Published in final edited form as:
Alcohol. 2010 August ; 44(5): 401–406. doi:10.1016/j.alcohol.2010.05.008.

Relationship between the Serotonin Transporter Polymorphism and Obsessive-Compulsive Alcohol Craving in Alcohol Dependent Adults: A Pilot Study

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Abstract

A serotonin deficiency state has been implicated in alcohol dependent individuals' experience of obsessive-compulsive alcohol craving. Because the serotonin transporter functions to remove serotonin from the synapse, it is thought that increased re-uptake (indicated by the number of high-expressing L_A alleles present in the 5-HTT gene-linked polymorphic region [5-HTTLPR] of the SLC6A4 gene) is associated with an increase in obsessive-compulsive alcohol craving. The current pilot investigation sought to explore this hypothesis by examining the extent to which obsessive-compulsive alcohol craving varies by 5-HTTLPR genotype among participants enrolled in an ongoing pharmacogenetics trial. All participants were screened with a semi-structured diagnostic interview, completed self-report measures of alcohol-related behavior, and underwent peripheral venous blood draw for DNA genotyping. Cross-sectional data obtained at baseline from 176 currently drinking, alcohol dependent individuals were analyzed using multiple regression. Preliminary findings suggest that 5-HTTLPR is not predictive of Obsessive Compulsive Drinking Scale total and factor scores. Although the 5-HTTLPR polymorphism was not related to obsessive-compulsive alcohol craving in this pilot study, additional research is needed to clarify the possible role of serotonergic mechanisms in alcohol craving.

Keywords

5-HTTLPR; serotonin transporter; craving; obsession; compulsion; alcohol dependence

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Disclosures: Drs. Heffner, Strong, Ms. Thompson, and Mr. Blom have no financial disclosures to make. Dr. Anthenelli provides consultant, advisory, and/or speakers' bureau services to Sanofi-Aventis and Pfizer. The Tri-State Tobacco and Alcohol Research Center receives research support from Lilly, Nabi Biopharmaceuticals and Pfizer.

Introduction

Alcohol dependence (AD) remains a highly prevalent and disabling condition. Recent results from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) estimate the prevalence of lifetime AD to be 12.5% and show significant associations of AD with impairment in mental health, social and role functioning (Hasin et al., 2007). A complex interplay between genetic and environmental influences has been implicated in the etiology of AD. Estimates of heritability suggest that between 40% and 60% of the variance associated with AD may be accounted for by genetic influences (Lin and Anthenelli, 2005). As a result, research has increasingly sought to uncover the genetic factors that might serve as biomarkers of AD vulnerability, severity and treatment response. This is a critical area of investigation because it holds much promise in helping the field to move toward targeted or individualized AD treatment approaches.

Obsessive-Compulsive Alcohol Craving

Alcohol craving has been identified as an important construct in phenomenological models of AD (Lowman et al., 2000) and is frequently related to relapse or alcohol-related treatment outcomes (e.g., Bottlender, and Soyka, 2004, 2005). One formulation of alcohol craving has been derived from the literature on obsessive-compulsive disorder (OCD) due to similarities between the cognitive and behavioral patterns of individuals with AD and OCD (Modell et al., 1992). Obsessive-compulsive alcohol craving is characterized by a loss of control over intrusive thoughts, compulsive drinking and difficulties resisting thoughts and compulsions to use alcohol. This construct is commonly measured among AD individuals because of its relationship with concurrent drinking patterns and alcoholism severity (e.g., Moak et al., 1998; Roberts et al., 1999). Among the candidate neurotransmitter systems that have been linked to obsessive-compulsive alcohol craving, a serotonin deficiency state has been postulated to account for AD individuals' undercontrol of intrusive alcohol-related thoughts and inability to restrain impulses to engage in drinking behaviors (Anton, 1999; Verheul et al., 1999). Surprisingly, a limited amount of research has actually investigated the role of serotonergic mechanisms in obsessive-compulsive alcohol craving among AD individuals, and the influence of genetic factors on the relationship between serotonergic systems and obsessive-compulsive craving has been particularly understudied. Given that the upcoming diagnostic revisions proposed for substance use disorders in DSM-V specify craving as a key component of addictive behavior (American Psychiatric Association, 2010), understanding the biological underpinnings that may impact one's experience of alcohol craving is of timely importance.

