RESEARCH ARTICLE | ALCOHOL

Alcohol Consumption Induces Endogenous Opioid Release in the Human Orbitofrontal Cortex and Nucleus Accumbens

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Abstract

Excessive consumption of alcohol is among the leading causes of preventable death worldwide. Although ethanol modulates a variety of molecular targets, including several neurotransmitter receptors, the neural mechanisms that underlie its rewarding actions and lead to excessive consumption are unknown. Studies in animals suggest that release of endogenous opioids by ethanol promotes further consumption. To examine this issue in humans and to determine where in the brain endogenous opioids act to promote alcohol consumption, we measured displacement of a radiolabeled μ opioid receptor agonist, [^{11}C]carfentanil, before and immediately after alcohol consumption in both heavy drinkers and control subjects. Drinking alcohol induced opioid release in the nucleus accumbens and orbitofrontal cortex, areas of the brain implicated in reward valuation. Opioid release in the orbitofrontal cortex and nucleus accumbens was significantly positively correlated. Furthermore, changes in orbitofrontal cortex binding correlated significantly with problem alcohol use and subjective high in heavy drinkers, suggesting that differences in endogenous opioid function in these regions contribute to excessive alcohol consumption. These results also suggest a possible mechanism by which opioid antagonists such as naltrexone act to treat alcohol abuse.

Introduction

Alcoholism is a common problem, affecting the health and socioeconomic function of millions of people worldwide. Understanding how alcohol produces reward, motivates further consumption, and eventually leads to addiction is necessary to design treatments for alcohol abuse, dependence, and relapse. Currently, only three drugs are approved for alcoholism treatment in the United States: disulfiram (Antabuse), acamprosate (*N*-acetyl homotaurine), and naltrexone, a nonselective opioid receptor antagonist considered to be the most effective (***1***, ***2***).

In rodents, ethanol consumption leads to the release of endogenous opioids. Opioids acting at the μ opioid receptor (MOR) modulate further consumption (***3***): Opioid agonists enhance ethanol consumption (***4***), whereas opioid antagonists reduce both ethanol consumption (***5***) and preference for an environment previously paired with ethanol (***6***). In human alcoholics, the opioid antagonist naltrexone reduces alcohol consumption (***7***), craving (***8***), and relapse (***1***). Although naltrexone is a nonselective opioid receptor antagonist, it preferentially blocks the MOR. Results from animal studies are consistent with the idea that its clinical efficacy is largely a result of antagonism at the MOR, because MOR knockout mice drink less alcohol and do not develop ethanol place preference (***9***, ***10***). Additionally, humans with a genetic variant affecting MOR function drink more alcohol and exhibit an improved naltrexone treatment response (***11***, ***12***).

Specific regions of the frontal cortex and their subcortical projection targets are critically involved in processing reward value, including alcohol reward. For example, alcohol-related olfactory cues activate the human prefrontal cortex (PFC) (***13***), and PFC lesions can impair reward processing (***14***). Additionally, the extent of connectivity between the striatum and the dorsolateral PFC (dlPFC) correlates with impairments in reinforcement learning and magnitude of alcohol craving (***15***), whereas connectivity between the orbitofrontal cortex (OFC) and the striatum is altered in abstinent alcoholics (***16***).

In rodents, the nucleus accumbens (NAc) region of the ventral striatum is critical for opioid regulation of ethanol consumption and may be a site where ethanol acts directly on neurons. Although the molecular mechanism by which alcohol affects the opioid system is still unknown, alcohol-preferring rats self-administer ethanol directly into the NAc (***17***), and the MOR selective agonist DAMGO ([D-Ala^2,*N*-MePhe^4,Gly-ol^5]enkephalin) injected into the NAc increases ethanol consumption (***4***). Additionally, positron emission tomography (PET) imaging has shown reduction of psychostimulant-induced dopamine release in the NAc of abstinent alcoholics (***16***), as well as an inverse correlation between striatal dopamine receptor binding and alcohol craving (***18***), and increased MOR binding in the striatum of alcoholics following protracted abstinence (***19***). Although both animal and human studies implicate the NAc and opioids in ethanol reward processing and motivation (***20***), the contribution of NAc MOR has not been directly studied in humans.

