Biological Psychiatry: Celebrating 50 Years

Archival Report

The Kappa Opioid Receptor Is Associated With Naltrexone-Induced Reduction of Drinking and Craving

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ABSTRACT

BACKGROUND: Naltrexone is a nonselective opioid receptor antagonist used as a treatment for alcohol use disorder. However, only modest clinical effects have been observed, possibly because of limited knowledge about the biological variables affecting the efficacy of naltrexone. We investigated the potential role of the kappa opioid receptor (KOR) in the therapeutic effect of naltrexone.

METHODS: A total of 48 non-treatment-seeking heavy drinkers (16 women) who met DSM-IV criteria for alcohol dependence participated in two alcohol drinking paradigms (ADPs) separated by a week of open-label naltrexone (100 mg daily). Craving, assessed with the Alcohol Urge Questionnaire and the Yale Craving Scale, and drinking behavior were recorded in each ADP. Prior to naltrexone initiation, KOR availability was determined in the amygdala, hippocampus, pallidum, striatum, cingulate cortex, and prefrontal cortex using positron emission tomography with [^{11}C]LY2795050.

RESULTS: Participants reported lower levels of craving (Yale Craving Scale: -11 ± 1, $p < .0001$; Alcohol Urge Questionnaire: -6 ± 0.6, $p < .0001$) and consumed fewer drinks (-3.7 ± 4, $p < .0001$) during the second ADP following naltrexone therapy. The observed reduction in drinking was negatively associated with baseline KOR availability in the striatum ($p = .005$), pallidum ($p = .023$), and cingulate cortex ($p = .018$). Voxelwise analysis identified clusters in the bilateral insula, prefrontal, and cingulate cortex associated with the reduction in drinking ($p < .0001$). In addition, KOR availability in all evaluated brain regions was associated with craving measured in both ADPs.

CONCLUSIONS: The KOR is implicated in drinking and craving following naltrexone therapy in alcohol use disorder.

Keywords: Alcohol drinking paradigm, Alcohol use disorder, Craving, Kappa opioid receptor, Naltrexone, Positron emission tomography

https://doi.org/10.1016/j.biopsych.2019.05.021

Heavy alcohol use is estimated to result in 5.3% of all deaths worldwide. Moreover, this percentage is higher in younger groups; for example, 13.5% of deaths in those between 20 and 39 years of age are attributable to alcohol (1). This high toll has spurred an ongoing global research effort to develop and optimize suitable therapies to treat alcohol use disorder (AUD). Currently, the U.S. Food and Drug Administration has approved three pharmacotherapies for the treatment of AUD: disulfiram, acamprosate, and naltrexone. Naltrexone, a nonselective opioid receptor antagonist, has been approved since 1994, but a low rate of naltrexone prescriptions has been reported (2). An analysis of prescribing behavior showed that addiction medicine physicians prescribed naltrexone to only 13% of their patients with AUD and that prescription frequency was associated with physicians' perception of naltrexone efficacy. Although numerous clinical trials have shown significant effects of naltrexone on primary and secondary drinking outcomes, the effect size is modest (3). For example, a recent meta-analysis of 27 randomized clinical trials including 2253 patients found that naltrexone decreased the chance of relapse to heavy drinking by only 15% compared with placebo (4,5). In an attempt to explore possible ways to increase the effect size, potential moderators of the response to naltrexone have been sought (6,7).

