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Purple Paper

Susceptibility of Solvent Users to HIV and Hepatitis C

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NCCID Comments

Inhalation of widely available volatile substances for their unintended psychoactive effects is gaining prominence and is clearly a concern for public health practitioners and policy makers. This paper is the second issue of a 2-part mini-series that explores the association between solvent use and the increased susceptibility to HIV and other sexually transmitted and bloodborne infections (HIV/STBBIs).

The last paper presented some epidemiological data on the prevalence of solvents use in Canada and the US, and evidence of an association between solvent use and HIV/STBBIs. This current paper discusses potential biological mechanisms that may be contributing to the observed phenomena of increased susceptibility to and progression of HIV and HCV in solvent users.

Introduction

Inhalants are volatile compounds that produce an altered state of consciousness when inhaled. They are generally inexpensive, legal, and widely available. Although very diverse, there are three major groups of inhalants. The first group is products that contain nitrous oxide, for example whipping cream aerosol cans. The second group is volatile alkyl nitrites, sometimes called poppers. The final group includes a wide array of aliphatic, aromatic, and halogenated hydrocarbons, often referred to as solvents. Solvents are the focus of this paper and include household items such as hair spray, paint thinners, glues, lacquers, and gasoline (Baydala, 2010).

The natural history and pathogenesis of both human immunodeficiency virus (HIV) and hepatitis C virus (HCV) infection is the product of both viral and host factors, including host genetics and environmental factors. Solvent use may be an environmental factor that influences susceptibility to and progression of HIV and HCV disease. Epidemiological evidence suggests that solvent users are at an increased risk for HCV and HIV infections (Shaw et al, 2010). This paper will explore the biological mechanisms that may be contributing to increased susceptibility to and pathogenesis of HIV, HCV, and HIV/HCV co-infections in solvent users.

Inhalant Use and the Immune System

There is limited information regarding the impact of inhalant use on the immune system. The impact of volatile alkyl nitrites (i.e. poppers) on the immune system has previously been investigated due to a still inconclusive link to HIV and Kaposi's sarcoma.

In murine models, nitrite inhalation was found to impair $CD4^+$ T cell-dependent B cell activity, inhibit $CD8^+$ cytotoxic T Lymphocyte (CTL) induction, impair macrophage tumoricidal activity, reduce natural killer (NK) cell cytotoxicity, and elevate levels of inflammatory cytokines, such as TNF-alpha (Soderberg, 1998; Guo et al, 2000). Mice exposed to nitrite inhalants experienced a significant reduction in spleen cell counts that was non-selective of $CD4^+$ or $CD8^+$ T cell subsets (Guo et al, 2000). The spleen is involved in immune surveillance of blood and is an important site for mounting both innate and adaptive responses to bloodborne pathogens (Mebius and Kraal, 2005). In a human study from the early 1990's, nitrite inhalation resulted in immunosuppression with a reduction of absolute lymphocyte counts that rebounded following drug cessation. The NK cell population was the most dramatically affected and required more time to rebound. (Dax et al, 1991). In both murine and human models, increased usage of nitrite inhalants

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was associated with more dramatic effects (Soderberg, 1998; Guo et al, 2000; Dax et al, 1991). In general, nitrite inhalants have the ability to impair both humoral and cell mediated immunity, especially NK cells, while promoting HIV viral replication through increased TNF-alpha (Soderberg, 1998).

Natural killer cells are important innate cells for combating viral infections. They are essential for the first line of defense against HIV and HCV, and are likely important at all stages of infection and co-infection. NK cells generally comprise 5-20% of the lymphocytes in systemic circulation and approximately 30% of intrahepatic lymphocytes. Impaired NK function and skewed phenotypic ratios are common with both HIV and HCV infection (Gonzalez et al, 2010). During HCV infection, NK cells inhibit HCV replication via IFN-γ (Gonzalez et al, 2010). In the context of HIV infection, NK cells are able to kill virally infected cells, and also produce large amounts of ligands for CCR5 that act to competitively inhibit receptor binding and block viral entry (Gonzalez et al, 2010).

It is possible that solvent use impairs the immune system in a similar manner to nitrite inhalant use. If this is the case, solvents may be immunosuppressive and drastically alter NK cell populations which are important for viral and tumor defense. If solvent use is, in fact, immunosuppressive, regular use could prevent the rebounding of lymphocyte counts observed following cessation of nitrite use (Dax et al, 1991). Among regular solvent users, this could increase the risk of contracting HCV and HIV while impacting pathogenesis and disease progression. Additionally, since NK cell populations are involved in anti-tumor defense, solvent users may be at a greater risk for developing HIV-related cancers, such as Kaposi's sarcoma, or developing HCV-induced liver cancer. More research is needed to determine if this theoretical risk is a reality.

