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Tryptophan Degradation is Associated with Risk-Taking Propensity in Methamphetamine Users with Treated HIV Infection

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Abstract

Few studies have examined neuroimmune pathways that could contribute to impulsivity in people living with HIV who use substances. Eighty-four methamphetamine-using, sexual minority men with an undetectable HIV viral load were administered the Balloon Analogue Risk Task (BART), a behavioral measure of risk-taking propensity. We examined the associations between kynurenine/tryptophan ratio and phenylalanine/tyrosine ratio with BART scores using multiple linear regression. A higher kynurenine/tryptophan ratio was independently associated with greater BART scores (Beta = 0.25; 95% CI = 0.05 – 1.23; $p = 0.034$). The phenylalanine/tyrosine ratio was not significantly associated with BART scores. Findings support the need for further research to elucidate the neuroimmune mechanisms linking tryptophan degradation with impulsivity to catalyze the development novel pharmacologic treatments for people living with HIV who use methamphetamine.

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Keywords

HIV; Risk-taking propensity; Impulsivity; Methamphetamine; Tryptophan

Introduction

The use of methamphetamine and other amphetamine-type stimulants has been a growing comorbidity among people with HIV (Gamarel et al. 2016). This is particularly among sexual minority men (i.e., gay, bisexual, and other men who have sex with men) where prevalence estimates are between 7.2 and 18.8% (Hickson 2007; Koblin et al. 2007). More frequent stimulant users also experience difficulties along the HIV care continuum as well as display faster clinical HIV progression (Carrico et al. 2011; Carrico et al. 2014; Cook et al. 2008).

Inextricably linked to methamphetamine use is the comorbid behavioral trait of impulsivity. Impulsivity has not only been cited as a moderator that facilitates both methamphetamine use and condomless sex among sexual minority men living with HIV (Semple et al. 2006), but has also been associated with bodily and interpersonal self-harm (Chamberlain et al. 2017). Because impulsivity is an important risk factor in the development and maintenance of substance use disorders (Verdejo-Garcia et al. 2008) as well as other risk behaviors, there is increasing interest in understanding its neurobehavioral mechanisms.

In people with substance use disorders, impulsivity may be partially attributable to deficits in response inhibition (Smith et al. 2014), which stem from dysfunction in the prefrontal cortex (Goldstein and Volkow 2011). Methamphetamine users display heightened resting-state connectivity of the mesocorticolimbic system that is associated with hypo-activation of the dorsolateral prefrontal cortex during the Balloon Analogue Risk Task (BART), a validated behavioral measure of risk-taking propensity and strongly associated with measures of impulsivity (Kohn et al. 2014; Lejuez et al. 2002). Active methamphetamine users also report greater impulsivity when compared to former methamphetamine users and display unique patterns of microstructural abnormalities indicative of ongoing neuroinflammation (Andres et al. 2016). Bearing in mind that there are currently no pharmacologic treatments for stimulant use disorders approved by the Food and Drug Administration (Stoops and Rush 2014), elucidating neuroimmune pathways relevant to impulsivity could accelerate the development of novel pharmacotherapies.

Even among those receiving effective HIV treatment, persistent immune dysregulation amplifies risk for neuropsychiatric impairments such as deficits in attention and executive functioning (Lederman et al. 2013; Price 2017). Although the pathogenesis of neuropsychiatric impairments in people living with HIV is fiercely debated, impaired penetration of anti-retroviral therapy medications into central nervous system is thought to be a major contributing factor (Nightingale et al. 2014). One recent study found that HIV RNA replication in the brain serves as the primary driver for the inflammation that underlies the histopathologic changes seen in HIV-associated cognitive impairment (Levine et al. 2016). These HIV-associated neuropsychiatric impairments may be further exacerbated by co-occurring methamphetamine use (Borgmann and Ghorpade 2018; Minassian et al. 2013;

Rippeth et al. 2004). An important gap, addressed in the present study, is that relatively little is known about how persistent immune dysregulation in people living with HIV who use methamphetamine influences cognitive processes relevant impulsivity.

