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Self-reported lifetime marijuana use and interleukin-6 levels in middle-aged African Americans

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ABSTRACT

Background: Research examining the relationship between marijuana and cytokine function has been well developed in the biochemical literature. However, scant literature exists regarding this relationship between inflammatory markers and marijuana use in public health or behavioral studies and is virtually nonexistent in non-neurologically compromised African American samples.
Methods: The current study examined the differences in serum interleukin-6 (IL-6), a proinflammatory cytokine, between non-drug users ($n = 78$), marijuana only users ($n = 46$) and marijuana plus other drugs users ($n = 45$) in a community-based sample of middle aged African Americans. Participants included 169 African American adults (50.30% female), with a mean age of 45.68 years (SD = 11.72 years) from the Washington, DC metropolitan area. Serum was drawn upon entry into the study and the participants completed a demographic questionnaire, which included questions regarding drug use history.
Results: After adjusting for demographic and physiological covariates, analysis of covariance revealed a significant difference between the three groups, $F(2, 158) = 3.08$, $p = 0.04$). Post hoc analyses revealed lifetime marijuana only users had significantly lower IL-6 levels ($M = 2.20$ pg/mL, SD = 1.93) than their lifetime nonuser counterparts ($M = 3.73$ pg/mL, SD = 6.28). No other comparisons among the groups were statistically significantly different.
Conclusion: The current findings extend previous cellular and biochemical literature, which identifies an inverse association between IL-6 and marijuana use. Examining this relationship in the psychological and behavioral literature could be informative to the development of clinical interventions for inflammatory diseases.

1. Introduction

Marijuana is the most commonly used illicit drug in the United States, with over 18 million Americans reporting use in the past month in 2011 (NIDA, 2012). Of all the illicit drugs, only marijuana has significantly increased in usage over the past decade (NIDA, 2012). Given that most people initiate illicit drug use by using marijuana during their teenage years, many researchers have explored the deleterious psychological (Block and Ghoneim, 1993; Ranganathan and D'Souza, 2006; Anderson et al., 2010), neuroanatomical (Matochik et al., 2005; Lopez-Larson et al., 2011), and peripheral (Mittleman et al., 2001; Tashkin, 2005; Mehra et al., 2006) influences of marijuana use. Literature has also examined the impact of marijuana on immunity. For instance, marijuana alters a variety of innate and adaptive immune system responses (Klein et al., 1998, 2003). Though researchers have explored the immunomodulatory effects of psychoactive components of marijuana in animal studies (Snella et al., 1995; Matsuda et al., 2005; Ribeiro et al., 2012), the literature showing this relationship in humans is focused primarily on the cellular effects of marijuana (Klein et al., 1998; Reiss, 2010). Though there is a growing body of research examining the association between marijuana usage/abuse and human immunity, this literature is still in its infancy (Baldwin et al., 1997; Aggarwal et al., 2009). Examining this association is especially imperative given the lack of presence in substance abuse and public health literature. Identifying both the harm to the immune system and the susceptibility to opportunistic infections is critical in informing substance use intervention programs as well as potential medicinal uses of marijuana.

Previous research has examined the effects of marijuana use on immune response in organs, such as the lungs (Baldwin et al.,

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1997). This research demonstrated that cells from marijuana smokers' lungs produced significantly less than normal amounts of proinflammatory cytokines when stimulated than those of their non-smoking and tobacco-smoking counterparts. Sarafian et al. (1999) supported and expanded upon this finding, demonstrating that oxidative stress may be a mitigating factor in the reduced proinflammatory cytokine production and activation in lung cells by contributing to cell damage. Moreover, researchers have reported a similar reduction in interleukin-2 when compared to their non-cannabis smoking counterparts in a first-episode psychosis sample (Di Nicola et al., 2012).

Ultimately, marijuana use induces anti-inflammatory processes, including the inhibition of macrophage function and natural killer cells (Klein et al., 1998; Chang et al., 2001; Klein, 2005). Previous studies have identified a non-psychoactive constituent, cannabidiol, as having a primary anti-inflammatory influence within humans (Durst et al., 2007). The anti-inflammatory influence produced by marijuana, specifically cannabidiol, has led to the researchers and clinicians examining marijuana's therapeutic utility (Croxford and Yamamura, 2005). However, there seems to be some inconsistency in reported findings, as some have found an upregulation of IL-6 (Monnet-Tschudi et al., 2008). This could be due to the different physiological locations from which the cells are extracted and examined. Or, it could be the differential effects of the two major constituents in marijuana, THC and cannabidiol (Kozela et al., 2010).

Much of the previous research examined the relationship between marijuana and immune function in healthy non-human animal models, which are not truly generalizable to humans, given our diverse health conditions. Various health-related constructs influence IL-6 levels, such as age (Wei et al., 1992; Ershler and Keller, 2000), socioeconomic factors (Brydon et al., 2004), obesity (Mohamed-Ali et al., 1997), and gender (Chae et al., 2001; Fernandez-Real et al., 2001). Given the physiological constructs such as cardiovascular health looming as mitigating factors in central and peripheral nervous system function, it is imperative to examine the effects of marijuana use in the presence of other risk factors. Additionally, given potential concomitant marijuana use with other illicit drugs (Fergusson et al., 2006), it is imperative to examine the unique effects of marijuana use on IL-6 levels in addition to the effect in the presence of other illicit drugs.

