Brief report

Influence of the A118G Polymorphism of the *OPRM1* Gene and Exon 3 VNTR Polymorphism of the *DRD4* Gene on Cigarette Craving After Alcohol Administration

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Abstract

Introduction: The current study examined whether the presence of the G allele of the A118G polymorphism of the *OPRM1* gene (rs1799971) and the long allele of exon 3 VNTR polymorphism of the *DRD4* gene moderate the effect of alcohol administration on urge to smoke. These polymorphisms have been associated with greater alcohol induced-urge to drink. Urge to drink and alcohol consumption increase urge to smoke. Therefore, these polymorphisms may also sensitize urge to smoke after alcohol consumption.

Methods: Individuals smoking 10–30 cigarettes per day and reporting heavy drinking were recruited from the community. Caucasians ($n = 62$), 57.3% male, mean age 39.2, took part in a three-session, within-subjects, repeated-measures design study. Participants were administered a placebo, 0.4 g/kg, or 0.8 g/kg dose of alcohol. A118G genotype, exon 3 VNTR genotype, and urge to smoke (baseline and three times after receiving alcohol) were assessed.

Results: G allele carriers showed greater urge to smoke across all assessments. Additionally, a significant interaction indicated that G carriers, compared to homozygotes (AA), evinced a significantly greater increase in urge to smoke after high dose alcohol relative to placebo. The interaction between condition, *DRD4* polymorphism, and time was not significant.

Conclusions: Presence of G allele of the A118G polymorphism of the *OPRM1* gene may lead to greater increases in urge to smoke after a high dose of alcohol. Pharmacotherapies targeted to opiate receptors (eg, naltrexone) may be especially helpful in aiding smoking cessation among G carriers who are heavy drinkers.

Introduction

Interactions between alcohol use and cigarette smoking have been documented extensively in the literature, both in terms of increased use of alcohol in cigarette using populations,¹⁻⁴ and increased difficulty with smoking cessation in alcohol using populations.⁵⁻⁹ Studies examining temporal precedence within this relationship indicate that alcohol consumption increases the risk of a smoking lapse (ie, any smoking, even a puff) after quitting.¹⁰ Research examining pathways contributing to increased risk for lapse suggest that this risk may be mediated, in part, by urge to smoke.¹¹ Given that a significant portion of smoking lapses lead to relapse,¹²⁻¹⁴ individual differences affecting alcohol's effects on urge to smoke may be important to consider.

One individual factor known to influence risk and course of treatment in addiction is genetic variability.^{15,16} Two genetic polymorphisms have been studied quite extensively in the context of addiction and have been shown to be associated with several alcohol phenotypes: the A118G polymorphism (rs1799971) of the *OPRM1* μ -opioid receptor gene and the exon 3 VNTR polymorphism of the *DRD4* D4 dopamine receptor gene. The frequency of the A118G polymorphism in the general population is approximately 10%,¹⁷ and affects receptor activity by altering binding strength for the endogenous B-endorphin which may result in behavioral differences in responses mediated by B-endorphins.¹⁷ This polymorphism has been associated with greater subjective intoxication, stimulation, sedation, happiness, and urge to drink after exposure to alcohol,¹⁸ and this increased urge to drink may be blunted by μ -opioid receptor antagonist pharmacotherapies (eg, naltrexone),¹⁹ although contrary evidence has been reported.²⁰ Similarly, the exon 3 VNTR polymorphism has also been associated with urge to drink after exposure to alcohol.²¹⁻²³ This polymorphism impacts the length of the protein in the receptor, which in turn alters receptor sensitivity.²⁴ Alcohol-induced drinking urge has been shown to be diminished with the use of pharmacotherapies with D4 antagonist properties (eg, olanzapine), an effect which may be dependent on *DRD4* genotype in some conditions.²⁵ In sum, previous findings suggest that both polymorphisms are associated with increased urge to drink after alcohol consumption.

