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Mentholated Cigarettes are Related With Abnormal Brain-Derived Neurotrophic Factor Levels among Smokers Living with HIV

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Abstract

Brain-Derived Neurotrophic Factor (BDNF) plays a prominent role in protecting the brain from insults such as HIV. In addition to HIV, animal studies suggest that cigarette smoking, may also affect BDNF levels. However, the influence of smoking on BDNF levels among People Living with HIV (PLWH) has not been studied, despite the high prevalence of smoking within this population.

To determine the independent and interactive effects of smoking and HIV on plasma BDNF levels.

Keywords: Mentholated cigarettes; HIV; Nicotine addiction; Smoking cessation; Brain derived neurotrophic facto

Introduction

While in the beginning of the HIV epidemic, the effect of cigarette smoking in PLWH was uncertain, increasingly available data indicates that smokers are in fact highly susceptible to a number of health complications specifically related to smoking cigarettes [1] It has been estimated that smoking is a major contributor of morbidity and mortality in this population [2,3]. Smoking rates are two to three times higher among PLWH (41-66 %) compared to the general population (19 %) [4-8]. Yet, there is a dearth of information regarding the mechanisms underlying the enhanced susceptibility to nicotine dependence in this population. It is therefore critical to better understand the specific effects of smoking in this population.

Animal studies suggest that cigarette smoking, specifically the nicotine in cigarettes, may induce alterations in BDNF gene expression and its protein level within the mesocorticolimbic system [9]. Studies have also demonstrated that BDNF regulates dopamine and serotonin, both of which are involved in the reward system [10,11]. Yet, studies in humans have reached inconclusive observations. For example, Chan and colleagues did not find significant differences in serum BDNF levels between smoker and non-smoker cohorts [12]. Bhang, et al. (2010) found that baseline plasma BDNF levels were significantly lower in smokers compared to nonsmokers and study participants abstaining from smoking [13]. Similarly, Kim et al. (2007) reported higher BDNF levels in chronic smokers following a 2-month smoking cessation period compared their BDNF levels at baseline [14]. These inconsistencies indicate the need of additional studies. Furthermore, the influence of cigarette smoking on BDNF levels of people living with HIV (PLWH) has not been studied. Such information is highly relevant considering BDNF has been shown to plays a prominent role in protecting the brain from insults like HIV [15] . Our team, along with others, has demonstrated that alterations on BDNF among PLWH are associated with several cognitive and mood disorders that may further impact decision making and risk behaviors regarding the use of tobacco, abuse of drugs and alcohol [14,16].

Another unanswered question is whether or not the effect of cigarettes on the Central Nervous System (CNS) varies by type of cigarette (menthol vs. non-menthol) being used. Menthol is a chemical compound (2-isopropyl-5-methyl-cyclohexan-1-ol) extracted from either peppermint or corn mint plants, or it is created synthetically; virtually all menthol in cigarettes is tobacco-derived. Although it has been thought that the main goal of adding menthol to cigarettes was to reduce the harshness of tobacco, industry documents from Philip Morris suggest that menthol was added due to its perceived effects on the Central Nervous System (CNS) [17].

In fact, Morris researchers identified the effects of menthol on electrophysiological measures of brain activity (PREP P1 latencies, and P1-N2 amplitudes (both objective electrophysiological measure of brain activity) [18]. They also reported measurable effects of menthols over chemosensory event-related potential - an established method used to measure both sensory and cognitive changes [19]. This information is relevant in light of evidence that mentholated cigarettes may augment addiction by providing additional sensory stimulations. Unfortunately, beyond this evidence, *how* mentholated cigarettes impact the CNS is generally unknown. Moreover, with the high prevalence of menthol cigarette use among PLWH, as well as African-Americans (84.5 % compared to 26.9 % of White smokers [20,21], this study seeks to better understand interactive effects of smoking, menthol use, and HIV on plasma BDNF levels. Given the widespread use of menthol in other at risk populations (i.e. minorities, women and youth), it is imperative to

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determine their plausible effects on the CNS to better educate, protect and prevent further damage.

Accordingly, in this paper, we examine the potential effects of menthol versus non-menthol cigarette smoking in a large, racially diverse cohort of men and women, with and without HIV. Since animal studies have suggested an important role of BDNF in many behaviors related to nicotine addiction, and critical role of protecting neurons from external damages, we focus on the effect of smoking on BDNF levels.