The efficacy of naltrexone has long been attributed to its interactions with the mu opioid receptor despite its nonselectivity among all three opioid receptor subtypes (mu, delta, and kappa) (8). This perspective is largely driven by the affinity profile of naltrexone, with higher affinity for mu (K_i = 1.0 nM) compared with delta and kappa (K_is = 149 and 3.9 nM, respectively) (9). Furthermore, polymorphisms of the mu opioid receptor gene, *OPRM1*, have been observed to modify naltrexone efficacy (10–12), although not in all studies (10,13). Meanwhile, recent evidence has also implicated the delta opioid receptor and

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ISSN: 0006-3223

kappa opioid receptor (KOR) and their endogenous ligands in AUD (14,15). For example, neuroimaging studies using positron emission tomography (PET) imaging with the selective KOR radioligand [^{11}C]LY2795050 found that individuals with AUD have lower kappa receptor densities than matched control subjects (16). In addition, the endogenous ligands of all three receptors have been reported to be released in rats upon acute alcohol administration (17–19). Consistent with their role in AUD, it has been suggested that therapeutic approaches targeting the KOR have the potential to achieve greater efficacy in reducing drinking than nonselective antagonists such as naltrexone (20). This implies that the mechanism through which naltrexone exerts its effect extends beyond mu pharmacology and emphasizes the potential influence of the KOR on successful naltrexone treatment outcome.

Further understanding of the factors involved in moderating naltrexone treatment outcomes could lead to greater overall therapeutic efficacy through identification of either susceptible patient groups or specific pharmacological targets. We hypothesized that KOR availability would be related to behavior and craving during an alcohol drinking paradigm (ADP) and that it modulates the effect of naltrexone on these behaviors during the ADP. [^{11}C]LY2795050 PET was used to investigate the potential involvement of the KOR in craving and drinking behavior among alcohol-dependent heavy drinkers during an ADP (21,22) following 1 week of treatment with open-label 100-mg daily naltrexone.

METHODS AND MATERIALS

Subjects

We recruited non-treatment-seeking participants who met DSM-IV criteria for alcohol dependence and were drinking at or above 20 drinks/week for women and 25 drinks/week for men as determined with a 90-day timeline followback assessment (23). Written informed consent was obtained for each participant, followed by psychiatric and physical evaluations and laboratory assessments, including urine toxicology and liver function tests. Exclusion criteria included current use of psychotropic medications, medical contraindications to naltrexone or alcohol, a history of significant alcohol withdrawal or current Clinical Institute Withdrawal Assessment for Alcohol–Revised scale withdrawal score greater than 8, diagnosis of DSM-IV substance abuse or dependence other than alcohol or nicotine, pregnancy, and breastfeeding (24). Procedures were approved by the Yale Human Investigation Committee and followed the National Institute on Alcohol Abuse and Alcoholism guidelines for administering alcohol in human experimentation (25).

Subjects participated in two PET scans and ADP sessions. The first PET scan and ADP session (ADP1) were conducted prior to initiation of naltrexone treatment. The second PET scan and ADP session (ADP2) were conducted after 7 or 8 days of naltrexone treatment. The second PET scan, conducted 2 hours after the last naltrexone dose, was used to measure receptor occupancy, i.e., what fraction of the receptors was occupied by naltrexone. (Results will be reported in a separate publication.) ADPs were performed, on average, 2.2 ± 0.5 days after the corresponding PET scan and never on the same day. A progressive dosing regimen was used to minimize the chance of adverse effects. According to this regimen, participants received 25 mg of naltrexone on the first day, 50 mg on the second day, and 100 mg on the remaining days up to and including the day of ADP2. Immediately prior to PET procedures and the ADPs, urine toxicology screens and breath alcohol tests were conducted to verify overnight abstinence from alcohol and other substance use. All women of childbearing age received urine pregnancy tests to confirm that they were not pregnant prior to either procedure.

