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Brain activation in response to craving- and aversion-inducing cues related to alcohol in patients with alcohol dependence

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ABSTRACT

Background: Episodes of alcohol consumption produce use-limiting aversive effects as well as use-promoting euphoric effects. The brain regions associated with the reward circuit in patients with alcohol dependence (PAD) show signs of conditioning for alcohol craving. Alternatively, brain structures in the medial temporal region are known to be crucial for aversive conditioning. In this study, we compare differences in patterns of brain activation in response to cues that induce cravings versus aversion in PAD.

Methods: Thirty-eight PAD and 26 healthy volunteers were administered cue reactivity tasks while undergoing functional magnetic resonance imaging (fMRI) to examine brain response to craving-inducing cues (CIC) and aversion-inducing cues (AIC).

Results: Activation of the right medial frontal gyrus (right orbitofrontal cortex) during CIC was greater in PAD than in healthy volunteers. Participants in the PAD group displayed less activation in the right amygdala and the right middle temporal gyrus during AIC than did the healthy volunteers. Brain reactivity within the right medial frontal gyrus in response to CIC was positively correlated with the scores of PAD on the Korean Alcohol Urge Questionnaire (AUQ-K) and the Michigan Alcohol Screening Test (MAST). Reactivity within the amygdala in response to AIC was negatively correlated with AUQ-K scores among PAD.

Conclusion: The dysfunction of the orbitofrontal cortex that results from repeated exposure to alcohol accounts for craving and relapse in PAD. Additionally, PAD seem to be less sensitive to cues related to aversive consequences of alcohol overuse in comparison with healthy individuals.

1. Introduction

Craving is defined as an intense desire to consume a substance of potential abuse, and it is important in maintaining addictive disorders, including alcohol dependence (Tiffany and Conklin, 2000). Environmental stimuli related to any abused substance can act as conditioned cues that evoke a drug-like effect, stimulating the brain reward circuit and triggering a craving for the substance (O'Brien et al., 1998). Improved understanding of the neurobiological factors involved in conditioning and craving for a substance is important because these areas are potential targets for new behavioral and pharmacological treatments.

A hypothesis has been put forward to explain incentive salience to cues and cravings related to alcohol, which argues that repeated activation of the brain reward circuit by alcohol results in dysfunction of the reward circuit pathways (Kalivas and Volkow, 2005). Functional neuroimaging techniques have been used to understand the neurobiological mechanisms underlying cravings, wherein cue-elicited brain alteration is considered an objectively observable measure of craving in patients with alcohol dependence (PAD). Researchers have investigated the brain regions correlated with cravings using alcohol-related visual cues (Braus et al., 2001; Tapert et al., 2004; Wrase et al., 2002), olfactory cues (Bragulat et al., 2008), and combined visual and taste stimuli (George et al., 2001). According to functional magnetic resonance imaging (fMRI) studies focused on alcohol dependence, the prefrontal cortex, the anterior thalamus, the ventral striatum, the anterior cingulate, and the bilateral insular region are the regions that show greater cue-elicited responses in PAD, relative to healthy volunteers (Braus et al., 2001; George et al., 2001; Tapert et al., 2004; Wrase et al., 2002).

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Aversive conditioning has a long and extensive history as one of the behavioral treatments for substance use disorders (Elkins, 1975). In aversive conditioning, aversive experiences are linked to existing conditioned drug cues in order to help patients reduce or eliminate their substance use behavior (McLellan et al., 2000). For instance, disulfiram is a drug that inhibits aldehyde dehydrogenase, a liver enzyme that facilitates alcohol metabolism, and thereby induces a highly unpleasant physical experience in patients who ingest alcohol together with the drug (Jorgensen et al., 2011). The method of pairing drinking imagery with unrelated but unpleasant imagery has also been used in aversive conditioning in PAD (Rimmele et al., 1995). Lee et al. (2009) developed a treatment program that strategically uses aversive conditioning by repetitively pairing emotionally neutral alcohol-related stimuli with scenes of aversive consequences of drinking. However, aversion therapy does not appear to be widely used in actual clinical practice today (Witkiewitz and Alan Marlatt, 2011).