Serotonin Transporter Gene-Linked Polymorphic Region

The serotonin transporter (5-HTT) has received much attention as a marker for AD risk because of evidence supporting a relationship between serotonergic function and alcohol consumption (Feinn et al., 2005). 5-HTT functions to remove serotonin from the synapse, which influences serotonin's availability at post-synaptic receptors. A deletion/insertion polymorphism (5-HTTLPR) in the 5′ flanking regulatory region of the *SLC6A4* gene yields differential expression of 5-HTT. The homozygous long allelic variant (L/L) of this polymorphism is linked to increased pre-synaptic 5-HTT number and functionality, resulting in more efficient serotonin reuptake and reductions in synaptic serotonin levels, as compared to the short (S/S) and heterozygous variants (S/L) (Heils et al., 1996; Greenberg et al., 1999). However, more recent literature also suggests that 5-HTTLPR may be functionally triallelic rather than biallelic, with a single nucleotide polymorphism (SNP) in the 5-HTTLPR regulatory region resulting in two variants of the L allele (L_A and L_G; Parsey et al., 2006; Wendland et al., 2006). The functional effects of this SNP are that the L_G allele behaves similar to the lower-functioning S allele, whereas the L_A allele is associated with greater 5-HTT transcription (Wendland et al., 2006).

5-HTTLPR and Alcohol Seeking Behavior

Because decreased serotonergic neurotransmission has been linked to increased alcohol consumption (Le Marquand et al., 1994; Johnson, 2000), it has been hypothesized that individuals with the L/L genotype should be at greatest risk for AD susceptibility and obsessive-compulsive craving as a result of increased 5-HTT action and consequent decreased synaptic 5-HT availability. Only one published study to date has examined the relationship between 5-HTTLPR and obsessive-compulsive alcohol craving and found evidence linking the L allele to increased experience of compulsive alcohol craving among AD men entering detoxification (Bleich et al., 2007). This finding is not surprising given the body of literature that supports a connection between 5-HTTLPR L allele frequency and obsessive-compulsive symptomatology (Bloch et al., 2008; Hu et al., 2006). However, the results were limited by their use of biallelic genotyping and an all male, inpatient sample. In the current pilot, we evaluated the relationship between 5-HTTLPR and obsessive-compulsive alcohol craving in a more diverse sample of men and women seeking outpatient treatment for mild to moderate AD, capitalizing on recent advances in the genotyping of 5-HTTLPR to more precisely characterize the sample by genotype. The overall objective of this exploratory study is to evaluate the extent to which 5-HTTLPR genotype may be related to individuals' experience of obsessive-compulsive alcohol craving and to obtain preliminary information regarding the strength of this association through effect size estimation. We hypothesized that the number of high-expressing L_A alleles would predict participants' experience of obsessive-compulsive alcohol craving, with increased frequencies (i.e., L_A/L_A) being associated with a significant increase in craving.

Method

Participants

One hundred and seventy-six participants (61% male, 39% female) were recruited from the community via newspaper, radio, and television advertisements to participate in an ongoing pharmacogenetics trial investigating the efficacy of a selective serotonin reuptake inhibitor (SSRI), citalopram, in the treatment of AD (ClinicalTrials.gov Identifier: NCT00249405). All participants underwent diagnostic and medical screenings in order to determine eligibility for study involvement. The Semi-Structured Assessment for the Genetics of Alcoholism – II (SSAGA-II; Bucholz et al., 1994) was completed by a trained rater in order to assess participants for the presence of Axis I psychopathology. The SSAGA has been shown to be both a reliable and valid clinical diagnostic tool with utility in discriminating between substance-induced and independent psychiatric comorbidities (Bucholz et al., 1994; Hesselbrock et al., 1999). Individuals were able to participate if they were between 21 and 65 years of age, met DSM-IV criteria for AD and expressed a desire to quit or significantly reduce their alcohol consumption. Individuals were excluded if they met diagnostic criteria for a current Axis I psychiatric condition other than nicotine dependence or an alcohol-induced disorder, showed any clinically significant laboratory evidence of medical illness, or presented with a history of seizure disorder or severe alcohol withdrawal. For more detailed information on study design and methods, see Heffner et al. (2010). Participation was voluntary and participants gave written informed consent prior to their study involvement. All study procedures were implemented in accordance with the ethical standards for conducting research on human subjects as stipulated by the local Institutional Review Board and with the Helsinki Declaration of 1975 (as revised in 1983).