PET Procedures

Dynamic PET scans were acquired on a high-resolution research tomography scanner (Siemens/CTI, Knoxville, TN) for 90 minutes starting with [^{11}C]LY2795050 bolus injection over 1 minute. Arterial lines were placed in the arms of the participants to obtain blood samples for measurement of [^{11}C]LY2795050 concentrations in plasma. After reconstruction and motion correction, partial volume correction was performed as described earlier (26). A structural T1 image was acquired on a 3T scanner (Trio; Siemens Medical Systems, Erlangen, Germany) for anatomical registration of the PET data. Individual images were registered to Montreal Neurological Institute space, and six bilateral regions of interest were identified; amygdala, pallidum, striatum, hippocampus, frontal cortex, and cingulate cortex. For every region, a time–activity curve was extracted and modeled using the multilinear analysis 1 method (t^* = 30 minutes) to estimate the total volume of distribution (V_T) (27), where V_T is equal to the sum of nonspecific and specific binding. Because we have previously shown that exposure to alcohol does not change nonspecific binding, we use V_T as a surrogate measure of kappa receptor availability (16). In addition, a voxelwise analysis was conducted using the same model. Because of noise in the dynamic PET data at the voxel level, the multilinear analysis 1 model occasionally produced poor fits and nonphysiological V_T values at individual voxels. Therefore, voxels with a V_T below 0 or above the 95th percentile were replaced with the median of their 26 nearest-neighbor voxels. Voxelwise regression was performed in SPM12 using variables of interest as covariates (28). For the craving measures, the area under the curve was used as a summary statistic in these voxelwise regressions. Thresholds in SPM were set at $p < .005$ uncorrected at the voxel level and cluster extent > 150.

ADP Procedures

Subjects were admitted to the Hospital Research Unit at Yale–New Haven Hospital on the day of each ADP. At 4 PM, participants began the alcohol drinking session using procedures based on our earlier work (21,22,29). Briefly, following completion of baseline measures of craving and other subjective reports, participants consumed a priming alcoholic drink (0.03 g/dL), followed by a 50-minute monitoring period, and were then exposed to three 1-hour self-administration periods. During each of the three self-administration periods, participants were offered a choice between consuming up to 4 alcoholic drinks (0.015 g/dL) or receiving $3 for each drink declined; drinking during the ADP was quantified as the total number of drinks consumed from the 12 drinks offered during the three self-administration periods. Subjects could participate in the study only if they liked and regularly drank mixed

drinks. Based on their own reports, the drinks presented during the ADP were each participant's favorite combination of juice and ethanol. Drinks were mixed to contain 10% volume/volume ethanol, which is similar to commercial mixed-drink cocktails.

In addition, craving was assessed throughout the laboratory session with the Yale Craving Scale (YCS) and the Alcohol Urge Questionnaire (AUQ) (30,31) (Figure 1). After completion of the ADP session, participants spent the night at the Hospital Research Unit for monitoring and were discharged the next morning. Subsequently, participants received once-daily oral generic naltrexone for 6 days as outpatients; participants came in daily (between 10 AM and noon) to take their naltrexone dose and report any adverse events. On the seventh or eighth day (depending on scheduling at the Hospital Research Unit), they completed the ADP procedure again, following administration of a last dose of naltrexone at 10 AM. On discharge, participants received an intervention that included feedback about their heavy drinking behavior from a licensed clinical psychologist (32). ADP outcomes were the total number of drinks consumed during the self-administration periods in each session, and craving was assessed using the YCS and AUQ (obtained at 17 time points).

Analysis

Data analyses were conducted using JMP Pro 13 (SAS Institute, Cary, NC). Two primary outcomes were investigated: the difference in the total number of drinks consumed from the first ADP to the second ADP, and the craving experienced during each ADP. Least absolute shrinkage and selection operator (LASSO) regressions evaluated the associations between the difference in drinking and baseline KOR availability, whereas the longitudinal craving data (AUQ and YCS) were modeled with linear mixed models. Mixed models included experimental period and ADP number and their interaction as fixed effects and subjects as a random effect. Variance–covariance structure of repeated measures per ADP was modeled using a first-order autoregressive structure. Multiple testing correction was performed using the Benjamini–Hochberg procedure (33). Demographics and descriptive statistics are reported as median and range. Statistical outcomes are reported with their standard error, and significance was defined at the .05 level.