Methods

This cohort study consists of 200 PLWH and 200 PLWOH smokers and non-smokers chosen to represent relatively "pure" smokers with minimal drug use, and without major confounding factors. Semi-annual visits consisted of a brief medical exam, survey questionnaires and a fasting blood sample, to assess general health, tobacco, immune status, and, BDNF levels.

Study population

Florida International Liaison For Trans disciplinary And Educational Research On Smoking, "Filters" is a single site cohort that currently has enrolled 380 participants (205 HIV positive and 175 HIV negative participants), fluent in English or Spanish, classified as having either no addictions, or tobacco as their primary drug of abuse. The main goal is to evaluate biological mechanisms whereby tobacco use may influence the development of tobacco-related diseases (TRD), particularly among certain racial and ethnic groups. The study was approved by Florida International University and the University Of Miami Miller School Of Medicine Committee for the Protection of the Rights of Human Subjects. All participants signed both written informed consent and HIPAA forms.

Participants were also excluded if they possessed a significant history of medical and immunological illnesses that may confound the interpretation of the main outcomes of the study. These illnesses include liver cirrhosis, myopathies, pregnancy, malignancies, and congenital or acquired immunosuppressive conditions, such as recipients of transplants, and autoimmune diseases. Participants currently using anti-inflammatory drugs, corticoids, lipid lowering medications (e.g., statins), or hormonal therapy were excluded (i.e. transgender, fertility treatments). To reduce the confounding effects of liver disease and/or illegal drugs use; we also excluded injection and dependent drug users, and any participants who had cirrhosis (redundant—see second sentence—this paragraph), active viral hepatitis, or liver enzymes two standard deviations above normal values.

Smoking

The Fagerstrom Test for Nicotine Dependence, (FTND 97) [22], a standardized questionnaire extensively used in research, was used to assess smoking habits. The FTND incorporates questions about the number of cigarettes smoked per day, the time between awakening and smoking the first cigarette of the day, and the episodes in which the smoker lost control of smoking behavior (such as smoking at inappropriate times or places). Information regarding the age of initiation, number of years smoking, and kind of tobacco used (cigarettes, length, mentholated or not, use of filters, cigars, pipes, etc.) was also collected.

Following the NHIS guidelines, a participant was defined as a current smoker if he/she had smoked at least 100 cigarettes, and now smoke either every day or some days. A non-smoker was defined as anyone who has never smoked, or that at some time smoked cigarettes, cigars, or pipes for less than three months [23] based on these definitions, participants were assigned into four groups based on their HIV serostatus (positive/negative) and their smoking status (smoker/non-smoker).

BDNF

Circulating levels of BDNF were selected as a target because prior studies have demonstrated that, although different from those in the cerebrospinal fluid (CSF), levels are correlated with CSF measures in other CNS diseases.

Samples were identified with the study ID, and assayed by a laboratory technician blind to the clinical information. Plasma BDNF levels were measured using a commercially available ELISA kit (R&D System) according to the manufacturer's instructions. Briefly, 50 µl of standards and 20-fold diluted samples were pipetted into wells of a 96-well immunoplates. An enzyme-linked monoclonal antibody specific for BDNF was added to the wells. Following a wash to remove any unbound antibody-enzyme reagent, a substrate solution was added to the wells, and color developed in proportion to the amount of BDNF bound in the initial step. The color development was stopped, and the intensity of the color was measured. BDNF concentration in serum was calculated based on a standard curve and according to the manufacturer levels mostly reflect mature BDNF. However, it can also detect a small proportion of pro-BDNF as a result of cross-reactivity. The minimum detectable dose of BDNF is typically less than 20 pg/ml.

Covariates

Structured questionnaires were used to obtain socio-demographic information, tobacco and other drugs used and a medical history, including antiretroviral treatments. Race/ethnicity data were self-reported, with race categorized as Black or White; and ethnicity as Hispanic or non-Hispanic. Participants were questioned regarding their level of physical activity (regular physical activity refers to leisure-time physical exercise). Participants were defined as physically inactive when they reported less than weekly exercise; otherwise they were categorized into the group "exercising regularly".

