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BRIEF REPORT

Effects of Citalopram on Cue-Induced Alcohol Craving and Thalamic D_{2/3} Dopamine Receptor Availability

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Abstract

Background: Selective serotonin reuptake inhibitors are often used in alcohol use disorders. Clinical trials with selective serotonin reuptake inhibitors for alcohol use disorders, however, have yielded mixed results. The goal of this project was to assess whether a single i.v. dose of a selective serotonin reuptake inhibitor reduces craving for alcohol and/or simultaneously increases striatal dopamine concentration in individuals with alcohol dependence.

Methods: Alcohol-dependent (DSM-IV-TR criteria) volunteers and matched controls (n = 10/group) underwent a double-blind, placebo-controlled, within-subjects study. Participants received i.v. citalopram (40 mg) or saline (counter-balanced) followed by a cue-induced craving assessment and [¹⁸F]-fallypride positron emission tomography scanning.

Results: In the alcohol-dependent individuals, the citalopram (compared with saline) resulted in decreased cue-induced craving for alcohol. For the whole study group, cue-induced alcohol craving was inversely correlated with thalamic (but not striatal) dopamine D_{2/3} receptor availability.

Conclusions: Acute serotonin reuptake inhibition reduces cue-induced alcohol craving. Furthermore, thalamic dopamine abnormalities and the striatal hyperdopaminergic hypothesis of alcohol use disorder are supported.

Keywords: citalopram, antidepressant, alcohol, PET, craving

Introduction

Misuse of alcohol is a major global public health issue. Alcohol misuse remains extremely common in the United States, where it is estimated that roughly 6.4% of the population age 12 years or older meets criteria for alcohol use disorder (NSDUH, 2015), and alcohol misuse results in roughly 88 000 deaths per year

(including alcohol-related motor vehicle accidents) (Stahre et al., 2014).

Alcohol use disorders are frequently comorbid with depressive symptoms in psychiatric clinical populations, and the combination results in an increased severity of both conditions,

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including an increased risk for suicidality (reviewed in Nunes and Levin, 2004). Human and animal data have provided ample justification to test antidepressants in clinical trials for alcohol use disorders with (and without) comorbid depressive symptoms; however, results from these studies have been disappointing, especially with regard to continued alcohol use (Nunes and Levin, 2004; Kenna, 2010).

Citalopram, a highly selective selective serotonin reuptake inhibitor (SSRI), has been used clinically since 1989, is available in generic formulations, and is FDA-approved for the treatment of major depressive disorder (Bezchlibnyk-Butler et al., 2000). The i.v. administration of serotonergic agents has been studied as a means to speed the time needed to remit depressive symptoms in patients with major depressive disorder (reviewed in Moukaddam and Hirschfeld, 2004).

In alcohol-dependent (AD) participants, visual and olfactory cues reliably increase craving in a manner that is sensitive to pharmacological and environmental manipulation (Ray et al., 2007). Cue-induced craving accompanies increased blood flow, specifically in the nucleus accumbens/ventral striatum in AD individuals, as an indirect measure of increased dopamine signaling, and this cue-induced craving is associated with lower baseline levels of dopamine $D_{2/3}$ receptor availability (Heinz et al., 2004, 2005). Additionally, AD individuals, on average, have been shown to have lower striatal dopamine receptor $D_{2/3}$ receptor availability than control participants, as measured with positron emission tomography (PET) and the dopamine $D_{2/3}$ receptor radioligand [^{18}F]-desmethoxyfallypride (Heinz et al., 2004).

Chronic oral citalopram (20 mg/d for 14 days) results in decreased striatal dopamine receptor binding potential compared with placebo (using PET scanning and the dopamine $D_{2/3}$ receptor ligand [^{11}C]-raclopride), an indication of increased intrasynaptic dopamine concentration, but a single dose of oral citalopram has not been shown to affect striatal dopamine binding potential (Tiihonen et al., 1996). A single i.v. infusion of citalopram (40 mg) decreased dopamine $D_{2/3}$ receptor binding potential in the human striatum to a degree comparable with that seen in the earlier study of chronic oral citalopram dosing (Tiihonen et al., 1996; Smith et al., 2009). Therefore, we chose to study single-dose i.v. citalopram administration to test for SSRI-induced changes in cue-induced craving for alcohol and concomitant dopamine signaling in subcortical regions in AD research participants compared with matched healthy non-drinking control participants.