RESULTS

Baseline Characteristics

Participants (32 male and 16 female) were 32 (21–61) years of age [median (range)] and identified as African American (47%), Caucasian (41%), or Hispanic (12%). Participants were balanced in family history of alcoholism (41% negative and 59% positive) and smoking status (57% nonsmokers and 43% smokers). Participants reported to have been drinking for 14 (4–47) years. Recent drinking as quantified by the 30-day Timeline Followback showed 6.1 (3.8–7.0) drinking days per week with 7.1 (3.9–18.4) drinks per drinking day. No baseline characteristics were significantly associated with baseline KOR availability except for a positive correlation with age and the number of years of drinking; significant effects were found only for age and years of drinking on the KOR availability in the cingulate cortex ($t_{48,1}$ = 2.94, p = .0052 and $t_{48,1}$ = 2.74, p = .0088, respectively) and prefrontal cortex ($t_{48,1}$ = 3.05, p = .0038 and $t_{48,1}$ = 2.76, p = .0083, respectively). Because age and years of drinking are highly correlated (r = .93, $p < .0001$) and age has previously been shown to have no effect on KOR availability, only years of drinking was included in the analysis as a covariate (16).

Alcohol Drinking Paradigm

Participants consumed significantly fewer drinks during the self-administration period in the second ADP [2 (0–12)] than in the first ADP [8 (1–12)] ($Z = -4.4$, $p < .0001$). In parallel, craving in the second ADP was significantly lower than that in the first ADP (AUQ: effect, -6.4 ± 0.55, $F_{1,1399}$ = 136, $p < .0001$; YCS: effect, -12.8 ± 0.85, $F_{1,1590}$ = 226, $p < .0001$). The temporal pattern of craving was also found to be different between ADPs for the AUQ ($F_{2,1398}$ = 5.8, p = .003) and YCS ($F_{2,1590}$ = 9.6, $p < .0001$).

Kappa Receptors and Drinking

An analysis including all regions showed that a greater reduction in drinking was observed in subjects with a lower KOR availability (effect: -2.9 ± 1.3), that is, average reduction in drinking per 1 increase in [^{11}C]LY2795050 V_T (χ^2 = 5.5, p = .019). Post hoc tests localized this effect in the striatum (effect: -3.4 ± 1.2, χ^2 = 8.1, R^2 = .21, p = .005) and found trends in the pallidum (effect: -1.8 ± 0.8, χ^2 = 5.2, R^2 = .19, p = .023), cingulate cortex (effect: -2.7 ± 1.2, χ^2 = 5.5, R^2 = .18, p = .018), and prefrontal cortex (effect: -2.7 ± 1.4, χ^2 = 5.81, p = .059) (Figure 2) that did not survive multiple testing correction. No significant relationships were found between KOR availability and drinking during either ADP1 or ADP2 for any region.

The greater reduction in drinking by particpants with lower KOR was also observed in the voxelwise analysis, which showed three significant clusters of voxels in the bilateral insula (left: X = 40, Y = 24, Z = −6, extent = 157, $p_{Cluster}$

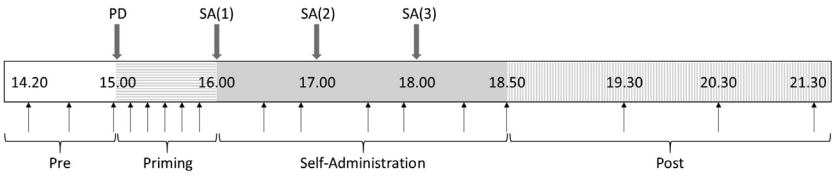

Figure 1. Detailed overview of the alcohol drinking paradigm. Gray downward arrows indicate times at which either the priming drink (PD) was presented or 4 drinks were presented for self-administration (SA). Black upward arrows indicate times at which craving was assessed using the Alcohol Urge Questionnaire and the Yale Craving Scale. Post, period following SA when drinks are no longer available; Pre, baseline period; Priming, period starting from priming drink consumption.

