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Full-Length Review

HIV-1 infection and alcohol abuse: Neurocognitive impairment, mechanisms of neurodegeneration and therapeutic interventions

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ABSTRACT

Clinical studies indicate that alcohol dependence has an additive effect on cognitive deficits associated with HIV-1 infection. Findings in humans and animal models suggest that alcohol, similar to HIV-1, induces inflammatory processes in the brain leading to neurodegeneration. The causes of HIV-1-associated neurotoxicity are comparable to those mediating alcohol-induced neuronal injury. This review aims to present the mechanisms of the combined effects of HIV-1 and alcohol abuse in the brain and to discuss neuroprotective therapies. Oxidative stress, overproduction of pro-inflammatory factors, impairment of blood–brain barrier and glutamate associated neurotoxicity appear to play important roles in alcohol driven neurodegeneration. Diminution of neuroinflammation constitutes a logical approach for prevention of HIV-1 and alcohol mediated neurodegeneration. Agonists of cannabinoid receptor 2 (CB_2) possess potent anti-inflammatory and neuroprotective properties. We address multifaceted beneficial effects of CB_2 activation in the setting of HIV-1 brain infection and alcohol abuse.

1. Introduction

The clinical and neuropsychological complex of HIV-1 associated dementia (HAD) is usually described as a frontal-subcortical pattern of impairment. The following cognitive areas demonstrate deterioration: fine motor coordination and speed, sustained attention, processing speed, executive function, learning efficiency and working memory (Grant et al., 1995). Three forms of HAD have been described, including (1) frank HAD, characterized by severe impairment in two or more cognitive areas with marked impact on everyday function; (2) mild neurocognitive disorder with impairment in two or more cognitive functions that produces modest interference with everyday functioning (equivalent to minor cognitive motor disorder, MCMD); and (3) asymptomatic neurocognitive impairment, documented by impairment in two or more ability areas without apparent effect on everyday functioning.

One quarter of adults and 50% of children used to develop significant neurocognitive complications as a consequence of infection at a period of immunosuppression or AIDS before the introduction of anti-retroviral therapy (ART) (Navia et al., 1986). While subclinical metabolic and structural abnormalities are detectable in neurologically asymptomatic subjects, overt HAD usually develops as a late complication and is accompanied by immunosuppression (Koralnik et al., 1990).

Introduction of ART considerably changed the clinical evolution of HIV-1 infection (Palella et al., 1998). ART diminished the incidence and prevalence of major opportunistic infections and resulted in improvement in survival rates. Patients (10–15%) are now over 50 years of age and, with continued advances in treatment, many will reach normal life expectancy (Navia and Rostasy, 2005). Markedly improved survival rates brought to light other factors not previously considered to any great extent, including the effects of aging, chronic infection and the neurotoxic effects of ART itself. Indeed, nucleoside reverse transcriptase inhibitors (NRTIs) suppress HIV-1 replication, but they are associated with mitochondrial toxicity (Schweinsburg et al., 2005). Reduction of the neuronal marker, *N*-acetylaspartate, in frontal lobe white and gray matter was found in individuals taking NRTIs, didanosine and/or

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stavudine, as a result of depleted brain mitochondria and/or alterations in cellular respiration (Schweinsburg et al., 2005).

2. Combined effects of alcohol and HIV infection on neurocognitive performance

According to the 2001–2002 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) survey, more than 20% of men, age 18–29, met the criteria for a diagnosable alcohol use disorder (AUD): Alcohol Abuse (9.3%) and Alcohol Dependence (13%). More than 50% of HIV-infected clinic patients reported heavy alcohol use (Samet et al., 2004; Conigliaro et al., 2006). Alcohol abuse is associated with increased immune suppression (Wang and Watson, 1995; Wang et al., 2002). While some investigators reported a limited effect of alcohol exposure on the acute plasma viral load in an animal model for HIV infection, macaques infected with simian immunodeficiency virus (SIV), other studies showed opposite results – greater SIV viral load at various times post-infection (Bagby et al., 2006; Poonia et al., 2006). Bagby et al. (2006) demonstrated a significantly more rapid progression to end-stage disease in SIV-infected monkeys. Underlying causes can be associated with diminished circulating memory CD4 + T cells and increased levels of monocytes expressing the viral co-receptor, CCR5, found in macaques exposed to alcohol (Marcondes et al., 2008). Another aspect of alcohol exposure is accelerated AIDS wasting that has been suggested as a mechanism by which alcohol might result in more rapid HIV disease progression (Molina et al., 2008). Most importantly, alcohol administration in SIV-infected monkeys produced greater behavioral deficits than either alcohol or SIV alone (Winsauer et al., 2002).

With the widespread use of ART, the incidence of cognitive and motor deficits related to HIV infection has declined (Sacktor et al., 2002); however, specific neuropsychological deficits persist (Sacktor et al., 2002; Cysique et al., 2004). These changes may be exacerbated by other conditions, like alcohol use disorders, that affect neural systems. ART, including NRTIs and protease inhibitors (PIs), are metabolized by the human cytochrome P450 system. It is known that alcohol can affect the metabolism of ART by two different mechanisms, enzymatic induction (Lieber and DeCarli, 1970), associated with chronic alcohol use, and enzymatic inhibition, due to competition of ethanol for various cytochrome P450 isozymes, associated with acute ethanol use. Since the P450 pathway metabolizes multiple drugs, chronic alcohol users may be affected by altered drug concentrations in plasma.