To address this issue, we used PET imaging to measure binding of the selective MOR agonist [^{11}C]carfentanil (CFN) following alcohol consumption in both heavy alcohol drinkers and control subjects. We tested the hypothesis that alcohol causes the release of endogenous

endogenous opioid release correlate with the extent of problem drinking.

Results

PET imaging was performed on 25 subjects (13 heavy drinkers and 12 matched healthy controls) before and after a standardized drink of alcohol. Voxelwise analysis of the whole brain revealed that drinking alcohol induced a significant reduction in MOR binding in the left OFC, independent of whether the individual was a control subject or a heavy drinker (**Fig. 1**). This result indicates that irrespective of how much one usually drinks, alcohol consumption leads to the release of an endogenous opioid that acts at MORs in the OFC.

Fig. 1

Changes in MOR binding (statistical parametric mapping) following alcohol consumption. Voxelwise ANOVA (2 × 2 mixed factorial design) showing MOR binding (in red) within the OFC, irrespective of subject group ($P < 0.001$, $k = 100$, $N = 25$, peak voxel = 6, 60, 12 mm).

Because voxelwise approaches are exploratory in nature, we also conducted a hypothesis-based region of interest (ROI) analysis to examine changes in binding in brain regions involved in reward and motivation: the OFC, NAc (**Fig. 2A**), insula, amygdala, and caudate. There was no difference in CFN binding within any of the ROIs between control subjects and heavy drinkers ($P > 0.05$ for all comparisons, unpaired t test). This was true for both the pre-alcohol scan and the post-alcohol scan, demonstrating that heavy drinkers and control

CFN binding in both the left ($P = 0.02$) and the right ($P = 0.02$) medial OFC in control subjects but had no significant effect on binding in heavy drinkers (**Fig. 2B**). In addition, there was a significant decrease in CFN binding in the left ($P < 0.0001$) and right ($P = 0.002$) NAc in all subjects (**Fig. 2B**). This decrease in NAc MOR binding is likely not a residual effect of the first CFN injection: The decay half-life of ^{11}C is 20 min, and the second scan was taken six half-lives later. Furthermore, previous work has demonstrated that a second administration of CFN at a short interscan interval (~2 hours) is not associated with decreased binding (***21***).

Fig. 2

Changes in MOR binding in ROIs following alcohol consumption. (**A**) Spatially co-registered coronal MRI (left) and PET (right) images from a single representative control subject indicating designation of individually drawn NAc ROIs. Left: a coronal section MRI with the NAc ROI hand-drawn in orange. Right: carfentanil binding potential, with highest binding potential in hot colors (see color scale). (**B**) Binding potential (B_{max}/K_d) for each brain region examined. *$P < 0.05$; **$P < 0.01$, on paired t tests for heavy drinking ($n = 12$) and control subjects ($n = 13$) before and after alcohol consumption.

Within the ROI analysis, there was a significant correlation between the changes in binding in the left medial OFC and the left NAc ($R = 0.42$, $P = 0.03$, $n = 25$; **Fig. 3A**) but not in the right OFC and the NAc (**Fig. 3B**) for all subjects, suggesting that connectivity between the left OFC and the NAc contributes to opioid regulation of alcohol intake. Additionally, all subjects showed a significant positive correlation between change in binding in the left NAc and the Subjective High Assessment Scale (SHAS) rating of feeling the "best ever" ($R = 0.45$, $P =$

0.024, $n = 25$; **Fig. 3C**), indicating that as endogenous ligand release increased in the NAc, the individuals' subjective report of feeling good increased as well. Subjects with the greatest increase in endogenous ligand release in the left (**Fig. 3D**) and the right (**Fig. 3E**) medial OFC following alcohol consumption also reported the greatest feelings of "drunk or intoxicated" ($R = 0.45$, $P = 0.023$, $n = 25$ and $R = 0.51$, $P = 0.009$, $n = 25$, respectively). These data are consistent with the idea that endogenous opioid ligand release in the OFC contributes to the subjective report of feeling drunk or intoxicated.