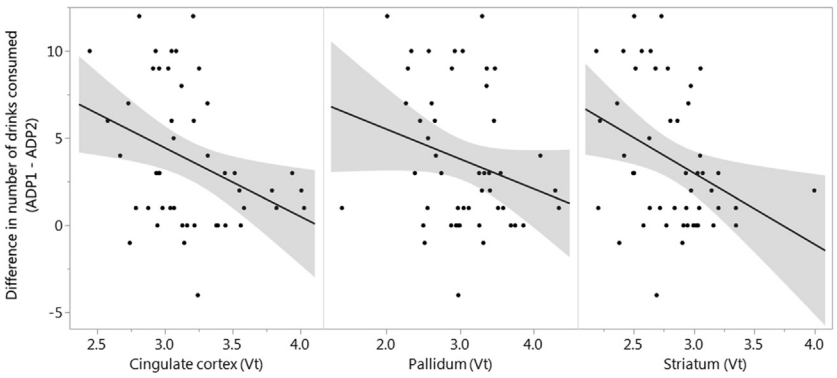

Figure 2. Greater kappa opioid receptor availability in the cingulate cortex as measured with [^{11}C]LY2795050 at baseline is associated with a smaller reduction in the number of drinks consumed in an alcohol drinking paradigm after a week of 100 mg/day naltrexone (effect: -2.7 ± 1.2, $\chi^2 = 5.5$, $p = .018$). Similar effects were observed for the pallidum (-1.8 ± 0.8, $\chi^2 = 5.2$, $p = .023$) and the striatum (effect: -3.4 ± 1.2, $\chi^2 = 8.1$, $p = .005$). Only the association in the striatum survived multiple comparison correction. ADP1, first alcohol drinking paradigm session; ADP2, second alcohol drinking paradigm session; Vt, total volume of distribution.

$_{\text{familywise error}} < .0001$; right: X = −36, Y = −4, Z = 6, extent = 159, $p_{\text{Cluster familywise error}} < .0001$) as well as in the left prefrontal cortex and bilateral anterior cingulate cortex (X = −2, Y = −10, Z = 36, extent = 173, $p_{\text{Cluster familywise error}} < .0001$) (Figure 3).

Kappa Receptors and Craving

Analysis over all regions showed a significant association between KOR availability at baseline and craving as assessed with the YCS ($F_{3,9808} = 12.6$, $p < .0001$). Post hoc analysis showed that higher kappa availability was associated with higher time-varying craving during both ADPs in all regions, that is, the amygdala ($F_{3,949} = 7.1$, $p = .0001$), hippocampus ($F_{3,957} = 5.5$, $p = .0009$), pallidum ($F_{3,954} = 3.9$, $p = .009$), striatum ($F_{3,963} = 8.3$, $p < .0001$), cingulate cortex ($F_{3,953} = 8.3$, $p < .0001$), and prefrontal cortex ($F_{3,951} = 10.3$, $p < .0001$). Higher KOR availability in the hippocampus was also associated with higher overall level of craving in both ADPs ($F_{1,89} = 5.6$, $p = .020$), although this relationship did not survive multiple testing correction. To illustrate the relationships described above, we divided the cohort by KOR availability in the hippocampus at baseline using a median split. Figure 4 shows craving for the resulting high and low KOR availability groups.

Using the AUQ, a significant association between KOR availability and craving was also found over all regions ($F_{3,8657} = 4.2$, $p = .0053$). Post hoc analysis showed that higher KOR availability was associated with higher time-varying craving during both ADPs in the hippocampus ($F_{3,680} = 5.7$, $p = .0007$), with a trend in the cingulate cortex ($F_{3,682} = 4.1$, $p = .007$) and prefrontal cortex ($F_{3,685} = 2.7$, $p = .048$). Higher KOR availability in the hippocampus was also significantly associated with a higher overall level of craving in both ADPs ($F_{1,85} = 5.3$, $p = .024$), although this relationship did not survive multiple testing correction.

Voxelwise analyses covarying for the YCS and AUQ did not find any clusters of significant association between kappa availability and craving.