Few studies have considered the influence of these polymorphisms on smoking urge after drinking. Given that individuals with these polymorphisms evince greater urge to drink after alcohol consumption, they may also be more susceptible to increased urge to smoke after alcohol consumption, given that urge to smoke and urge to drink are often correlated²⁶ and may perhaps have common biological underpinnings.^{16,27} The current study investigated the extent to which these polymorphisms moderate the effects of alcohol consumption on urge to smoke. We hypothesized that individuals carrying the G allele of the A118G polymorphism in the *OPRM1* μ -opioid receptor gene, and individuals carrying the long allele (seven or more repeats) of the *DRD4* VNTR polymorphism, respectively, would demonstrate increased urge to smoke following alcohol consumption, compared to placebo.

Methods

Participants

Full details of procedures used in the current study have been previously outlined.¹¹ Participants were recruited from the community and met the following inclusion criteria: 21–65 years old, use of 10–30 cigarettes daily, carbon monoxide level > 10 ppm, current heavy drinking defined by at least five drinks per occasion for men or at least four drinks for women, at least twice a month, and endorsement of no history or intention to seek alcohol treatment. Exclusion criteria

were: use of other tobacco (other than cigarettes) or nicotine replacement therapy, plan to quit smoking within 30 days, inability to abstain from alcohol for 24 hours without significant withdrawal symptoms, current affective disorder or psychotic symptoms, current pregnancy/nursing, illicit drug use on more than four occasions in the past month, medical issues contraindicated with alcohol, and weight > 250 lbs.

Analyses were limited to the Caucasian subsample ($N = 62$) as a means to reduce the possibility of population stratification. Mean age was 39.2 ($SD = 10.84$), and 57.3% were male. Mean cigarettes per day = 15.8 ($SD = 5.3$), and mean Fagerstrom Test for Cigarette Dependence²⁸ was 5.1 ($SD = 2.0$). Participants drank on 53.1% ($SD = 27.2$) of the 60 days prior to baseline, averaging 6.0 ($SD = 2.5$) drinks per drinking day, and 67% had a history of alcohol dependence (0% met criteria for current alcohol dependence).

Procedure

A repeated-measures design included three counter-balanced sessions (mean days between = 9.23 [$SD = 2.13$]), in which participants received placebo (trace alcohol; glass swabbed with alcohol to provide olfactory cues), 0.4 g/kg, and 0.8 g/kg dose of alcohol (80 proof vodka) (breath alcohol concentration peak mean = 0.036 [$SD = 0.005$] and 0.085 [$SD = 0.02$], respectively). Dose was adjusted for weight, and sex. Participants smoked as they typically would prior to testing and smoked one of their usual brand cigarettes in the laboratory 3 hours prior to beverage consumption in order to standardize time since last cigarette at time of testing and thus induce stronger effects of alcohol on urge to smoke.²⁹ Participants refrained from alcohol use for 24 hours prior to testing, and .000 breath alcohol concentration was confirmed via Alco-Sensor IV (Intoximeters Inc, St Louis, MO). In all conditions, the beverage was divided into three glasses in equal-sized portions; with 5 minutes allowed for drinking each glass, for a total of 15 minutes. Urge to smoke was measured at four time points; 15 minutes prior to beverage consumption, directly after consuming all beverages, 13 minutes after, and 25 minutes after. Urge was measured prior to an incentivized delay to smoking (previously outlined: 11) in order to approximate urge experienced during a quit attempt.

Measures

DSM-IV Axis I diagnoses were determined with the Structured Clinical Interview for DSM-IV Non-Patient Edition.³⁰ Urge to smoke was assessed using the 10-item Brief Questionnaire of Smoking Urges, which utilizes a 7-point Likert scale indicating responses ranging from strongly disagree to strongly agree; total score is the mean of all items.³¹ The Timeline Followback Interview³² was used to assess past 60-day alcohol use.