Fig. 3

Correlations between MOR binding and measures of problem alcohol use and subjective reward. (**A**) Regression analysis showing alcohol-induced change in binding in the left medial OFC versus change in binding in the left NAc across all subjects. (**B**) Lack of a correlation between alcohol-induced change in binding in the right medial OFC versus change in binding in the right NAc across subjects. (**C**) Change in binding in the left NAc versus change in SHAS report of feeling the best ever across subjects. (**D**) Change in binding in the left medial OFC versus change in SHAS report of drunk or intoxicated in all subjects. (**E**) Change in binding in the right medial OFC versus alcohol-induced change in SHAS report of drunk or intoxicated in all subjects. (**F**) Change in binding in the right and left medial OFC versus change in total SHAS score in heavy-drinking subjects. (**G**) Change in binding in the right and left lateral OFC versus change in total SHAS score in heavy-drinking subjects. (**H**) AUDIT score versus alcohol-induced change in binding in the right and left lateral OFC in heavy-drinking subjects.

In addition, in the heavy drinkers but not the healthy controls, there were positive correlations between the alcohol-induced change in binding in the medial ($R = 0.49$, $P = 0.01$, $n = 26$; **Fig. 3F**) and the lateral ($R = 0.47$, $P = 0.015$, $n = 26$; **Fig. 3G**) OFC and the change in the total SHAS score after alcohol consumption, again indicating that as endogenous ligand

release increases, the global change in subjective high increases as well. Heavy drinkers also showed a positive correlation between the Alcohol Use Disorders Identification Test (AUDIT) score and the change in binding in the lateral OFC ($R = 0.59$, $P = 0.0002$, $n = 26$; **Fig. 3H**). That is, endogenous ligand release in the lateral OFC following alcohol consumption was larger in subjects with greater problem alcohol use and was associated with greater subjective intoxication. These data suggest that differences in endogenous opioid function in the OFC contribute to subjective reward value of alcohol and to excessive alcohol consumption in alcohol abusers.

Following alcohol consumption, peak blood alcohol concentration and the change in blood alcohol concentration over time were not different in heavy drinkers and controls (**Fig. 4A**). As expected, heavy drinkers scored significantly higher than control subjects on all three measures of problem drinking (**Fig. 4B**) and reported significantly greater craving for alcohol during both the pre- and the post-alcohol scans (**Fig. 4C**). However, blood alcohol concentration did not correlate with either subjective craving or subjective high in either group. In our ROI analysis, there were no significant changes in MOR binding in the insula, amygdala, or caudate, although these areas have been implicated in reward processing.

Fig. 4

Relationship between heavy drinking, alcohol craving, and blood alcohol concentration. (**A**) Blood alcohol concentration in response to a standardized dose of alcohol in heavy drinkers and control subjects. (**B**) Scores on inventories that assess problem alcohol and drug use (AUDIT and DUSI) and alcohol craving and compulsion (OCDS) in heavy drinkers and control subjects. (**C**) Craving scores (BSCS) pre- and post-alcohol consumption in heavy drinkers and control subjects. *$P = 0.001$; **$P < 0.0001$, unpaired t test.

Discussion

Our data are consistent with the hypothesis that drinking alcohol leads to the release of an endogenous opioid, which binds to MORs in the OFC and NAc, two brain regions critical for reward processing. Although the reduction in NAc MOR binding did not correlate with blood alcohol concentration, it did correlate with left OFC MOR displacement, suggesting that endogenous MOR ligand release in both the OFC and the NAc contributes to the rewarding actions of alcohol.

The results of our study also implicate the OFC in opioid regulation of ethanol reward. Although the OFC contributes to the processing of both natural and drug reward in rodents, primates, and humans (***22***, ***23***), the reduction in OFC MOR binding after alcohol consumption was unexpected. Although microinjection of opioids into the OFC has previously been shown to produce analgesia (***24***), our data implicate OFC opioid release in ethanol consumption and reward. In addition, this study confirms and extends preclinical studies indicating that endogenous opioids acting at MORs in the NAc promote drinking. In rodents, ethanol produces a dose-related release of the endogenous opioid met-enkephalin in the ventral striatum (***25***). Further, direct microinjection of the MOR selective agonist DAMGO in the rodent ventral striatum increases ethanol consumption but not water consumption (***4***), whereas antagonism of the MOR decreases ethanol-induced NAc dopamine release (***26***). Together, these data also suggest neural regions (OFC and NAc) and mechanisms by which the opioid antagonist naltrexone, an effective pharmacotherapeutic for alcohol abuse, may work to reduce ethanol craving and consumption.

