tobacco through physical/genetic interactions leading to altered metabolism of NNRTIs and PIs. While decreased metabolism of NNRTIs and PIs may slightly increase the efficacy of HAART, their increased metabolism is likely to decrease the efficacy of HAART in the target cells. In both the cases, however, HAART is expected to increase drug toxicity through accumulation of the parent NNRTIs and PIs or their toxic metabolites (Figure 1). The toxic metabolites may increase oxidative stress, especially in microglia, astroglia, and neurons, leading to neurotoxicity. Although HIV-1 replication, response to HAART and HAART toxicity are independently affected by alcohol, tobacco, or HAART, their effects are also interdependent. For example, decreased response to HAART may increase HIV-1 replication and HAART toxicity and increased HAART/metabolites toxicity may also increase HIV-1 replication. An increase in HIV-1 replication, decrease in response to HAART, and increased HAART/metabolite toxicity either independently or together can increase neuroAIDS and associated neurodegenerative disorders, such as HAND. Therefore, there is a critical need to examine the proposed pathway and hypotheses.

Current findings

To test these hypotheses, the author's group has initiated several studies using in vitro and ex/in vivo systems. The current findings have shown that: 1) CYP2A6 is predominantly expressed in macrophage cell line U937(35% of the total CYP), astrocyte cell line SVGA (56% of the total CYP), and primary human monocytes (34% of the total CYP), and CYP2A6 is induced by alcohol and nicotine [17]; 2) CYP2A6 metabolizes nicotine in the macrophage and astrocyte cell lines and generate ROS [18]; 3) CYP2E1 is significantly expressed in these macrophage and astrocyte cell lines, as well as in primary human monocytes [17]; 4) CYP2E1 is induced by alcohol leading to increased production of ROS [17]; 5) CYP2A6 and CYP2E1 are highly induced, while anti-oxidant genes, such as catalase and superoxide dismutase are significantly reduced in the monocytes of HIV-infected individuals who are smokers and alcoholics [unpublished observations]. These findings clearly indicate that alcohol and nicotine/tobacco generate oxidative stress through CYP2A6 and CYP2E1 pathways, respectively, in macrophages and astrocytes.

Our recent unpublished observations demonstrated that CYP2A6 is induced by acute alcohol treatment through oxidative stress generated by CYP2E1-mediated alcohol metabolism. The increase



in oxidative stress translocates nuclear E2-related factor 2 (Nrf2) transcription factor into nucleus through protein kinase C (PKC)/mitogen-activated protein kinase kinase (MEK) pathway, resulting in the expression of CYP2A6 in monocytes and astrocytes. The increased level of CYP2A6 is expected to further increase oxidative stress among chronic smokers by CYP2A6-mediated nicotine metabolism through a feedback mechanism. Similarly, CYP2E1 is induced by acute alcohol treatment through oxidative stress generated by CYP2E1-mediated alcohol metabolism. The increase in oxidative stress translocates c-Jun into nucleus through (PKC)/c-Jun N-terminal kinases (JNK) pathway, resulting in the expression of CYP2E1 in monocytes and astrocytes. The increased level of CYP2E1 is expected to further increase oxidative stress among individuals who consume alcohol by CYP2E1-mediated alcohol metabolism through a feedback mechanism. Furthermore, since acute treatment of nicotine has been shown to increase oxidative stress through CYP2A6-mediated nicotine metabolism into cotinine and nicotine-derived nitrosamine (NNK) in macrophages and astrocytes, it is likely that nicotine will also induce CYP2A6 and CYP2E1 through the oxidative stress pathway. Since the co-abusers of alcohol and tobacco are highly prevalent in HIV-infected individuals, it is likely that these individuals produce very high level of oxidative stress. Thus in the case of co-abusers, there may be further increase in HIV-1 replication in macrophages and astrocytes leading to neuroAIDS development and associated neurodegeneration, such a HAND.

The author's group has also shown that alcohol differentially alters CYP3A4-PIs (amprenavir, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, topinavir) interaction, which may alter the metabolism of these PIs as well as NNRTIs in a differential manner leading to altered response to HAART medication [19]. Emerging unpublished studies from our as well as other laboratories suggest that darunavir/ritonavir and lopinavir/darunavir mediate increase in oxidative stress and expression of cytokines in astrocytes and neurons (personal communications). It is possible that these drugs and/or their metabolites, formed by CYP3A4, accumulate in the brain and cause neurotoxicity through oxidative stress and/or cytokines mediated

pathway.

Based on the findings from the author's laboratory, it is likely that oxidative stress generated by CYP pathways is responsible for increased HIV-1 replication, as well as activation of microglia and astrocytes in alcohol and tobacco users. HAART-alcohol/tobacco interactions may further exacerbate CYP pathway mediated HIV-1 replication and neuronal damage leading to neuroAIDS and associated HAD and HIVE. Therefore, future study using large cohort of HIV-infected alcohol and tobacco users may provide an opportunity to find novel interventions, as well as optimization of drug dose/regimen in HIV-infected alcohol, and/or tobacco users.

Conclusion

Based on the evidence so far the author in this highlight suggests an important role of CYP pathway in HIV-1 replication and response to HAART medication in individuals who consume substances of abuse, especially alcohol and tobacco. The altered substance of abuse-mediated HIV-1 replication and HAART efficacy may be responsible for AIDS progression, neuroAIDS development, and associated neurological conditions, such as HAND. Therefore, it is imperative to perform large scale study using cohort of HIV-infected alcohol and tobacco users to confirm the current findings on the role of CYP pathway in HIV-1 pathogenesis. However, it does not rule out the role of receptor-mediated signaling pathway in HIV-1 pathogenesis. It is also possible that oxidative stress generated through CYP pathway may fire signaling cascade that induce inflammatory proteins and cause HIV-1 pathogenesis and neurotoxicity. This editorial highlights the need for novel therapeutics, as well as drug dose adjustments in HIV-infected individuals who are addicted with substances of abuse. This will help improve the overall health and quality of life styles of these individuals.

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