Measures

Each participant completed baseline measures of alcohol-related behavior before initiating SSRI or placebo treatment. The Alcohol Dependence Scale (ADS; Skinner and Allen, 1982) is a 25-item questionnaire measuring AD severity over the past year. The Alcohol Time-Line

Followback (TLFB; Sobell and Sobell, 2003) was administered by a trained rater to obtain a retrospective estimate of daily drinking quantity over the 90 days prior to screening using a calendar-based form. The Obsessive Compulsive Drinking Scale (OCDS) is a 14-item measure of alcohol craving over the past week, with higher scores suggestive of increased intrusive thoughts, strong urges to use and difficulties resisting or controlling alcohol-related thoughts and behaviors. Reliability and validity studies have demonstrated high levels of test-retest reliability, internal consistency, content and criterion validity (Anton et al., 1995; Roberts et al., 1999). Results from factor analytic studies on the OCDS, however, have been somewhat mixed (e.g., Bohn et al., 1996; Kranzler et al., 1999; Roberts et al., 1999). Based on our review of the literature, the factors reported by Roberts et al. (1999; i.e., a 3-factor solution reflecting resistance/control impairment [RCI], obsession, and interference), along with the OCDS total score, served as the criterion variables in the main regression analyses.

DNA Analysis

Genomic DNA was extracted from peripheral venous blood. The genotyping protocol for the S/L polymorphism was based on a report by Kaiser et al. (2002), (see also Yonan et al., 2006): to avoid genotyping errors due to Mg^{2+}-sensitive unequal amplification of the L and S alleles, we amplified using Expand Long-template polymerase (Roche) and 7-deaza-dGTP (Roche; substituted for ½ of the GTP), and found that the resulting genotypes were stable over a range of Mg^{2+} concentrations. Genomic DNA was amplified (36 cycles of 95°C: 30 s., 62° C: 30 s., and 72°C: 1 min with final extension of 7 min at 72°C) using a Mg^{2+} concentration of 1.75 mM, forward primers GGC GTT GCC GCT CTG AAT GC, and reverse primer GAG GGA CTG AGC TGG ACA ACC AC. Products were resolved by agarose gel electrophoresis.

The more recently described functional SNP (rs25531) within the L/S promoter polymorphism was genotyped by a modification of the method described by Wendland et al. (2006). DNA was amplified using the primers TCC TCC GCT TTG GCG CCT CTT CC (forward) and TGG GGG TTG CAG GGG AGA TCC TG (reverse), with Expand long template polymerase, 3 mM Mg^{2+}, and without the 7-deaza-dGTP substitution. Thermal cycling protocol was 15 min at 95°C followed by 35 cycles of 94°C (30 s), 65.5°C (90 s) and 72°C (60 s) each, with a final extension step of 10 min at 72°C. Predicted products of 512 bp (L) and 469 bp (S) were in agreement with the initially determined genotypes and were stable over a range of Mg^{2+} concentrations. The PCR product was purified with a Qiagen Minelute PCR product purification kit (Qiagen, Valencia, CA, USA) and digested with restriction enzyme HpaII (New England Biolabs, Ipswich, MA, USA) for 3 hours at 37°C. The G allele introduces a new HpaII site; the larger predicted HpaII product (using these primers) is 400 bp from either the S or L allele.