The present study suggests how alcohol consumption leads to excessive intake in some individuals. Alcohol is consumed as a beverage, often flavored. Animal and human studies show that OFC neurons encode the hedonic value of gustatory stimuli (***27***). Our data raise the intriguing possibility that local opioid release in the OFC enhances the palatability of orally ingested ethanol and that this stimulates further consumption. If alcohol consumption is at least partially mediated by palatability, the release of endogenous MOR ligands would be expected to promote further consumption. In keeping with this hypothesis, recent data indicate that an alcohol infusion, which bypasses gustatory mechanisms, does not alter blood oxygen level–dependent (BOLD) signal in the OFC of either subjects with a family history of alcoholism or matched controls (***13***). Although our data are consistent with the idea that drinking alcohol induces endogenous opioid release in the OFC, our study cannot distinguish between the contributions of the characteristic taste and smell of alcohol and a direct action of alcohol on the brain. If it were possible to construct a control drink that both tasted and smelled like alcohol but did not contain any alcohol, this question could be directly addressed.

In addition to the role of the OFC in processing reward value, dysfunction of the OFC has been implicated in impulsivity, which is a risk factor for a variety of addictions, including alcoholism (***28***). OFC lesions increase impulsive behaviors in rodents and humans (***14***), and opioid administration increases impulsive choice in rodents (***29***). In humans, using a delay-

discounting task to measure impulsive choice, we have previously shown that abstinent alcoholics are significantly more likely than normal controls to choose a small immediate reward as opposed to a larger, delayed reward. This tendency to choose the immediate reward was inversely correlated with the functional magnetic resonance imaging (fMRI) BOLD signal in the left OFC, which was increased following treatment with naltrexone (***30***). Together with the current evidence for endogenous opioid release in the OFC after drinking alcohol, these findings suggest that by increasing impulsivity and enhancing ethanol palatability, endogenous opioids may modulate OFC activity in a manner that contributes to increased ethanol consumption.

Our evidence that endogenous opioids acting at the MOR contribute to the rewarding actions of alcohol directly supports the clinical value of targeting the endogenous opioid system for the prevention and treatment of alcoholism. Furthermore, these data expand our understanding of the brain region and mechanism of action of the nonselective opioid antagonist naltrexone. Naltrexone is an effective treatment for alcohol abuse, reducing the number of heavy drinking days (***31***), alcohol craving (***8***), and relapse to drinking (***32***). However, unpleasant side effects, including nausea and dysphoria, lead to low patient compliance (***33***). Because several endogenous ligands act at the MOR, determination of how and where each of these ligands contributes to ethanol reward will lead to greater understanding of excessive alcohol consumption and, consequently, to improved treatment. By reverse-engineering naltrexone's therapeutic actions, it may be possible to parse the contribution of each opioid ligand at different opioid receptor subtypes and to design a more clinically efficacious compound.

In summary, following a standardized drink of alcohol, there is a significant reduction in MOR agonist binding in the OFC. There is also a significant reduction in MOR agonist binding in the NAc, which is correlated with the change in the OFC on the left side, suggesting that the two brain regions interact to increase alcohol reward and promote consumption. These data are consistent with previous studies implicating endogenous opioids and MOR activation in alcohol reward and suggest that MOR activation in the OFC contributes to ethanol reward processing. Furthermore, our finding that changes in OFC MOR binding correlate significantly with problem alcohol use and subjective feelings of well-being after alcohol consumption in heavy drinkers but not in controls suggests that dysfunction of the OFC contributes to excessive consumption of alcohol.