Blood was drawn to obtain cotinine levels, and a biochemical profile (serum albumin levels, liver enzymes, urine function (BUN, creatinine, glucose and lipid profile). Participants' viro-immune profile was obtained (T Lymphocytes phenotypic analysis, using flow cytometry and viral load, using Roche AMPLICOR HIV-1 monitor test). In addition, a medical chart abstraction was performed to confirm self-reports.

Income was categorized as 1: $ 0–500 /month; 2: $ 501–1000 / month; 3: $1001–$2000 /month; 4: $ 2001–2500 /month; 5: $ 2501–3000 /month, and 6: > $ 3000 /month. Educational level was coded 1–16, to account for each year of schooling through college or vocational training.

Statistical analyses

The normality of the distribution of primary outcomes of interest was examined with a normal probability plot. Descriptive statistics, such as minimum, maximum, median, and mean with Standard Deviation (SD) were used to summarize the data, as well as to detect outliers and missing values. Log transformations were performed with variables not normally distributed. T-tests and chi-square analyses were used to compare means and proportions across the three smoking groups. Percentages and frequencies were used to describe categorical

variables. Differences in demographic, nutritional variables, and obesity were assessed using the chi-square test for categorical variables, two sample Student's t-test for normally distributed continuous variables and the Wilcoxon rank sum test for non-parametrically distributed continuous variables. We employed the Bonferroni correction because of the multiple comparisons. To examine potential mediators, linear regression models were employed for these analyses. The validity of model assumptions was evaluated using analysis of residuals. P values less than 0.05 (2-tailed) were considered significant. Data analyses were performed using SPSS version 18.

Results

Socio demographics

Analyses were conducted to identify differences between non-smokers, smokers of mentholated cigarettes, and non-mentholated cigarettes. (Table 1) shows the descriptive characteristics in the total sample, as well as by smoking status. No significant differences were found across the groups at baseline in two measurements of social inequalities, education and income. Participants were on average 39.8 years old; the majority was African American or Hispanic.

While females tended to be less likely than males to be current smokers (OR 0.6; 95 % CI; 0.5-0.9, $p = 0.07$); but females were more likely to be users of mentholated cigarettes than males (OR 1.6; 95 % CI: 1-3, $p = 0.04$). Use of mentholated cigarettes was more notorious among African Americans than Non-Hispanic Whites (OR = 2 95 % CI 1.1-3.1, $p = 0.006$), or Hispanics (OR = 7; 95 % CI: 2.2-20, $p = 0.0009$). Neither education nor income, two commonly used markers of socioeconomic status, differed across smoking groups. The proportion of users of mentholated cigarettes was similar between HIV seronegatives and seropositives.

BDNF

The mean BDNF plasma levels measured at baseline were 4635 ± 3329 pg/ml. We found age (< 40 years old: 3430.3 ± 3386 vs. > 40 years old: 5286.8 ± 3127 pg/ml) related differences. Although differences were not statistically significant, females exhibited slightly higher BDNF values than the male counterparts (6359 ± 2744 vs. 5977 ± 4130 pg/ml, $p = 0.5$). Analyses uncovered significant differences in plasma BDNF levels between PLWH and PLWOH (6738.5 ± 3.048 vs. 3048 ± 1710 pg/ml, $p = 0.001$).

BDNF and smoking

The baseline plasma BDNF levels showed a significant correlation with smoking, as assessed by the nicotine levels ($r = -0.25$, $p = 0.002$). A negative correlation between BDNF with age at start of smoking was also observed ($r = -0.391$, $p = 0.002$). An analysis of covariance (ANCOVA) with age and gender, as covariates, showed that the baseline plasma BDNF level was higher in the smokers (9276 ± 662 pg/ml) than in the non-smokers (7945.4 ± 358.1 pg/ml) (F (df1, df2) = 4.41, $p = 0.05$).