People living with HIV experience dysregulated metabolism of essential amino acid precursors for neurotransmitters that are only partially reversed by effective treatment, amplify neuropsychiatric impairments, and predict faster clinical HIV progression (Gostner et al. 2015; Hunt et al. 2014; Martinez et al. 2014). Although prior studies focused extensively on examining the implications of altered tryptophan metabolism for depressive symptoms, investigations are beginning to examine the implications of dysregulated metabolism of essential amino acid precursors for cognitive impairment, particularly in regards to major depressive disorder in people living with HIV who treated with ART (Gostner et al. 2015; Keegan et al. 2016). Prior research in people with HIV has demonstrated that increased immune activation stimulated by interferon-gamma (IFN- γ) is associated with faster degradation of tryptophan as evidenced by a higher kynurenine/tryptophan (K/T) ratio (Fuchs et al. 1990). Similarly, immune activation is thought to lead to diminished conversion of phenylalanine to tyrosine as evidenced by a higher phenylalanine/tyrosine (P/T) ratio (Gostner et al. 2015). Findings from our team and others also highlight that stimulant use could amplify immune activation, inflammation, and tryptophan degradation in people living with treated HIV infection (Carrico et al. 2018a; Carrico et al. 2018b; Carrico et al. 2008; Fulcher et al. 2018).

An important, unanswered question is whether dysregulated metabolism of essential amino acid precursors for neurotransmitters could amplify neuropsychiatric impairments in people living with HIV who use substances. The overarching goal of this cross-sectional study was to examine the associations of the K/T and P/T ratios with risk-taking propensity in sexual minority men living with HIV who use methamphetamine. We hypothesized that higher K/T and P/T ratios would be independently associated with greater risk-taking propensity, measured using the BART.

Methods

Sexual minority men living with HIV who use methamphetamine were recruited from substance use disorder treatment programs, HIV medical clinics, AIDS service organizations, the community, and referrals from active participants for a randomized controlled trial (Carrico et al. 2016). At an in-person screening visit, participants completed a signed informed consent that included consent for specimen banking. All enrolled participants met the following inclusion criteria: 1) 18 years of age or older; 2) man who has sex with men; 3) documentation of HIV-positive serostatus (i.e., letter of diagnosis or ART medications matched to photo identification); and 4) urine or hair sample confirmed to be reactive for methamphetamine.

Enrolled participants completed a separate baseline assessment approximately one week later that included a detailed battery of psychosocial measures, a second urine sample for on-site toxicology testing, and a peripheral venous blood sample to measure HIV disease markers. Participants also provided an additional two 10 mL EDTA tubes for specimen

banking. Only those with undetectable HIV viral load (< 40 copies/mL) were included in the present study. All relevant procedures were approved by the Institutional Review Board for the University of California, San Francisco with reliance agreements from the University of Miami and Northwestern University.

Measures

Demographics and ART measures.—Participants completed a demographic questionnaire assessing age, race/ethnicity, education, and income. Participants also disclosed their current ART regimen. In the present study, we examined whether participants were prescribed Efavirenz or a Protease Inhibitor as there is some evidence suggests that both drugs are associated with higher levels of inflammatory markers compared to other ART drug classes (Hileman and Funderberg 2017).

On-site urine screening.—Urine samples provided at baseline were assessed on-site for methamphetamine and cocaine metabolites using the iCup (Redwood Biotech, Inc.; Santa Rosa, CA). Those with reactive urine toxicology results for stimulants were compared to participants who non-reactive for stimulants. The iCup is designed to detect stimulants within 72 hours of use.

HIV disease markers.—Viral load testing for plasma HIV RNA was carried out via the Abbott Real Time HIV-1 assay (Abbott Molecular Inc.; DesPlaines, IL) and featured a lower limit of detection of 40 copies/mL. CD4+ T-cell count was quantified via flow cytometry of whole blood, and assays performed by Quest Diagnostics.