Statistical Analysis

Genotypes were assessed for deviation from the Hardy-Weinberg equilibrium using a chi-square test. One-way ANOVAs and chi-square analyses were conducted to test for differences among the genotype groups on demographic and clinical characteristics. Any variables that illustrated significant differences between groups were considered for use as a covariate in the main study analyses. Study hypotheses were tested in SPSS 17.0 using four multiple regression analyses. The number of L_A alleles present in the 5-HTTLPR genotype (0, 1 or 2) served as the predictor variable, while OCDS total and factors scores (i.e., RCI, obsession and interference) were the criterion variables. Age was entered as a covariate in the first step of the regression models in order to control for potential cohort effects. A power analysis was performed to determine what effect size could be detected when testing the null hypothesis ($\beta = 0$) in the four regression analyses. Using our sample of N = 176, a significance level of $\alpha = 0.05$ and a power of 80%, the resulting detectable effect size was approximately 0.20. The power analysis was conducted using nQuery Advisor 4.0.

In a series of additional exploratory analyses, we first repeated the four multiple regressions to predict OCDS total and factor scores after limiting the sample to individuals of European descent (n =153). This was done to reduce the possibility that racial effects on allele frequency (i.e., population stratification) might confound results. Second, consistent with other studies (e.g., Ait-Daoud et al., 2009), we further probed the association in the entire sample by conducting the analyses with 5-HTTLPR genotype dichotomized by L_A carrier status. The analyses were conducted using two different dichotomization groupings to determine whether the method of genotype classification would affect the results: (1) homozygous L_A individuals versus all other genotypes and (2) L_A carriers versus non-carriers.

Results

Findings from the preliminary data analyses are reported in Table 1. No significant differences emerged between 5-HTTLPR subgroups on demographic or clinical characteristics. Differences among groups on the ADS trended toward significance (p = .06), with the L_A homozygotes having the highest scores. Observed 5-HTTLPR genotype frequencies did not deviate from Hardy-Weinberg equilibrium (χ^2 = .83, p = .55). Observed n values of the allele variants were L_A = 188, L_G = 22 and S = 142.

Contrary to study hypotheses, results indicated that the triallelic 5-HTTLPR genotype did not predict OCDS total score or any of the three factor scores (see Table 2). With the exception of younger age predicting a higher OCDS obsessive factor score (t (173) = −2.10, p = .04), age was not significantly related to alcohol craving. When we conducted these same four multiple regression analyses in a Caucasian sample limited to individuals of European descent, the only change in the pattern of results was that age was no longer a significant predictor of the OCDS obsessive factor score (p = .12). Results from the second set of exploratory regression analyses further confirmed these findings, showing no significant relationship between L_A carrier status on OCDS total and factor scores (p-values ranged between .14 and .99).

Discussion

The present study is the first investigation to utilize triallelic genotyping methods to examine the association between 5-HTTLPR genotype and obsessive-compulsive alcohol craving in a pilot sample of treatment-seeking men and women with AD. Results from the regression analyses revealed that the number of high-expressing L_A alleles in the 5-HTTLPR genotype was not related to obsessive-compulsive alcohol craving, with effect size estimates suggestive of a negligible impact. Our preliminary findings are discrepant with those of the only other study to date that has examined this association, the results of which provided evidence for a significant relationship between L allele frequency and compulsive alcohol craving upon admission to alcohol detoxification (Bleich et al., 2007). However, the authors of the Bleich study also reported only a trend towards significance when this association was tested after one week of treatment. Thus, the pattern of findings across the Bleich et al. (2007) study and the present investigation may be attributable to the level of intoxication of the participants at the time that alcohol craving was assessed, as our sample showed relatively higher OCDS total scores and breathalyzer levels not suggestive of current intoxication.

The lack of support for the hypothesized relationship between 5-HTTLPR genotype and obsessive-compulsive alcohol craving may, in part, also be due to sample size and demographic characteristics. Power analysis indicated that the sample size was adequate to detect an approximate effect size of .20 with 80% power. Though the sample was relatively homogeneous with regard to race and age (i.e., predominately white and middle-aged), it was heterogeneous due to the inclusion of both males and females falling within a wider range of AD severity. Taken together, such a sample might have resulted in lower power to detect a

meaningful effect of 5-HTTLPR on obsessive-compulsive craving, thus the current pilot should not be interpreted as a conclusive test of the proposed hypothesis.