Results uncovered that menthols produce up-regulation of BDNF. The BDNF plasma levels among PLWOH, non-smokers had the lowest mean BDNF levels (2480 ± 1367 pg/ml), followed by those of smokers

Variables	Non Smokers N=138	Smokers of regular Cigarettes N=65	Smokers of Mentholated Cigarettes N=152	P value
Age	39.3 ± 9	40.4 ± 8.5	40.8 ± 8.5	0.7
Men Women	44 % 66 %	69 % 31 %	58 % 42 %	0.3
Black Hispanic White	57 % 40 % 3 %	17 % 71 % 12 %	68 % 25 % 7 %	0.006
Less than $ 10,000 $ 11,000 - 20,000 $ 20,000 - 49,000 > $ 50,000	80 % 15 % 3 % 2 %	91 % 6 % 0 % 3 %	92 % 6 % 2 % 0 %	0.2
HIV yes No	65 % 35 %	52 % 48 %	57 % 43 %	0.1
Albumin	4.2 ± 0.5	4.2 ± 0.4	4.1 ± 0.6	0.9
Liver Enzymes AST ALT Alkaline Phosphatase	 38 ± 22 35 ± 25 108 ± 50	 45 ± 22 41 ± 39 107 ± 37	 36 ± 18 35 ± 19 97 ± 38	 0.6 0.8 0.9
CD4 cell counts	508.9 ± 311	462.6 ± 299	470 ± 322	0.4
Viral Load Log	2.4 ± 1.4	2.6 ± 1.3	2.5 ± 1.2	0.1

Values are means ± SD or percentages.
No significant differences in sociodemographic characteristics were found between groups.

Coefficients [a]

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
(Constant)	10535.730	1045.558		10.077	0.000
HIV POSITIVE	-2928.940	510.432	- 0.441	- 5.738	0.000
Mentholated Cigarettes	-1053.419	509.977	- 0.159	- 2.066	0.041

a = Dependent Variable: BDNF

Table 1: Baseline Socio-Demographic Information of HIV Infected Patients by Smoking Group

of regular cigarettes (2859.7 ± 2009), with the highest levels observed among menthol users (3,511.2 ± 1,641, $p = 0.03$). Among PLWH, a similar trend was observed with smokers of menthols, exhibiting the highest levels of all the other groups (6738.5 ± 3930; regular cigarettes: 5477 ± 4295; non-smokers: 5148 ± 2539, $p = 0.03$). Multivariate analyses confirmed that HIV, smoking, and age were independent predictors of BDNF levels.

BDNF and nicotine addiction

Based on the premise that the phenotype of a highly addicted smoker includes the use of more than 25 cigarettes a day, and smoking within 5 minutes of waking up. We analyzed BDNF levels in relationship with these parameters. Analyses demonstrated that subjects that have the first cigarette within 5 minutes of waking exhibited higher BDNF levels (6974 ± 698; 6-30 minutes: 6,504 ± 626; > 60 minutes: 4,353 ± 809, $p = 0.04$). Compared to subjects that smoke less than 25 CPD, those smoking more exhibited higher BDNF levels (6693 ± 414; > 25 CPD: 7716 ± 813), though differences were not statistically significant. However, when analyses were based on cotinine levels subjects (both PLWH and PLWOH) with cotinine levels in the top quartile (cotinine log > 2.5) exhibited significantly higher BDNF levels (8072 ± 4834; < 2.5: 6073 ± 4559, $p = 0.03$). Nonetheless, PLWH were more likely to exhibit cotinine levels in the top quartile (log-cotinine > 2.5, OR = 1.4, 95 % CI: 1.4-1.7, $p = 0.02$).

Multivariate analyses confirmed that HIV status and smoking of menthol-flavored cigarettes were independent predictors of BDNF levels. In other words, seropositives had higher levels of BDNF than seronegatives. Menthol-flavored cigarette smokers had higher levels of BDNF, compared to regular cigarette smokers and non-smokers. Neither gender, race, age, nor dependence scales were significant.

Discussion

Despite all benefits associated with antiretroviral treatment, our data uncovered that treated PLWH did not reach BDNF levels comparable to those of negative individuals from the same source population. Even more important was to establish that smoking further increases BDNF levels in our study population. These findings are in line with prior studies indicating that structural brain damage can occur as a consequence of smoking. However, a major contribution of this study emerged to uncover that there are distinctive effects of menthol flavored and non-menthol flavored cigarettes on BDNF. These findings are of great concern given that a sizable portion of our South Floridian study population (70 %) used mentholated cigarettes. Collectively, these findings have important clinical and public health implications. As the discovery of antiretroviral therapy (ART) heralds a paradigm shift in HIV-related morbidity and mortality [23,24-27], the time is perfect to address the widespread use of smoking as a bottleneck to enhance the quality of life and the life expectancy of PLWH. From the public health perspective our findings are also significant. In 2009, the government ordered a ban on candy-, fruit-, and spice-flavored cigarettes, but it fell short of eliminating menthol flavoring, because it was ruled that there was not sufficient evidence that menthol-flavored cigarettes could be more dangerous than non-menthol cigarettes [28]. Contrary to the lack of previous evidence, our study uncovers a deleterious effect of smoking mentholated cigarettes on BDNF.