Overall, the body of research exploring the influence of marijuana use on immune function in the behavioral and substance use literature is still in its infancy. Examining the relationship between marijuana use and proinflammatory cytokine function may help to inform both clinical and non-clinical research paradigms. The purpose of the current study was to examine the differences in serum IL-6 levels among three groups: lifetime nonusers of illicit drugs, lifetime users of marijuana only, and lifetime users of marijuana and other illicit drugs. It was hypothesized that lifetime users of marijuana only would have significantly lower serum IL-6 levels compared to lifetime nonusers and lifetime users of marijuana plus other illicit drugs.

2. Methods

2.1. Subjects

One hundred sixty-nine African-American adults were recruited by the Minority Organ Tissue Transplant Education Program through flyers posted in Howard University Hospital and community based health fairs conducted by the Hospital in the Washington, DC metropolitan area for a parent study entitled, "Stress and Psychoneuroimmunological Factors in Renal Health and Disease." Health fairs were conducted by the Howard University Hospital to educate local African Americans on a variety of health concerns, such as heart disease, hypertension, renal health and obesity. Inclusion criteria for the parent study included individuals who were 18 years of age and older with no history of traumatic brain injury or psychiatric diagnosis. The Howard University institutional review board approved this study. A total of 212 individuals participated in the parent study, but only those with complete IL-6 and illicit drug use data were included in the current study.

2.2. Procedures

Study procedures entailed one study visit lasting approximately 4 h. Upon entering the Howard University Hospital General Clinical Research Center, researchers obtained informed consent from the participants. After informed consent was received, a registered nurse obtained a peripheral venous blood sample and the first of three blood pressure readings. Following these collections, study participants completed a demographic, medical history, and behavioral health questionnaire. After completion of the demographic questionnaire, participants underwent neuropsychological testing, provided a second blood pressure reading, completed a battery of psychological instruments, and provided a final blood pressure reading. Participation was voluntary and participants were remunerated $50 for their time.

2.3. Assessment of illicit drug use

Several questions on the demographic, medical history, and behavioral health questionnaire assessed history of illicit drug use. The first question was: "Have you ever used an illicit drug or narcotic?" Participants who responded "yes" then answered a series of follow-up questions that probed for the type of drug(s) used, i.e., "Have you ever used (insert drug type here; e.g., "marijuana")?" Response choices were "yes" or "no".

2.4. Quantitation of serum IL-6

A venous blood sample of approximately 2 mL was collected from each participant. Samples were centrifuged for 30 min, aliquoted into six vials, and stored at −70 °C at the Howard University General Clinical Research Center until sent to Quest Diagnostics for analyses. Serum interleukin-6 (IL-6) concentrations (pg/mL) were quantified using enzyme-linked immunosorbent assay.

2.5. Assessment of covariates

Age (in years), sex, years of education, and annual income was collected via a demographic questionnaire administered by a trained researcher. Self-reported medication use was obtained by asking the question "Are you currently taking any medication?" Participants were given two options for responses, "yes" or "no". A trained member of the nursing staff in the General Clinical Research Center obtained height, weight, and blood pressure.

2.6. Data analysis

Data were analyzed using the Statistical Package for Social Sciences, Version 20.0 (SPSS Incorporated). Continuous variables are presented as mean (standard deviation). Categorical prevalence are reported as the *n* of the subsample and the within group percentage. IL-6 levels were negatively skewed, so values were log transformed prior to analyses. Independent *T*-tests and Chi-square test were used to compare respectively continuous and categorical variables between groups. Analysis of covariance was performed in order to examine the potential differences among the groups adjusting for covariates. Demographic and physiological covariates that may confound a significant relationship between drug use and IL-6 were selected based on published literature (i.e., age, income, education, gender, body mass index (BMI), self-reported medication use, and systolic and diastolic blood pressure). Subsequent Tukey HSD post hoc comparisons were also conducted to identify where the significant differences were among the groups.

3. Results

Demographic and physiological information is displayed in Table 1. The mean age for the overall sample was 45.68 years (SD = 11.72 years) with 85 (50.30%) women and 84 (49.70%) men. On average the sample was obese, with BMI was 31.12 kg/m^2 (SD = 8.58 kg/m^2). The current sample had 13.89 (SD = 2.29) years of education.

3.1. Unadjusted group differences

There was a significant difference in age among the three groups ($F[2, 166] = 5.01$, $p = 0.01$; individuals in the marijuana and other group were the oldest (mean [*M*] = 48.58; SD = 7.56), followed by the non-drug using group (*M* = 46.58; SD = 13.02) and then the marijuana group (*M* = 41.33; SD = 11.71). The groups also differed by years of education ($F[2, 166] = 3.29$, $p = .04$), with the non-drug using group having the highest average years of education (*M* = 14.18

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