METHODS

Overview of Study Procedures

All procedures were approved by the Veterans Administration Greater Los Angeles institutional review board. Participants were enrolled and screened on the first visit. Qualifying participants were invited back for 3 subsequent visits: a structural MRI scan and 2 study medication/[^{18}F]-fallypride PET scanning days (citalopram 40 mg i.v., or saline placebo, double-blinded, administered in counter-balancing order) more than 1 week apart. All completing participants had breathalyzer-confirmed exhaled alcohol concentration of 0 and alcohol withdrawal scores (confirming no intoxication and minimal alcohol withdrawal symptoms) on all study visits (Clinical Institute Withdrawal Assessment for Alcohol [CIWA] < 10). On study medication/PET scanning days, the following procedures were completed in order: (1) breathalyzer, withdrawal, and psychiatric symptomatology screening; (2) i.v. citalopram (or saline placebo) infusion

(1 hour); (3) cue-induced craving assessment (approximately 20 minutes); and (4) [^{18}F]-fallypride PET scanning (approximately 3 hours). Smoking was allowed during study days but proscribed for 2 hours prior to PET scanning.

Research Participants

AD and healthy control (HC) participants were screened via the SCID-IV, excluding any participants with any Axis I psychiatric diagnosis within the last 6 months (aside from nicotine dependence in both groups and alcohol dependence in the AD group). Fourteen potential AD and 17 potential HC participants were enrolled and screened. Ten participants in each group completed the study. Alcohol dependence in potential participants was confirmed using the SCID-IV diagnostic criteria. AD participants were active drinkers with no history of complicated alcohol withdrawal symptoms who agreed to stop drinking by 6:00 PM on the day prior to all study procedure days; significant alcohol withdrawal symptoms on study procedure days (CIWA > 10) was exclusionary. Inclusion criteria included age 21 to 55 years and no recent use (last 30 days) of any psychoactive medications. All participants had a normal physical exam, EKG, and laboratory studies, along with negative alcohol breathalyzer and saliva toxicology screens for opiates, benzodiazepines, amphetamine, cocaine, and cannabinoids on study days. Of the participants who completed the study, 7 AD and 6 HC participants had analyzable PET scan data due to technical PET scanning issues (PET scanner malfunction or radiosynthesis failure).

Assessments

Baseline rating scales included the Beck Depression Inventory-II to test for current depression/suicidality (Beck and Steer, 1996) and the CIWA (Sullivan et al., 1989; score < 10 needed on all study days to ensure safe participation). Recent (last 90 days) average alcohol intake was assessed using the Timeline Follow Back assessment (Sobell et al., 1996). Craving for alcohol was assessed using the Alcohol Urge Questionnaire (AUQ) (MacKillop, 2006).

Intravenous Citalopram Infusions

Intravenous citalopram (Seropram) was provided by Lundbeck (Copenhagen, Denmark). On infusion days, participants received 40 mg i.v. citalopram or saline placebo in a double-blinded manner, followed by the assessments described below. Citalopram and counter-balanced saline placebo was infused in 250 mL of normal saline over 1 hour by infusion pump on separate scanning days. Two to 3 hours after the infusion was completed, participants underwent PET scanning. PET scans were acquired after administration of 5 mCi of [^{18}F]-fallypride, in two 80-minute blocks separated by a 20-minute break. The mean (SD) dose of [^{18}F]-fallypride received by participants was 4.96 (0.20) mCi. Participants returned at least 1 week later to complete the second infusion/PET scan, counter-balanced. They completed the study after the second infusion/PET scan day.

Cue-Induced Craving Assessment

Cue reactivity was assessed after each of the intravenous infusions (i.e., citalopram 40 mg or saline control) and followed standardized procedures as described (Monti et al., 1987; Ray et al., 2007). After each period, craving was assessed using the AUQ. The mean of the 3 AUQ determinations was used as a covariate in further data analysis to compare with PET results. Craving scores were assessed by repeated-measures ANOVA.

MRI and PET Scans and Analyses

Details of research structural MRI scans (acquired on a 3-T Siemens tomograph) and [¹⁸F]-fallypride (approximately 5 mCi) PET scans have been described previously (Okita et al., 2016a). [¹⁸F]-fallypride was synthesized in the cyclotron facility of the VA by procedures described previously (Lee et al., 2009), supported by an Investigational New Drug application (no. 78 226) from the FDA. Each batch of radiotracer was tested for quality control, including radiochemical purity, specific activity, and apyrogenicity. All complete scans were analyzed for all subjects, with the result being that no partially completed studies (e.g., having only one PET scan for a given subject) were available.