Substance abuse itself produces aversive effects that may be useful for determining a substance's acceptability as well as the likelihood of the substance's becoming a long-term self-administered drug (Davis and Riley, 2010). During a drinking episode, individuals may experience lightheadedness, loss of motor coordination, drowsiness, and other toxic metabolite-induced symptoms, such as flushing, nausea, and vomiting (Schramm-Sapyta et al., 2010). Following a drinking episode, individuals may experience the residual effects of an alcohol hangover, which include headache, gastro-intestinal symptoms, thirst, and fatigue (Rohsenow and Howland, 2010). Low sensitivity to the aversive effects of alcohol has been reported to be associated with increased risk of alcohol use disorders (Schuckit and Smith, 2006). In animal studies, lack of sensitivity to conditioned aversive effects is reported to facilitate the consumption of high amounts of ethanol, especially in genetically-susceptible mice and rats (Green and Grahame, 2008; Schramm-Sapyta et al., 2010).

Previous studies using functional neuroimaging techniques have found that the structures in the medial temporal region, especially the amygdala, are crucial for the acquisition, expression, and storage of a conditioned aversive response (Cheng et al., 2006; Phelps and LeDoux, 2005). Studies have reported impaired fear conditioning in patients who have received a unilateral temporal lobectomy (LaBar et al., 1995) and in patients with bilateral damage to the amygdala (Bechara et al., 1995). The anterior cingulate is also thought to be involved in the response of individuals to aversive stimuli and fear acquisition (Dunsmoor et al., 2007; Vidal-Gonzalez et al., 2006). However, no studies have yet investigated functional brain changes in PAD in response to cues regarding the aversive consequences of drinking.

Based on the results of previous studies, we hypothesized that exposure to cues that induce alcohol craving would activate the frontal regions associated with the reward circuit in PAD. Based on this hypothesis, we predicted that the functional brain reactivity in those regions would be positively correlated with the intensity of the craving, as assessed by behavioral measures. We also hypothesized that PAD would show reduced brain activation in the medial temporal structures, including the amygdala, in response to cues presenting aversive consequences due to alcohol drinking in comparison to healthy controls.

2. Methods

2.1. Study participants

Among patients who visited the Departments of Psychiatry at Chung-Ang University Medical Center and Eun-Pyeong Hospital for alcohol problems, 50 PAD agreed to participate in this study. The control group consisted of 26 healthy volunteers who were recruited through advertisement in hospital bulletins. The inclusion criteria for the PAD group were as follows: (1) alcohol dependence based on the Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Patient Edition (SCID-I/P; First et al., 2002), and (2) a score of >19 on the Michigan Alcohol Screening Test (MAST; Selzer, 1971), which includes self-assessment questions that focus on arespondent's problems related to heavy drinking, with the intention of measuring the severity of alcohol dependence. The inclusion criteria for the healthy control group were as follows: (1) no past or current alcohol abuse or dependence and (2) a MAST score of ≤19. The exclusion criteria for both groups were (1) past or current episodes of any other axis I psychiatric diagnosis based on the SCID-I or severe medical illness, (2) past or current substance abuse or dependence other than nicotine (both groups) or alcohol (PAD group), as verified by the SCID-I, (3) current psychotropic medication use, or (4) a history of head trauma or (5) claustrophobia. The Chung-Ang University Hospital Institutional Review Board approved the research protocol for this study, and all participants provided written informed consent.

Among the 50 enrolled PAD, 10 participants were excluded because they did not complete their detoxification program: four participants discontinued detoxification due to mood instability and six participants stopped detoxification because they were experiencing insomnia. An additional two participants missed their MRI appointments without giving notification. Ultimately, 38 PAD underwent fMRI and completed the study.