DISCUSSION

Reductions in drinking and craving following 100 mg/day of naltrexone in non-treatment-seeking heavy drinkers were

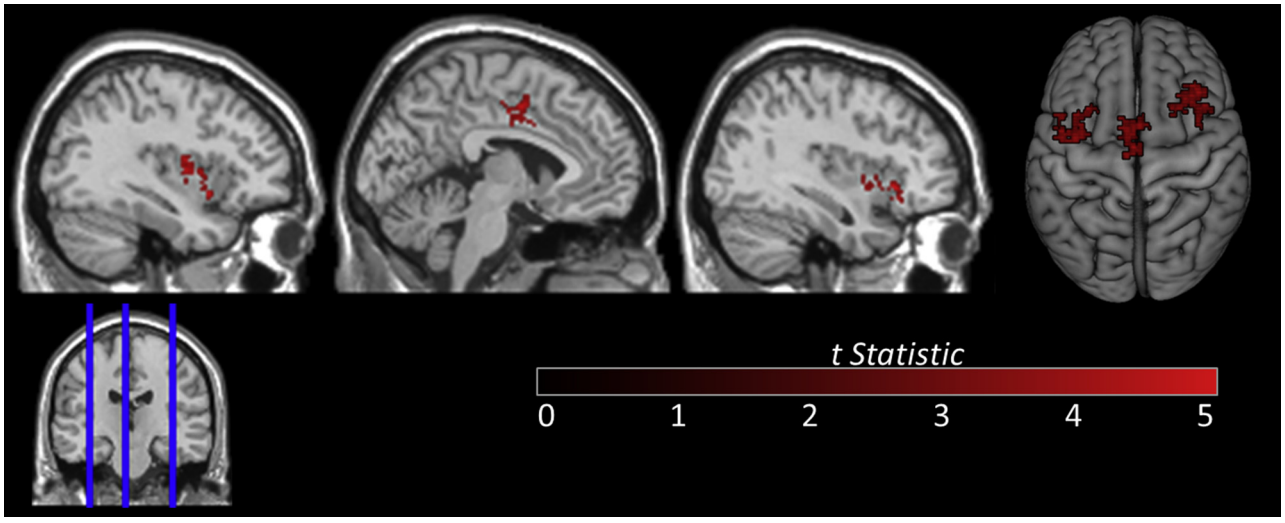

Figure 3. Voxelwise analysis reveals that the larger reduction in drinking between the first and second alcohol drinking paradigm sessions is associated with lower kappa opioid receptor availability in the bilateral insula, left prefrontal, and bilateral anterior cingulate cortex.

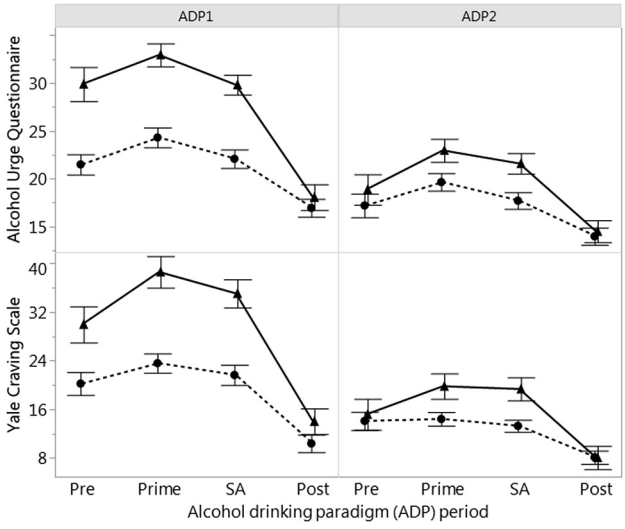

Figure 4. Self-reported craving in the different experimental periods measured with the Yale Craving Scale and the Alcohol Urge Questionnaire during the first alcohol drinking paradigm session (left half) and the second alcohol drinking paradigm session (right half). Triangles and full lines represent the average for individuals with median or higher kappa opioid receptor availability in the bilateral hippocampus. Circles and dotted lines show the average for individuals with below-median kappa opioid receptor availability. The x-axis describes distinct periods of the experiment. Post, self-administration has concluded and drinks are no longer available; Pre, baseline period; Prime, period starting from priming drink consumption; SA, self-administration period. Error bars represent standard error of the mean.