PET Volume of Interest (VOI) and Whole-Brain Voxelwise Analysis

Reconstructed PET data were automatically segmented into standardized subcortical VOIs, and VOI binding potential (BP_{ND}) was estimated using the simplified reference tissue modeling with the cerebellum as the reference region via PMOD Kinetic Modeling (PMOD Technologies Ltd., Zurich, Switzerland) (see Okita et al., 2016a, 2016b for more detail). VOIs were established for the following brain regions: striatum (caudate nucleus, putamen, and nucleus accumbens as separate VOIs), amygdala, hippocampus, globus pallidus, and thalamus.

Correlation analyses for region-specific dopamine D_{2/3} receptor BP_{ND} and mean cue-induced craving were done using Spearman rank coefficient testing. A further test of the association between cue-induced craving and regional BP_{ND} (group × BP_{ND} interaction) was conducted with a whole-brain voxelwise analyses. Voxelwise parcellation of BP_{ND} estimation was done using FSL. ANOVA for effect of craving and group was done using SPM12 (Friston, 2007). All whole-brain voxelwise BP_{ND} statistics were computed with a voxel height threshold of $F = 86.5$ ($P < .0001$), minimum cluster size of $n = 20$ voxels, and family-wise error correction of $P < .0001$ for correction for multiple comparisons.

RESULTS

Demographics

The AD and HC groups did not differ in mean age (38 [7.6] vs 41 [7.9] years, $P = .38$), sex distribution (8/10 vs 5/10 males, $P = 0.44$), fraction of ethnically white individuals (5/10 vs 4/10, $P = .52$), years education (12.9 [1.5] vs 13.8 [1.4], $P = .2$), or intake Beck Depression Inventory (9.5 [8.1] vs. 3.9 [4.2], $P = .08$). Therefore,

subsequent analyses were not adjusted for demographic or clinical variables that did not differ between study groups. Seven AD participants but none of the HC participants were current smokers (though 7 of the HC group were former smokers; $P = .003$). Current smoking and AD status were highly collinear, as smoking is highly prevalent in individuals with alcohol dependence; therefore, smoking status was excluded from subsequent analysis (Grant et al., 2004). AD participants reported consuming 6.9 (2.3) drinks per day on average in the 90 days prior to study entry, whereas HC participants reported consuming 0.1 (0.14) drink per day ($P < .0001$).

Cue-Induced Alcohol Craving: Effect of i.v. Citalopram

Cue-induced alcohol craving was decreased by a single infusion of i.v. citalopram compared with saline placebo in AD participants ($P = .003$). Notably, there was a low baseline level of cue-induced craving for alcohol in HC participants, and it tended to decrease with i.v. citalopram as well, compared with saline placebo ($P = .06$). There was no group × citalopram interaction ($F_{(1,17)} = 1.28$; $P = .27$).

Thalamic Dopamine D_{2/3} BP_{ND} Levels in AD Participants

Using ANOVA, there was a strong trend to decreased thalamic (but not striatal) dopamine D_{2/3} BP_{ND} in AD participants compared with HC participants (2.7 vs 2.1; uncorrected $P = .014$; see Table 1). However, after Bonferroni correction for multiple comparisons, the group difference in thalamic 18F-fallypride BP_{ND} did not meet $P = .05$ significance criteria (Table 1). No overall effect of condition (i.v. citalopram vs saline placebo) on regional BP_{ND} was found (Table 1), although a trend to reduced BP_{ND} is seen in the thalamus ($P = .06$ uncorrected).

Correlations between Cue-Induced Alcohol Craving and D_{2/3} BP_{ND}

There was a strong correlation between mean cue-induced craving for alcohol and thalamic D_{2/3} BP_{ND} across all participants and conditions, even after correction for multiple comparisons ($P = .0003$ uncorrected; Figure 1A). There were no correlations between mean cue-induced craving for alcohol and region-specific BP_{ND} values in other regions tested.

Whole-brain voxelwise BP_{ND} analysis with mean cue-induced craving for alcohol as a covariate demonstrates strong correlations in bilateral thalamic regions ($P < .0001$), with weaker correlations

Table 1. D_{2/3} Receptor Binding Potential ANOVA Results

Region	Group		Condition	
	F value	P value	F value	P value
Amygdala	0.01	.92	0.09	.77
Caudate	1.07	.32	0.98	.34
Hippocampus	0.96	.35	0.92	.36
Nucleus accumbens	0.03	.87	2.02	.18
Pallidus	3.55	.09	1.56	.24
Putamen	1.70	.22	0.87	.37
Thalamus	8.62	.01	4.47	.06

F and P values indicate ANOVA results for region BPND for group and condition effects. Condition = saline vs citalopram. Listed P values are uncorrected. After Bonferroni correction for multiple comparisons, none of the P values fall below the $P < .05$ significance threshold.