2.2. Study procedure

2.2.1. Detoxification period. After enrollment in the study, all participants in the PAD group underwent a three-day acute detoxification process with lorazepam (2–4 mg every 6 h for 4 doses, then 1–2 mg every 6 h for 8 doses), thiamine (100 mg/day orally), and multiple vitamin injections (containing folate). This detoxification protocol was previously validated for outpatient treatment (Asplund et al., 2004; Lejoyeux et al., 1998). After completion of acute detoxification, participants continued to receive medication with lorazepam (1–4 mg/day) according to the severity of their withdrawal symptoms, including tremors, sweating, agitation, and headache. Thirty-five of the PAD group participants underwent fMRI within 10 days of completing the program of acute detoxification. The other three participants underwent fMRI between days 11 and 21. All participants had their levels ofalcohol craving evaluated with the Korean Alcohol Urge Questionnaire (AUQ-K; Kim et al., 2008) shortly before fMRI assessment. The AUQ-Kassesses a respondent's thoughts and feelings about drinking alcoholic beverages in order to reflect his or her level of craving for alcohol. Additionally, the severity of illness and the level of depressive symptoms of participants were assessed using the Clinical Global Impressions-Severity (CGI-S) and the Beck Depression Inventory (BDI; Beck et al., 1961), respectively.

2.2.2. Assessment of brain activity and craving for alcohol. Brain activation in response to alcohol-related cues was assessed using the 1.5 T Espree MRI scanner (Siemens, Munich, Germany). All participants were presented with two types of videotapes: (1) a video of scenes intended to induce craving (A1; craving-inducing cues, or CIC) and (2) a video of scenes intended to induce an aversive response (A2; aversion-inducing cues, or AIC; Fig. 1). Each video was a silent 450-s clip, consisting of five continuous 90-s segments. Each 90-s segment consisted of three 30-s sub-segments. A white cross on a black background (B), a control scene (C, mosaic modification of alcohol-related scenes), and a video depicting alcohol-related scenes (either A1 or A2) were shown in a deliberately ordered fashion in these 90-s segments.

The videos were shown via an IFIS-SA™ system (MRI Device Corporation, Waukesha, WI, USA) during a single fMRI scanning session. The fMRI session comprised gradient-recalled echo planar images (EPI) that were recorded at 3-s intervals with the following parameters: 37 transverse slices, slice thickness = 5.0 mm, voxel size = 3.5 mm × 3.5 mm × 5.0 mm, TE = 30 ms, TR = 3000 ms, in-plane resolution = 64 × 64 pixels, and field of view (FOV) = 230 mm × 230 mm. For anatomical imaging, 3D T1-weighted magnetization-prepared rapid gradient-echo (MPRAGE) data were gathered with the following parameters: TR = 1500 ms, TE = 3.00 ms, FOV = 256 mm × 256 mm, 128 slices, and voxel size = 1.0 mm × 1.0 mm × 1.33 mm.

2.3. Functional MRI data analysis

Functional images were analyzed using Brain Voyager software (BVQX 1.9; Brain Innovation, Maastricht, Netherlands). During preprocessing, the fMRI data were co-registered to the anatomical 3D data sets for each participant using the provided multi-scale algorithm. Individual 3D structural images were spatially normalized to standard Talairach space (Talairach and Tournoux, 1988). A nonlinear transformation was applied to the $T2^*$-weighted fMRI time series data. Slice scan time and 3D motion correction were applied. The functional data were spatially smoothed using a Gaussian kernel with a full width at half maximum (FWHM) value of 6 mm, and temporally filtered using linear trend removal and Fourier analysis high-pass filtering with a cut-off of three cycles of the full time-course. Regional brain activation in response to CIC and AIC videos was examined by performing a first-level general linear model (GLM) analysis on a voxel-by-voxel basis for each participant. Model predictors for blood-oxygenation-level dependent (BOLD) signal time courses were boxcar time courses corresponding to each video stimulus paradigm (A1/A2 and B in Fig. 1), convolved with a gamma function to account for hemodynamic response.