Genotyping

Genomic DNA was isolated from buccal cells and was genotyped using methods published elsewhere.²² An exact test for Hardy-Weinberg proportions³³ indicates that our genotype frequencies for *OPRM1* and *DRD4* do not differ significantly from Hardy-Weinberg equilibrium: $P = .316$ and $P = .064$, respectively. See Table 1 for genetic descriptives. The current sample included only AG allele carriers of the *OPRM1* gene; no GG carriers were observed.

Analytic Strategy

Generalized estimating equations were used to examine urge to smoke cigarettes across four assessment points, with a normal distribution specified, and an exchangeable working correlation matrix.

Table 1. Genetic Frequencies and Tests of Group Differences

	OPRM1 (AA homozygotes)	OPRM1 (AG allele carriers)	<i>t</i>	<i>P</i>
<i>n</i>	48	14		
Gender (male) (<i>n</i>)	43.8% (21)	42.9% (6)	0.058	.954
Past alcohol dependence (<i>n</i>)	60.3% (30)	71.4% (10)	1.341	.184
Drinks per drinking day	5.97 (<i>SD</i> = 2.7)	5.36 (<i>SD</i> = 2.6)	0.844	.402
FTCD	5.12 (<i>SD</i> = 1.97)	4.85 (<i>SD</i> = 2.41)	0.424	.673

	DRD4 (short allele)	DRD4 (long allele)	<i>t</i>	<i>P</i>
<i>n</i>	46	14		
Gender (male) (<i>n</i>)	43.5% (20)	42.9% (6)	0.040	.968
Past alcohol dependence (<i>n</i>)	67.4% (31)	57.1% (8)	0.695	.490
Drinks per drinking day	5.78 (<i>SD</i> = 2.4)	3.08 (<i>SD</i> = 2.2)	0.418	.678
FTCD	5.26 (<i>SD</i> = 1.9)	4.5 (<i>SD</i> = 2.6)	1.195	.237

FTCD = Fagerstrom Test for Cigarette Dependence.

Two separate models containing five components were tested (labeled below); one model for each gene. First, main effects were examined, followed by an omnibus test of the three-way interaction, followed by dummy coded three-way interactions. The independent variables for the models were (1) genotype (G allele carriers vs. AA homozygotes) or (long allele carriers [seven or more repeats] vs. short allele homozygotes), (2) condition (within-subjects effect: placebo, low, or high alcohol, dummy coded with placebo as the reference group [0]), and (3) time (within-subjects effect: [four time points, coded as a linear effect: 0,1,2,3]), as well as (4) the four two-way interactions (gene by time, low dose by polymorphism, high dose by polymorphism, low dose by time, and high dose by time) and (5) the two three-way interactions (low dose by time by polymorphism, and high dose by time by polymorphism). We predicted a three-way interaction between beverage condition, genotype, and time on reported urge to smoke; reflecting that carriers of the G allele or long allele carriers would demonstrate more rapid increases in urge to smoke following a low or high alcohol dose compared to placebo. Session number was not associated with any outcomes of interest and was therefore dropped from all analyses. Centering was not necessary for the current data.

Results

First, we examined main effects and the two-way interaction between beverage condition and time. As graphed in Kahler et al.,¹¹ a significant main effect for time indicated that cravings increased as time progressed, $B = 0.127$, standard error (*SE*) = 0.032, 95% confidence interval (*CI*) = 0.064, 0.190, $P < .001$. A significant main effect for the *OPRM1* gene showed that the presence, versus absence, of the G allele was associated with greater urge to smoke overall, $B = 0.903$, $SE = 0.340$, 95% *CI* = 0.235, 1.571, $P = .008$. The main effect for exon 3 VNTR and the main effect for beverage condition were nonsignificant. The time by beverage condition interaction, for each alcohol dose compared to placebo was also nonsignificant.