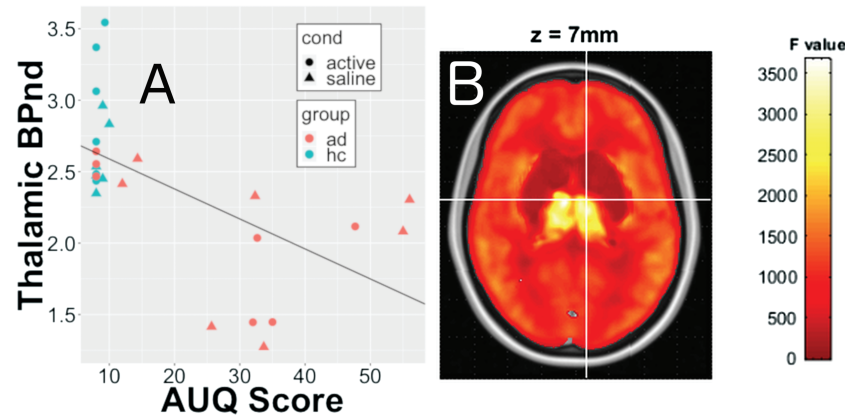


Figure 1. Thalamic dopamine binding potential (BP_{ND}) correlates with mean cue-induced craving scores in alcohol-dependent (AD) and healthy control (HC) subjects. Correlation between thalamic dopamine BP_{ND} and mean scores of cue-induced craving (Alcohol Urge Questionnaire [AUQ]). (A) Region-specific volume of interest (VOI) correlations. Group = participant group; cond = condition (active- citalopram, saline- placebo). Red indicates AD participants, blue indicates HC participants, circles indicate citalopram, triangles indicate saline. Diagonal line indicates linear correlation (coefficient $r = -0.59$) across conditions and participant groups. (B) Heat map of voxelwise correlation between dopamine $D_{2/3}$ receptor BP_{ND} and mean cue-induced craving. Coronal section at $z = 7$ mm representing a map of mean voxelwise correlation between dopamine $D_{2/3}$ receptor BP_{ND} and mean cue-induced craving. Average voxelwise binding was warped into a sample participant MRI for demonstration purposes. Colors correspond to the F value of relevant voxelwise correlations, with strongest correlations seen in the bilateral thalamus (F values > 3000) after family-wise error correction of $P < .0001$ for multiple comparisons.

in other subcortical regions, across conditions (Figure 1B). There were also weaker signals for bilateral amygdalae, and left stronger than right Brodmann's Area 38 cortical regions.

Discussion

Single-Dose i.v. Citalopram Reduces Cue-Induced Alcohol Craving

The results demonstrate that a single infusion of i.v. citalopram (40 mg) reduces cue-induced alcohol craving. Although many studies have shown the potential for a differential response to SSRIs in subtypes of AD individuals ("type I vs II" and "type A vs B"; Kenna, 2010), all of our participants had less craving for alcohol in the citalopram than the placebo condition. Given that there was no association between changes in dopaminergic neurotransmission and changes in cue-induced craving for alcohol, it is likely that the mechanism of action of single-dose i.v. citalopram craving attenuation is independent of changes in striatal dopamine.

No Effect of Single-Dose i.v. Citalopram on Striatal BP_{ND} as Assessed by Fallypride PET Scanning

Although a prior study with [^{11}C]-raclopride showed that a single dose of i.v. citalopram decreased striatal dopamine receptor availability significantly, albeit only by approximately 5% (Smith et al., 2009), the current results showed not even a trend for a change in striatal BP_{ND} with i.v. citalopram, as measured with [^{18}F]-fallypride PET scanning (Table 1). However, given the relatively lower affinity of [^{11}C]-raclopride for dopamine $D_{2/3}$ receptors compared with [^{18}F]-fallypride, these results may be explained by pharmacology and neurophysiology (see following section for a more complete explanation).