Future investigations may need a much larger, more homogeneous sample to detect what is likely a modest relationship between a single polymorphism in one neurotransmitter system and the complex phenomenon of alcohol craving. Since genetic mechanisms and phenotypic expression of alcohol craving may relate differently across different alcoholic subtypes and classes of individuals, these sample characteristics are important to consider when interpreting study findings. Examining the relative impact of duration of problematic drinking behavior may also be a fruitful avenue of future research, as prior investigations have shown that the environmental effects of years of problematic drinking may interact with 5-HTTLPR genotype to predict functional 5-HT neurotransmission differences (Ait-Daoud et al., 2009). Individuals with comorbid major depression and alcohol dependence may also represent a specific subgroup particularly vulnerable to experiencing alcohol craving as a result of 5-HT dysregulation (Pierucci-Lagha, 2003).

Acknowledgments

This work was supported by National Institute on Alcohol Abuse and Alcoholism (NIAAA) grant award #AA013957. The writing of this manuscript was supported, in part, by NIAAA grant award #R01AA013307, NIDA/VA CSP #1022, NIDA grant award #026517, and by the Department of Veterans Affairs Research Service.

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Table 1

Demographic and Clinical Characteristics by 5-HTTLPR Polymorphism

	2 L_A (*n* = 46)	1 L_A (*n* = 96)	No L_A (*n* = 34)	*p*-value
Age (years)	49.1 (8.5)	47.1 (8.9)	45.7 (8.7)	0.22
Male	26 (57%)	62 (65%)	20 (59%)	0.62
Caucasian	41 (89%)	85 (89%)	27 (79%)	0.35
Age of AD Onset (years)	34.1 (9.4)	34.1 (9.9)	35.7 (10.0)	0.69
Daily alcohol intake (standard drinks)[a]	4.7 (3.1)	5.1 (3.5)	4.5 (2.8)	0.65
ADS	16.1 (7.6)	13.5 (6.1)	13.1 (6.0)	0.06
OCDS[b]				
RCI	12.2 (4.6)	12.2 (3.6)	12.1 (3.8)	0.99
Obsession	7.8 (3.3)	7.3 (2.7)	7.1 (2.6)	0.43
Interference	2.6 (2.6)	2.6 (1.9)	2.6 (1.7)	0.99
Total	22.6 (9.1)	22.0 (6.6)	21.7 (6.1)	0.85
Substance-related diagnoses				
Alcohol-induced mood disorder	10 (22%)	15 (16%)	5 (15%)	0.61
Nicotine dependence	23 (50%)	44 (46%)	13 (38%)	0.58
Cannabis abuse or dependence (lifetime)	10 (22%)	19 (20%)	5 (15%)	0.72
Other drug abuse or dependence (lifetime)	4 (9%)	5 (5%)	5 (15%)	0.21

Note. Values in the table reflect *M (SD)* or no. (%), and *p*-values are based on results from ANOVA or chi-square tests. ADS: Alcohol Dependence Scale; OCDS: Obsessive Compulsive Drinking Scale; RCI: Resistance/control impairment subscale.

[a] Based on amount of alcohol consumed 14 days prior to screening.

[b] OCDS factors reflect 3-factor structural solution reported by Roberts et al. (1999).

Table 2

Prediction of OCDS Factor and Total Scores by 5-HTTLPR Genotype

	R^2 Change	Beta	t	*p*-value
Resistance/control impairment	.00	0.00	0.02	.98
Obsession	.01	0.12	1.52	.13
Interference	.00	0.02	0.21	.84
Total Score	.00	0.05	0.67	.51

Note. Age was entered as a covariate in the first step of the regression analyses. R^2 change values reflect the variance accounted for by the frequency of L_A alleles expressed, as entered in the second step. Reported Beta, *t* and *p*-values reflect the main effects of the 5-HTTLPR polymorphism in the hierarchical regression models.