Here we show that PLWH exhibited significantly higher BDNF levels than HIV controls, and suggests that despite viral control there is still ongoing damage inflicted on the central nervous system. The study is consistent with national reports indicating that neuropsychological problems are still present in the ART expanding era. Although at first, results seem to contrast with prior reports indicating that HIV depletes BDNF, it needs to be noticed that our participants are receiving antiretroviral therapy. Thus, the deleterious effect of HIV should be annulated for the most part. Second, since the BDNF kits used cross reacts with pro-BDNF, it could be possible that we are detecting both a mature and pro-BDNF. Notably, a prior study has found elevated levels of pro-BDNF among PLWH, which induces deleterious effects (i.e., apoptosis and terminal retraction [29,30].

Furthermore, our findings are in accord with animal models demonstrating that chronic nicotine exposure increases BDNF in the hippocampus of rats [31-33]. Although our study confirmed the findings made by Yang Zhang's study, the conclusions are at odds concluded that schizophrenic patients will be benefitted by smoking, because nicotine significantly increased their BDNF levels [34]. On the other hand, we believed that this increase in BDNF is the central nervous system's is a way of compensating for the chronic neuronal damage induced by smoking, not a beneficial effect.

A major contribution of this study emerged from uncovering the deleterious effects of mentholated cigarettes on BDNF which provides a plausible of explanation as to why menthol cigarette are so difficult to quit. First, BDNF alterations were not only more prominent among menthol users; they were associated with higher FNTDS. Particularly, those with excessive levels of BDNF have their first cigarette earlier and exhibited higher cotinine levels, suggesting increased addiction. Findings are also in accord with past research suggesting a link between BDNF and nicotinic acetylcholine receptor α4 β2 and α7 $nAChR_s$ in hippocampal interneurons [35,36] Although the observational nature of the study prevents the assertion of causal relationships, if trends hold true, the magnitude of the harm caused by the availability of menthol cigarettes to the public health is striking. This result provides additional evidence that menthol-cigarette smoking may have a greater potential for abuse, and thus, for the development of tobacco related disorders. Therefore, smokers may benefit from comprehensive health models that incorporate anti-smoking messages and specific information about the risks of smoking mentholated cigarettes. This could mean that mentholated cigarettes should be added to the list of banned flavored cigarettes, as they pose a threat beyond regular cigarettes. Such a strategy might directly decrease morbidity and mortality risks across many populations, including PLWH, women, and minorities.

Although the study population was limited to the clinical settings of South Florida, and current analyses were based on baseline information, our study benefitted from the inclusion of HIV positive and seronegative individuals. It is also notable for the large number of women involved in the study, allowing for enhanced generalization. \

Conclusions

This study is the first to describe the distinctive effects of menthol flavored and non-menthol flavored cigarettes on BDNF. Given the role BDNF plays in the pharmaco dynamic adaptation associated with the development of addiction, one can postulate that BDNF alterations are probably associated with the increased difficulties of menthol users to quit smoking [11,37-39]. Although the observational nature of the study prevents the assertion of causal relationships, if trends hold true the magnitude of the harm caused by the availability of menthol cigarettes to the public health is striking. In addition to PLWH, women, youth, and minorities also have a higher preference for menthol flavored cigarettes [20,40] and furthermore experience disproportionately higher rates of smoking-related health consequences. It is therefore important to further

establish the effects of menthol on other neurotrophic factors, and other neurotransmitters. Paper adds to the body of scientific evidence that provides information about the risks of mentholated cigarettes. The current finding suggests that menthol-flavored cigarettes may be more hazardous [than non-mentholated cigarettes, given its effects over the CNS. Public health professionals should work to address this important problem, to ensure that PLWH quit smoking mentholated cigarettes. This study shows that interventions may benefit from comprehensive health models that incorporate not only anti-smoking messages, but also provides specific information about the risks of mentholated cigarettes. These findings make suggest the importance of revisiting the notion of banning menthol-flavored cigarettes, or at least the need to educate individuals of the possibility of additional health threats.

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