Materials and Methods

Subjects

Heavy social drinkers (n = 13) and matched healthy control subjects (n = 12) were recruited online from http://www.craigslist.org. Recruitment was based on alcohol consumption and was categorized as follows: heavy-drinking subjects consumed between 10 and 16 drinks per week (women) or between 14 and 20 drinks per week (men). Control subjects all consumed fewer than 5 drinks per week (women) or 7 drinks per week (men). Between groups, subjects were matched on gender, age, and ethnicity (**Table 1**). Because a large proportion of our

sample was of mixed ethnicity, subjects were matched on at least one ethnic group. After consenting to study participation, subjects participated in a blood draw to assess routine blood counts, routine chemistry, and liver function. Additionally, subjects were required to provide a urine sample to screen for cocaine, amphetamines, methamphetamine, phencyclidine, and opioids and to take a pregnancy test (if female). Marijuana and nicotine use was not considered a ground for study exclusion. The study physician used DSM-IV (*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*) criteria to assess alcohol dependence. Alcohol-dependent subjects were excluded, and female subjects were excluded if pregnant. Blood alcohol concentration was assayed with a breathalyzer before each experimental session. A blood alcohol concentration of greater than 0.00 at the beginning of any experimental session was considered a ground for study exclusion. Subjects were required to fast for 4 hours and remain abstinent from alcohol for 3 days before scanning.

Table 1

Patient demographic data.

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The AUDIT (***34***) and Drug Use Screening Inventory (DUSI) (***35***) were used to measure hazardous drinking. Study visits took place at the University of California, San Francisco (UCSF) Clinical and Translational Science Institute site at Children's Hospital Oakland. All participants gave written, informed consent in accordance with the guidelines of the UCSF, the University of California Berkeley, Lawrence Berkeley National Laboratory, Children's Hospital Oakland, and the U.S. Department of Defense Committees for the Protection of Human Subjects. Additionally, all subjects were paid for their participation.

Image acquisition

To improve the spatial localization of the PET data, we collected MRI images for anatomical reference. These images were acquired with a Siemens Avanto 1.5-T system. All subjects underwent a single T1-weighted magnetization-prepared rapid gradient echo (MPRAGE) that was used for generation of ROIs. ROI volumes were defined with automated software (FreeSurfer), with the exception of the NAc, which was hand-drawn by a rater blind to subject classification using previously reported criteria and in-house software (see below). ROIs were selected on current fMRI experiments in alcohol versus control populations used for decision-making studies in our laboratory (***36***) and, additionally, on previous studies assaying the effects of alcohol and alcohol craving on PET activity (***18***, ***19***, ***37***). ROIs included the medial and lateral orbital frontal cortex, the NAc, the caudate, the insula, and the amygdala. CFN was synthesized at high specific activity with [^{11}C]methyl iodide (***38***). [^{11}C]CO_2 was made in-target by the ^{14}N(p,a)^{11}C nuclear reaction with 1% O_2/$^{14}N_2$ on the 11-MeV CTI RDS-111 medical cyclotron at the Biomedical Isotope Facility, Lawrence Berkeley

National Laboratory. The [^{11}C]CO_2 was converted to [^{11}C]methyl iodide by reduction to [^{11}C]methane followed by high-temperature iodination using in-house–built gas-phase radiochemistry. CFN was prepared from 1 mg of the desmethyl precursor in a Teflon loop at room temperature by in-house–built radiochemistry.

PET scans were conducted with a Siemens CTI ECAT EXACT (model 921) 47-section scanner in three-dimensional acquisition mode. PET data were acquired for a total of 90 min per imaging session according to the following schedule: 4 × 15, 8 × 30, 9 × 60, 2 × 180, 8 × 300, and 3 × 600 s. A 10-min positron transmission image was acquired before injection using a rotating ^{68}Ge source. Once subjects were positioned in the scanner, an intravenous catheter was inserted for tracer injection and was kept in place for the duration of the experiment. Each scan entailed the injection of 10 to 15 mCi of radiotracer.

After the first scan (pre-alcohol), subjects were removed from the scanner for 30 min to stretch and use the restroom. Subjects were then given 5 min to consume a standardized drink of alcohol [males = weight in kilograms × 1.2658 × 0.421 = milliliters ethanol (EtOH); females = weight in kilograms × 1.2658 × 0.356 = milliliters EtOH] mixed in a 2:1 volume ratio with juice and were then immediately repositioned in the scanner for a second imaging sequence identical to the first. A time delay of six radiotracer half-lives between scans assured lack of contamination of the second scan (post-alcohol) by the first. Data were reconstructed using an ordered subset expectation maximization (OSEM) algorithm with weighted attenuation, an image size of 256 × 256, and six iterations with 16 subsets. A Gaussian filter with 6-mm full width at half maximum was applied, with a scatter correction. Images were evaluated for patient motion and adequacy of statistical counts.