associated with KOR availability prior to naltrexone treatment. Specifically, higher KOR availability in the striatum, insula, cingulate cortex, and prefrontal cortex each was associated with smaller reduction in the number of consumed drinks during the ADP before and after naltrexone treatment. Higher KOR availability in both limbic and frontal regions was found to be associated with higher craving during the ADPs, as measured with the AUQ and YCS.

The current results agree with our previous findings that naltrexone decreases the amount of alcohol consumed and the urge to drink in individuals with AUD given a choice between alcohol and money (21). The exact molecular mechanism through which naltrexone exerts these effects is not clear, potentially because of the complex pathway through which alcohol exerts its rewarding effects; alcohol-induced dopamine release depends on dopamine, serotonin, glutamate, glycine, cannabinoid, and opioid receptors and is also the result of a direct excitatory effect (34–41). However, it has been established, preclinically, that naltrexone can attenuate ethanol-induced dopamine release in brain regions associated with reward such as the nucleus accumbens (42). This attenuation is thought to be a result of the regulatory opioidergic system, which may modify dopamine release through the opposing effects of the mu and kappa opioid systems. It has been shown that mu receptor agonist binding in the ventral tegmentum area, the origin of mesolimbic dopaminergic projections, increases tonic dopamine levels, whereas KOR agonists decrease basal dopamine (43–47). KOR activity induces a decrease in mood, whereas KOR antagonism can block drug withdrawal effects (48,49). Recent studies have suggested that the underlying KOR-mediated hyperpolarization of dopaminergic neurons could vary according to the target region of those neurons (50,51). KOR-mediated inhibition is thought to be caused by a direct effect on dopaminergic terminals, but KOR activation can disinhibit dopaminergic activity (49,52). This excitatory effect is based on the inhibition of somatodendritic dopamine release that would otherwise have had an inhibitory effect via the dopamine D_2 receptor on the dopaminergic neurons (52). Interestingly, dopamine D_2 receptor downregulation has been proposed as a mechanism for the enhanced dopamine release after repeated, but not acute, KOR agonist exposure observed in animals (47). Repeated KOR agonist exposure did not, however, decrease the number of available KORs (53). Finally, the respective timing of KOR agonists and dopamine release–inducing drugs is probably important (54).

If KORs decrease tonic dopamine levels, individuals with higher kappa receptor activity could have lower basal dopamine levels. It has been shown that a hypoactive dopaminergic system is linked with higher craving and alcohol consumption (55), which is consistent with our results. Nonselective opioid antagonists can decrease basal dopamine levels through their antagonistic effect on the mu receptor (56). Therefore, we would expect that individuals in a hypodopaminergic state would benefit less from nonselective opioid antagonist treatment. This explanation remains speculative because the dynamic between chronic KOR activation and dopamine levels, described above, is complex and not yet fully understood. We observed that participants with higher KOR availability in the striatum, pallidum, cingulate cortex, and prefrontal cortex had a smaller reduction in the number of drinks consumed during the ADP after naltrexone treatment. No association with baseline craving or a trend toward a positive association between craving and naltrexone efficacy has also been reported (57,58). Therefore, future investigations are warranted to elucidate what aspects there are to the association between craving and naltrexone efficacy.

More severe AUD has been associated with weaker functional connectivity between the striatum and cognitive control areas such as the insula, cingulate cortex, and prefrontal cortex (59). In addition, addictive behavior has been reported to influence the kappa opioid system in brain regions involved in cognitive control (60). This corroborates our results. We observed a relationship between the efficacy of naltrexone treatment and kappa receptor availability in the striatum, pallidum, insula, cingulate cortex, and prefrontal cortex. An important overlap exists between these regions and the regions for which mu opioid receptor availability was found to be predictive of treatment outcome in cocaine abusers (61). These observations provide further insight into the intricate balance between the pharmacological effects of mu and kappa (43). Therefore, future studies investigating both mu and KOR availabilities in these regions in the same participants would be of interest.