Despite a number of reports documenting cognitive deficits associated with HIV infection and chronic alcoholism separately, very few studies have addressed the combined effects of these diseases. Farinpour et al. (2000) reported impaired verbal working memory, and Martin et al. (2004) found enhanced cognitive impulsivity in studies of individuals with HIV infection and drug use disorders, including alcoholism, compared with seronegative drug users. Synergistic negative effects of HIV infection and concurrent heavy alcohol consumption were reported on motor and visual spatial tasks (Rothlind et al., 2005). Examination of HIV-infected individuals with past alcohol use disorders (Green et al., 2004) provided evidence for additive and interactive effects of previous alcohol abuse and HIV infection on verbal reasoning, auditory processing, and reaction time tasks. Using a novel test (Match-to-Sample Stroop Task), Schulte et al. (2005) demonstrated that HIV-infected individuals with alcoholism had normally reduced reaction times when a valid match cue introduced a Stroop stimulus, but were disproportionately slow when the cue was invalid, indicating impairment in attention disengagement.

Significantly impaired memory and executive functions were reported both in HIV infection and chronic alcoholism (Fein et al., 2006; Pitel et al., 2007a,b). Pitel et al. (2007a,b) examined both memory and executive function abilities in abstinent alcoholics and demonstrated that executive function impairments did not account for the majority of variance in memory scores, concluding the memory impairment to be "genuine" rather than solely the result of executive function deficits.

3. Mechanisms of HIV-1 and alcohol associated neurotoxicity

The causes of HIV-1-associated neurotoxicity include excitotoxic effects of glutamate, secretory products of chronically activated glial cells and oxidative stress (Boven et al., 1999; Zhao et al., 2004; Ellis et al., 2007), similar culprits to ones mediating alcohol-induced neuronal injury (Blanco et al., 2004; Blanco and Guerri, 2007). Dysfunction of the blood–brain barrier (BBB; a common feature of HIV-1 neurodegeneration) (Persidsky et al., 2006) was recently documented in the setting of inflammation and chronic alcohol exposure in animal studies (Singh et al., 2007). Taken together, alcohol abuse and HIV-1 infection of the central nervous system (CNS) could result in combined toxic effects leading to neuronal injury and cognitive dysfunction. Indeed, neuroimaging studies demonstrated more significant white matter abnormalities in HIV-1 positive alcohol abusers (especially with advanced infection) as compared to non-infected alcoholics (Pfefferbaum et al., 2007). While mechanisms of such injury are currently unknown, oxidative damage and glutamate imbalance contribute to neurodegeration in both conditions (Zhao et al., 2004; Melendez et al., 2005). Interestingly, clinical studies support the efficacy of glutamate-blocking approaches for treatment of alcohol withdrawal symptoms (Krupitsky et al., 2007) and dependence in humans (Ma et al., 2006) promoting the idea that glutamatergic activation contributes to alcohol abuse. These observations establish a link between dysfunction of glutamate transporters and increased alcohol intake. Chronic neuroinflammation (like HIV-1 CNS infection) could cause glutamate transporter dysfunction and promote an alcohol-craving phenotype and alcoholism.

Recent findings in humans and animal models suggest that alcohol induces inflammatory processes in the brain leading to neurodegeneration (Potula et al., 2006; He and Crews, 2008; Qin et al., 2008). Furthermore, neuroinflammation appears to promote alcohol addiction in animals making this finding very relevant for HIV-1 brain infection associated with chronic inflammation (Blednov et al., 2005). A linear relation between the number of drinks consumed and higher relative risk for stroke in a human cohort indicates dysfunction of the BBB (Bazzano et al., 2007). We have demonstrated alcohol-induced BBB impairment (Haorah et al., 2005a,b; Haorah et al., 2007a) and delineated molecular mechanisms of this formerly unrecognized phenomenon (Haorah et al., 2007a, 2008) that further promotes the neurodegeneration mediated by ethanol metabolism in human neurons (Haorah et al., 2008) and in human astrocytes (Floreani et al., 2010). Furthermore, we showed alcohol exposure increased neuroinflammation (Potula et al., 2006) in an animal model of HIV-1 encephalitis (HIVE), a pathologic correlate of HAD. Therefore, therapeutic strategies aiming at reduction of neuroinflammation is a logical approach to ameliorate, or reverse, CNS injury in the setting of alcohol abuse and HIV-1 CNS infection. Agonists of cannabinoid receptor 2 (CB_2) possess potent anti-inflammatory properties as demonstrated in animal models and *in vitro* systems and are devoid of the psychoactive effects of CB_1 stimulators. CB_2 activation affords neuroprotection in animal models of stroke, multiple sclerosis and Alzheimer's disease (Benito et al., 2008; Mestre et al., 2009; Zhang et al., 2009a,b).