Measures of craving

Subjects were administered the Brief Substance Craving Scale (BSCS) (***39***) and SHAS (***40***) 30 min into both the first (pre-alcohol) and the second (post-alcohol) scan. Additionally, blood alcohol concentration was measured at 0, 20, 40, and 60 min following alcohol intake.

Image analysis

Images were analyzed using both a voxelwise approach and an ROI approach that combined automated and manually defined ROIs. CFN PET data were preprocessed using the SPM8 software package. For each time point, frames corresponding to the first 20 min of CFN acquisition were realigned, averaged, and used to co-register to subject MRI data. Each subject's second CFN scan was then co-registered to their first. Using Logan graphical analysis and an occipital cortex gray matter reference region (a region devoid of MORs), defined as a composite of FreeSurfer generated areas (cuneus, lateral occipital, and lingual gyrus), we created binding potentials for each CFN image corresponding to 35 to 60 min after injection (***41***). Although changes in binding potential (which we assume to be B_{max}/K_d) could indicate changes either in the endogenous ligand concentration or in the receptor itself, it is a physiologically meaningful parameter because it accurately reflects the total receptor availability. It is most likely that the reduction of binding potential with alcohol consumption is a result of release of endogenous opioid ligand.

Data analysis

Voxelwise analyses. CFN binding potential images were used to run a voxelwise analysis of variance (ANOVA) in SPM8. A 2 × 2 mixed factorial design was chosen to represent the relationship. Time of scan and drinking condition acted as independent variables. Voxelwise CFN uptake, spatially normalized with parameters acquired from the normalization of subject MRIs to a whole-brain PET template, was the dependent measure. No other covariates were included in the model. This design allowed for the observation of within-group effects of time (pre- or post-alcohol), between-group effects of condition (social drinkers or abstinent), as well as any interaction between independent variables. Statistical maps were thresholded at $P < 0.001$ and were uncorrected for multiple comparisons.

ROI analyses. A priori ROIs were derived using FreeSurfer version 4.5.0. A single T1 MPRAGE scan for each subject was bias field corrected, intensity normalized, and skull stripped using a watershed deformation algorithm before undergoing a white matter–based segmentation using an automated parcellation procedure to define gray/white matter and pial surfaces (***42***–***44***). Cortical and subcortical ROIs were then generated for the whole brain in the subject's native space (***45***, ***46***). Bilateral medial and lateral orbitofrontal, caudate, NAc, amygdala, and insula from this step were used. Additionally, because the NAc is an area of particular interest, NAc ROIs were hand-drawn in the subject's native space to more accurately differentiate components of the striatum. Because previous studies have demonstrated laterality with respect to frontal function during decision-making (***47***), response inhibition (***48***), and impulse control (***49***), as well as in both nicotine (***50***) and cocaine craving (***51***) and in problem drinking (***52***, ***53***), in the present study, left and right components of each ROI were first analyzed separately and then combined. Image analysis was carried out using FSLView version 3.1.2 following a previously described technique (***54***). In brief, the boundary between the ventral striatum and putamen was drawn as a diagonal line adjoining the inner edge of the caudate and the outer edge of the putamen, passing through the midpoint of the anterior commissure transaxial plane as it overlays on the striatum. The remaining boundaries were visually identified on the basis of the density of gray matter compared to that of surrounding structures on the subject's MPRAGE. ROIs were resliced into PET space, and average distribution volume ratio (DVR) values were created for each ROI to be used in subsequent regression models. Statistical analyses on ROIs were conducted using both Microsoft Excel 2004 and MATLAB 2008.

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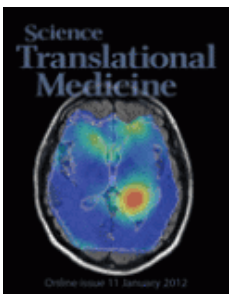

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