Next, we conducted an omnibus test for the three-way interactions (dose by time by gene) for each gene. We observed a significant effect, $\chi^2 = 10.02$, $P = .007$, for the *OPRM1* gene. Effects for the *DRD4* gene were nonsignificant. Therefore, we conducted follow-up analyses for the *OPRM1* gene only. The interaction between time and G allele polymorphism differed significantly between high alcohol dose versus placebo, $B = 0.304$, $SE = 0.103$, 95% *CI* = 0.102, 0.506, $P = .003$; indicating that the increase in urge to smoke over time following high dose alcohol was steeper for G allele carriers versus AA

homozygotes. The three-way interaction between genotype, time, and low dose alcohol versus placebo was in the same direction but was just above traditional significance levels, $B = 0.172$, $SE = 0.089$, 95% *CI* = -0.003, 0.347, $P = .054$. Taken together, results indicate that for individuals carrying the G allele, the effect of time on urge to smoke became progressively steeper from placebo to low dose to high dose conditions, $B = 0.06$ (95% *CI* = -0.04, 0.17), 0.24 (95% *CI* = 0.01, 0.45), and 0.34 (95% *CI* = 0.19, 0.48), respectively, suggesting a possible dose-dependent association (Figure 1). For individuals without the G allele, the effect of time was relatively constant between conditions, $B = 0.09$ (0.00, 0.19), 0.09 (0.00, 0.18), 0.06 (-0.05, 0.19), respectively, suggesting little effect of alcohol on urge to smoke.

Discussion

The current study found that G allele carriers experience greater urge to smoke independently of alcohol consumption, and that they may be more sensitive to the pharmacological effects of alcohol on urge to smoke. Contrary to our hypothesis, the *DRD4* exon 3 VNTR polymorphism did not appear to influence urge to smoke prior to or following alcohol administration. This is the first study to our knowledge to examine the influence of these polymorphisms on urge to smoke after alcohol consumption.

This study extends previous literature indicating a link between alcohol use and G allele carriers^{18,22,34-36} by demonstrating a link between alcohol use and increased urge to smoke in G allele carriers. Moreover, this study lends theoretical support to findings which suggest that opioidergic activity may be particularly important in decreasing vulnerability to smoking lapse after alcohol consumption.³⁷ Given that *OPRM1* moderates naltrexone's effect on alcohol induced urge to drink,¹⁹ it may be likely to do the same for alcohol-induced urge to smoke, and thus be particularly beneficial for G allele carriers.

The current results should be considered in light of several limitations. First, candidate gene studies are quasi-experimental in design and thus associations may be driven by unmeasured third variables including other genetic variants in linkage disequilibrium with the assayed polymorphisms, or population stratification. Furthermore candidate gene studies generally require replication samples, or, at a minimum, a strong biological rationale to justify the analyses. The A118G polymorphism and the exon 3 VNTR polymorphism have been previously associated with increased urge to drink in several studies,^{18,21} thus many problems commonly cited with interpretation of candidate gene analysis may be tempered. Additionally, due to

Figure 1. G allele carriers versus A Homozygotes on cigarette craving over time by condition with standard error bars and (Cohen's *d*).

variation in haplotype frequency within the genotypes examined in the current study, the sample was restricted to Caucasian individuals; therefore, generalizability of these results may be limited and cannot be assumed to generalize to non-Caucasians.

In conclusion, the current results highlight the important of the μ -opiate receptor in urge to smoke after alcohol administration. Modulated dopamine transmission via μ -opiate receptor activation may be an important common mechanism in observed increases in urge to drink and urge to smoke after alcohol consumption. Future studies should examine the potential for naltrexone to have increased therapeutic value for G allele carriers in terms of reducing urge to smoke after alcohol consumption.

Funding

This study was funded by the National Institute on Alcohol Abuse and Alcoholism, grant R01AA016978 to CWK, by a Senior Research Career Scientist award from the Department of Veterans Affairs to DJR, a shared equipment grant (S10RR023457) from the National Center for Research Resources and US Department of Veteran Affairs shared equipment program to JEM and by National Institute on Drug Abuse grant K08-DA029094 to NSS. The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs.

Declaration of Interests

None declared.

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