Microbial Translocation and Immune Activation

Microbial translocation involves the translocation of microbes or microbial products from one area of the body (i.e. the gastrointestinal [GI] tract) into systemic circulation without causing an overt bacterial infection (bacteremia) (Brenchley et al, 2006). Normally, healthy mucosal surfaces provide a barrier; however, when mucosal surfaces are compromised, microbial products can gain access to systemic circulation. Lipopolysaccharide (LPS), or endotoxin, is a constituent of the cell wall of gram negative bacteria and it is a potent stimulator of the immune system (Brenchley et al, 2006). The liver receives blood from the GI tract via the portal vein (Lucey et al, 2009), and plays a crucial role in LPS detoxification. Kupffer cells, liver macrophages, and hepatocytes recognize LPS via Toll-like receptor 4 (TLR4). As a result, pro-inflammatory and profibrogenic cytokines such as TNF-α, IL-1, IL-6, and IL-12 are up-regulated (Balagopal et al, 2008, Gonzalez et al, 2010). Kupffer cells and hepatocytes also play an important role in LPS tolerance as a mechanism to prevent liver injury due to excessive immune activation and pro-inflammatory cytokines (Gonzalez et al, 2010).

Solvent users may be more susceptible to HIV infection via microbial translocation-associated immune activation that generates additional viral targets.

Continued exposure to LPS and other microbial products can cause persistent immune activation (Fernandez et al, 2009). Immune activation has both beneficial and deleterious effects on the host and involves polyclonal B cell activation, increased turnover and activation of T cells, and increased pro-inflammatory cytokines and chemokines. Chronic immune activation can lead to a strain on T cell homeostasis, clonal exhaustion, and a reduction in memory T cell pools (Brenchley and Douek, 2008).

The impact of solvent use on mucosal barriers in humans is not well known. During routine clinical care, clinicians caring for HIV-infected solvent users in Winnipeg, who have performed both tracheal and GI endoscopies, have observed the presence of an erythematous mucosal lining in their patients, indicating ongoing inflammation (personal communication, Drs. Ken Kasper and Yoav Keynan). A study investigating the impact of gasoline

inhalation on guinea pig trachea found that exposure to gasoline vapors resulted in extensive inflammation and destruction of tracheal epithelium (Al Saggaf et al, 2009).

Solvent use appears to damage both upper respiratory and GI mucosal surfaces. However, the degree to which solvent use damages these surfaces and the impact of solvent use on microbial translocation and immune activation are completely unknown. Compromised mucosal surfaces leading to microbial translocation, combined with a heightened baseline immune activation state caused by solvent use, may have important implications for HIV and HCV infections.

Implications for HIV

HIV disease progression is characterized by two major phases. The first phase involves an initial depletion of $CD4^+$ T cells both peripherally and in the mucosa during acute infection and during the beginning of chronic infection. The second phase involves a state of persistent immune activation (Fernandez, 2007). Persistent immune activation results in the generation of additional HIV target cells (Brenchley and Douek, 2008), and has been demonstrated to be an excellent predictor of HIV disease progression (Brenchley et al, 2006). The depletion of $CD4^+$ T cells in the first phase is more severe at the mucosal compartments, such as the gut-associated lymphoid tissue of the GI tract, than in peripheral blood and is thought to result in a disruption of the GI mucosal barrier allowing microbial translocation and subsequent immune activation (Brenchley et al, 2006). Indeed, HIV-1 infected individuals who have progressed to AIDS have been shown to have elevated plasma LPS levels compared to uninfected individuals (Brenchley et al 2006; Nowroozalizadeh et al, 2010), and raised plasma LPS levels have been demonstrated in advanced HIV-1 and HIV-2 infections and shown to be correlated with severity of disease (Nowroozalizedeh et al, 2010).

Solvent users may be more susceptible to HIV infection via microbial translocation-associated immune activation that generates additional viral targets (Brenchley and Douek, 2008). Solvent users who are HIV^+ may also be at a heightened risk for enhanced pathology and rapid disease progression, since solvent use-associated microbial translocation may enhance the HIV-induced microbial translocation and immune activation that solvent users are already experiencing in the course of their infection. Indeed, clinicians from Winnipeg have noted that some of their patients who are HIV rapid progressors are also solvent users (personal communication, Drs. Ken Kasper and Yoav Keynan).