Amino acid precursors for serotonin and catecholamines.—A reverse-phase high performance liquid chromatography method in conjunction with fluorescence analysis was utilized to measure concentrations of tryptophan and kynurenine at 286 nm and 360 nm respectively. Concentrations of phenylalanine and tyrosine was measured via 210 nm excitation and 302 nm respectively (Laich et al. 2002; Neurauter et al. 2008).

The BART.—Participants completed a validated behavioral measure of risk-taking propensity in which they “inflated” a series of 30 virtual balloons where they can earn one cent per pump that is stored in a temporary bank (Lejuez et al. 2002). A trial ends when the participant either: 1) chooses to stop pumping and keeps their earnings, or 2) bursts the balloon and loses earnings accrued for that balloon. If a balloon bursts during the exercise, all monies accrued for that balloon are lost. Participants could earn a maximum of \$22.80 during the BART based on their performance. Tendency to engage in risk-taking was operationalized as the mean number of pumps on intact balloons. Higher scores indicate greater risk-taking propensity.

Statistical Analyses

Four linear regression analyses were performed to examine correlates of higher BART scores. The K/T and P/T ratios were tested in separate models as the primary independent variables. First, we conducted two simple linear regressions to examine the unadjusted, bivariate associations of the K/T and P/T ratios with BART scores (Models 1a and 2a).

Then, we conducted two multiple linear regression models to examine the independent associations of the K/T and P/T ratios with BART scores after adjusting for age, current prescription for Efavirenz or a Protease Inhibitor, CD4+ T-cell count, the ASI alcohol use score, and recent stimulant use (Models 1b and 2b). Because we hypothesized that recent stimulant use would be most closely linked to performance on the BART, it was included as a covariate in our final adjusted models. All analyses were performed using SAS 9.4 (SAS Institute, Cary NC).

Results

In total, 84 sexual minority men living with HIV who had an undetectable viral load and biologically confirmed recent methamphetamine use were included in this study. Half of the participants were ethnic minorities (50%), most were middle-aged (Mean = 43.4 SD = 8.7) and had a median CD4+ T-cell count of 646 (Interquartile Range = 428-816) cells/mm³. Approximately two-thirds reported completing at least some college or trade school (73%) with an annual income of less than \$25,000 per year (74%).

As shown in Table 1, a higher K/T ratio (Standardized Beta [β] = 0.23; 95% CI = 0.04 – 1.12; $p = 0.036$) was associated with greater log₁₀ BART scores in an unadjusted model. After adjusting for age, ART regimen, CD4+T-cell count, ASI alcohol use score, and recent stimulant use, the association of a higher K/T ratio with greater log₁₀ BART scores remained statistically significant ($\beta = 0.25$; 95% CI = 0.05 – 1.23; $p = 0.034$). In contrast, there was not a significant association of the P/T ratio with log₁₀ BART scores in unadjusted ($\beta = -0.05$; 95% CI = -2.48 – 1.50; $p = 0.625$) or adjusted ($\beta = -0.06$; 95% CI = -2.69 – 1.60; $p = 0.615$) analyses.

Discussion

This study is among the first to observe that a higher K/T ratio is independently associated with greater risk-taking propensity (and by extension, greater impulsivity) in people living with HIV who use methamphetamine. The vast majority of prior research in people living with HIV has focused on the relevance of the K/T ratio for depressive disorders and clinical HIV progression (Gostner et al. 2015). Although there is some evidence that people living with HIV who use stimulants display depleted tryptophan (Carrico et al. 2008), little is known about the potential clinical relevance of dysregulated serotonin synthesis with regard to impulsivity as a prevalent comorbidity in people living with HIV who use substances. Findings from the present study underscore the need for further research to characterize neuroimmune pathways linking tryptophan degradation to risk-taking and impulsivity in people living with HIV who use methamphetamine. Advancing our basic understanding of these neuroimmune pathways would accelerate the development of novel pharmacotherapies for stimulant use disorders.