Reduced Dopamine Receptor Availability in Alcohol Dependence: Thalamus in Fallypride Studies, Striatum in Raclopride Studies

Previous studies have shown mixed results when assessing whether AD individuals have lower striatal dopamine receptor availability than controls using various weakly binding PET ligands

(such as [^{11}C]-raclopride; cf Oberlin et al., 2015). However, one prior study showed that AD individuals at admission to a hospital program had lower thalamic (but not striatal) dopamine $D_{2/3}$ receptor availability than controls using the PET ligand [^{18}F]-fallypride (Rominger et al., 2012). Similarly, our study demonstrates a strong trend that actively drinking AD participants have lower thalamic dopamine $D_{2/3}$ receptor availability than comparison HC participants with [^{18}F]-fallypride, consistent with findings in (Rominger et al., 2012). Although fallypride has a greater affinity for dopamine D_2 receptors than D_3 receptors, a prior finding that the thalamus contains a higher level of D_3 receptors than D_2 receptors indicates that some of the thalamic differences we have observed may actually represent reduced thalamic D_3 receptors in alcoholics compared with matched controls (Sun et al., 2012). Future studies may consider investigating both thalamic dopamine D_2 and D_3 receptor availability separately in alcohol use disorder.

Alcohol Use Disorder: Aberrant Striatal Dopamine Signaling?

Our results and prior studies described above are consistent with the notion that alcohol use disorder represents a striatal hyperdopaminergic state (Hirth et al., 2016). Autoradiographic studies of human postmortem brain tissue (corroborated by a rodent model for alcohol use disorder) demonstrate that individuals with alcohol use disorder do not differ from controls in striatal dopamine D_2 receptor density or D_2 mRNA levels but do have lower dopamine transporter density (Hirth et al., 2016). However, it should be noted that the findings of Hirth et al. (2016) may conflict with some earlier animal and human postmortem findings. The possibility that striatal alterations in alcohol dependence are more likely due to increased dopamine release rather than reduced dopamine receptor availability is broadly consistent with the results of this study, but more studies are needed to confirm this hypothesis.

Correlation of Cue-Induced Craving for Alcohol With Thalamic Dopamine $D_{2/3}$ Receptor BP_{ND}

Our finding of a strong correlation between cue-induced craving for alcohol and thalamic dopamine $D_{2/3}$ receptor availability in a group of AD and HC individuals is novel. Thalamic dopamine signaling has been little-studied in the field of alcohol

use disorders. However, the results presented here, combined with the earlier demonstration that AD individuals had lower thalamic dopamine $D_{2/3}$ receptor availability than controls, should stimulate future studies on the role of aberrant thalamic dopamine signaling in alcohol use disorders (Rominger et al., 2012). Interestingly, these results parallel those of a prior study showing that methylphenidate-induced craving for cocaine in cocaine-dependent subjects was also correlated with reduced thalamic dopamine receptor availability, indicating that aberrant thalamic dopamine signaling may represent a more widespread feature of substance use disorders (Volkow et al., 1997).

Limitations

A limitation of the study is the modest sample size, which was (at least partly) due to the detailed study methods (including 2 full day sessions, including PET scanning, per participant). Another limitation was that, due to the extensive collinearity between smoking and alcohol dependence in the sample, we were unable to effectively disentangle any specific effect of smoking status on any of the measures reported. Additionally, we did not keep track of smoking behavior on study days of our smoking participants (aside from proscribing smoking for 2 hours prior to PET scanning), which may have influenced dopamine binding potential measurements. We did not keep track of the last drink consumed by participants prior to study procedures, though all participants were breathalyzer-negative during all procedures. Our samples represent approximately equal numbers of males and females and therefore may obscure any gender-specific effect on any of the reported measures. We excluded participants with active psychiatric illness and those taking psychoactive medications; thus, these findings may not generalize to clinical samples of patients with alcohol use disorder where psychiatric comorbidities are common.

Conclusions

A single dose of i.v. citalopram reduces cue-induced craving for alcohol in AD participants. As noted above, it is unlikely that our observed decrease in cue-induced craving with a single dose of i.v. citalopram is due to any changes in brain dopamine release. Cue-induced craving for alcohol is highly correlated with thalamic dopamine $D_{2/3}$ receptor availability in a mixed group of AD and HC research participants. The overall results are broadly consistent with the striatal hyperdopaminergic hypothesis of alcohol dependence, whereby increased dopamine release, rather than reduced postsynaptic dopamine receptor activity, is likely to be the major striatal dopaminergic neurochemical alteration.

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Interest Statement

None.

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