Implications for HCV

Acute HCV usually develops within 10-14 weeks following infection, with a rate of 20-25% for spontaneous viral clearance. In 75-85% of HCV cases, the individual will progress to chronic liver disease with a risk of subsequent progression to liver cirrhosis, advanced liver disease, and liver cancer (Akbar, 2011). Hepatocytes are the target cell for HCV, but the virus can also infect monocytes and lymphocytes (Gonzalez et al, 2010).

The risk factors associated with reduced rates of spontaneous viral clearance and enhanced disease progression are similar and include male sex, older age, immunosuppression (due to HIV or otherwise), and alcohol use (Chung, 2005; Akbar, 2011; Mallat et al, 2008; Szabo et al, 2010; Balagopal et al 2008). Conversely, a robust T cell response that manifests as symptomatic infection is associated with increased likelihood of spontaneous viral clearance (Chung, 2005).

If solvent use indeed exacerbates microbial translocation, this may lead to accelerated disease progression and worse outcome for solvent users who are co-infected with HIV and HCV.

Both alcohol abuse and HIV infection are known to increase microbial translocation, though through separate mechanisms, and microbial translocation is associated with HCV related liver disease progression (Balagopal et al, 2008). HCV infection is known to increase the sensitivity to LPS, resulting in chronic immune activation that leads to persistent liver inflammation (Gonzalez et al, 2010; Cesaro et

al, 2010). Indeed, increased microbial translocation has been found to be associated with progression of HCV infection (Balagopal et al, 2008).

Inhalant use has been linked to liver injury and hepatitis through an unknown mechanism (Marjot and McLeod, 1989; Baydala, 2010). Both HIV and alcohol use contribute to increased microbial translocation and a reduced rate of spontaneous clearance of the virus (Balagopal et al, 2008; Mallat et al, 2008). If solvent use does increase microbial translocation, this may be a mechanism that results in a reduced likelihood to clear the virus spontaneously. Additionally, solvent users may be at risk for increased liver pathology and accelerated progression to chronic HCV.

Implications for HIV/HCV Co-Infection

HIV/HCV co-infections are common, with 15-30% of HIV infected individuals also co-infected with HCV. Intravenous drug users are at high risk for co-infection since the viruses share the same transmission routes. As described above, HIV induces microbial translocation which places strain on the liver and results in heightened levels of immune activation. Co-infection is associated with very high levels of immune activation and this likely impairs the immune system's ability to control both infections, contributes to immunopathology, and hastens disease progression (Sandberg et al, 2010). HIV^+ individuals who acquire HCV are less likely to spontaneously clear the infection, are at higher risk for chronic infection, have higher HCV RNA levels, progress faster in their HCV disease course, and likely progress faster to AIDS (Gonzalez et al, 2010).

If solvent use indeed exacerbates microbial translocation, this may lead to accelerated disease progression and worse outcomes for solvent users who are co-infected with HIV and HCV.

Conclusions

Epidemiological and clinical evidence suggests that solvent use is associated with increased susceptibility to HIV and HCV infections and may have important consequences for disease progression and pathogenesis. This paper explored the biological mechanisms that may be contributing to this observed phenomena.

There are some data linking nitrite inhalation use to immunosuppression, especially immunosuppression of NK cell subsets. Solvents and nitrites belong to different groups of inhalants and it is not known if solvent use results in immunosuppression as well. However, if the effect is similar, solvent users may experience immunosuppression that makes them more susceptible to both HIV and HCV infections, and solvent use may impact disease progression and pathogenesis.

Clinical observation suggests that solvent users experience inflammation of both the upper respiratory and GI mucosa. This may result in increased microbial translocation and subsequently high levels of immune activation. This could lead to solvent users being at greater risk for acquiring HIV and also at a greater risk for rapid disease progression once HIV infection is established. In terms of HCV, it is possible that solvent-induced microbial translocation plays an important role in reducing the likelihood of spontaneous clearance of HCV, enhancing liver injury, and accelerating HCV disease progression. Individuals with HIV/HCV co-infections may also be at greater risk of disease progression due to increased microbial translocation. A greater understanding of the biological mechanisms involved in solvent use exacerbation of HIV and HCV infection and pathogenesis is needed to truly determine the extent of harm that is occurring in users. These data, along with other important social factors, would provide the impetus to implement prevention, treatment and cessation programs for solvent users that are so urgently needed.

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