At the same time, there was not a significant association of the P/T ratio with greater risk-taking propensity in the present study. Like tryptophan, phenylalanine metabolism is highly sensitive to immune activation in HIV infection such that phenylalanine metabolism to tyrosine is slowed (Gostner et al. 2015). Impaired conversion of phenylalanine to tyrosine is

thought to contribute to dopamine deficiency in people living with HIV. Although one post-mortem study observed that people living with HIV displayed lower dopamine levels in caudate nucleus, putamen, globus pallidus, and substantia nigra relative to HIV-negative controls (Kumar et al. 2011), this HIV-related dopamine deficiency was not associated with cognitive impairment. From a physiologic standpoint, both HIV infection and methamphetamine use have been shown to downregulate the expression of striatal D₂ receptors and have been associated with pre-frontal cortex dysfunction, mediating risk-taking propensity in both human and animal studies (Kesby et al. 2017; London 2016; Schier et al. 2017). Further research is needed to examine whether peripheral dysregulation of catecholamine synthesis is indirectly influencing risk-taking propensity and other neuropsychiatric comorbidities through these and other well characterized neuroimmune pathways.

Findings from the present study should be interpreted in context of some important limitations. Given the cross-sectional design, it is not possible to determine the potentially bi-directional associations of the K/T and P/T ratios with risk-taking propensity. It remains plausible that dysregulation of neurotransmitter synthesis in the periphery is amplifying risk-taking propensity. Risk-taking may also serve as a proxy for greater severity of methamphetamine use, which could in turn alter neurotransmitter synthesis through biological and behavioral pathways (Carrico et al. 2008). Further longitudinal research is also clearly needed to examine whether and how the K/T and P/T ratios are linked to neuroimmune and neurobehavioral alterations in the central nervous system. Future research in this area would likely benefit from collecting cerebrospinal fluid samples to measure viral load and immune dysregulation to provide a more comprehensive understanding of the role of neuroinflammation in risk-taking propensity. Finally, the present study focused on a well-characterized sample of sexual minority men with treated HIV infection who use methamphetamine. Future studies should enroll intact groups as a function of methamphetamine use and HIV status to disentangle the potentially interactive effects of methamphetamine and HIV on neuroimmune dysregulation.

Despite these limitations, this study is among the first to observe that a higher K/T ratio is independently associated with greater risk-taking propensity in sexual minority men living with HIV who use methamphetamine. These findings will provide support for the scientific premise of more definitive longitudinal research to shed light on the biological underpinnings of risk-taking and impulsivity in co-occurring methamphetamine use and HIV.

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Table 1.

The kynurenine/tryptophan ratio is independently associated with risk-taking propensity in sexual minority men with an undetectable viral load who use methamphetamine (N = 84).

	β (95% CI)	p-value
Model 1a:		
Kynurenine/Tryptophan ratio (unadjusted)	0.23 (0.04, 1.12)	0.036
Model 1b:		
Kynurenine/Tryptophan ratio (adjusted)	0.25 (0.05, 1.23)	0.034
Age	-0.04 (-0.01, 0.01)	0.705
Prescribed a Protease Inhibitor	0.05 (-0.17, 0.26)	0.692
Prescribed Efavirenz	0.05 (-0.33, 0.52)	0.672
CD4+ T-Cell Count	0.05 (-0.0002, 0.0004)	0.689
Alcohol Use Score	0.08 (-0.41, 0.83)	0.500
Reactive Urine Toxicology for Stimulants	-0.05 (-0.22, 0.14)	0.656
Model 2a:		
Phenylalanine/Tyrosine ratio (unadjusted)	-0.05 (-2.48, 1.50)	0.625
Model 2b:		
Phenylalanine/Tyrosine ratio (adjusted)	-0.06 (-2.69, 1.60)	0.615
Age	-0.03 (-0.01, 0.01)	0.802
Prescribed a Protease Inhibitor	0.05 (-0.18, 0.26)	0.706
Prescribed Efavirenz	0.01 (-0.42, 0.45)	0.951
CD4+ T-Cell Count	0.05 (-0.0003, 0.0004)	0.725
Alcohol Use Score	0.04 (0.54, 0.72)	0.769
Reactive Urine Toxicology for Stimulants	-0.07 (-0.24, 0.13)	0.546