KORs may have a role in decreasing the hedonic state of an individual, thereby increasing the tendency to restore the hedonic state through exogenous drugs (62,63). On the one hand, this hypothesis is based on literature showing that polymorphisms in delta and KORs (*OPRD1* and *OPRK1*, respectively) influence the effect that naltrexone can have on the subjective experience of alcohol exposure (64). In addition,

OPRK1 polymorphisms have also been associated with higher cortisol levels, greater stress-induced craving, and greater relapse risk in cocaine addiction (65). On the other hand, this hypothesis is based on preclinical literature showing that KOR agonists reinstate drug- and alcohol-seeking behavior (66–69), whereas KOR antagonists attenuate the development of depressive-like behaviors in cocaine withdrawal (70). Our finding that participants with higher KOR availability experienced a higher craving level during an ADP is consistent with the latter hypothesis and its underlying evidence. An additional finding is that KOR availability in the hippocampus was associated with the craving levels in each experimental phase during both ADPs. This region has been implicated before in a functional magnetic resonance imaging study that compared opioid receptor kappa 1 variant groups during stress cues (65). Although more research is required, these previous results combined with our results suggest a potential link among the KOR, stress sensitivity, and craving.

Two major limitations of this study should be considered. First, low radiotracer binding may be related to low receptor availability, high endogenous ligand, or both. The competing endogenous ligand for [^{11}C]LY2795050 is dynorphin. Heavy alcohol use has been reported to increase dynorphin levels in humans in some brain regions (60,71). In contrast, we have previously shown that the low KOR availability in individuals with AUD compared with healthy control subjects is homogeneous throughout the brain (16). In healthy control subjects, a strict balance exists between dynorphin concentrations and kappa receptor expression (60), but it is unclear whether alcohol abuse could shift this balance. Therefore, we cannot rule out the possibility that differences in dynorphin concentrations contributed to the observed effects. Second, this study did not include a placebo group; as a result, it is possible that factors other than naltrexone contributed to the observed reduction in drinking and craving during ADP2. Although our study reports on an association between behavior and the KOR, and not on the efficacy of naltrexone, a placebo effect cannot be ruled out completely.

We showed a reduction in both drinking and craving during a controlled lab drinking session after a week of open-label naltrexone. Moreover, the reduction in drinking was associated with KOR availability in frontal and limbic brain regions. KOR availability was also associated with craving during the ADPs. In summary, we believe that we have established for the first time in vivo that the KOR has a role in both craving and the reduction in drinking after naltrexone. Future studies are necessary to understand the exact molecular mechanisms that underlie these observations. However, these results are an important advancement toward understanding the role of the KOR in motivational processes in AUD.

ACKNOWLEDGMENTS AND DISCLOSURES

This work was supported by National Institute on Alcohol Abuse and Alcoholism Grant No. AA021818 (to EDM and SK-S), National Center for Advancing Translational Sciences Grant No. UL1 TR000142 (to Yale School of Medicine–Hospital Research Unit), National Institute of Mental Health Grant No. MH091537 (to YH), and the Yale Center for Translational Neuroscience of Alcoholism (to SK-S and SSO).

This work would not have been possible without the work of the Yale PET center chemistry team, imaging technologists, and nurses. Special thanks go to Ralitza Gueorguieva, Ph.D., for her advice on the statistical analysis.

SK-S received donated research study medications from AstraZeneca and Novartis. EDM has received travel and lodging from Shandong Madic Technology; it was not related to the current study. SSO discloses having been a consultant or an advisory board member for Alkermes, Amygdala, Indivior, Mitsubishi Tanabe, and Opiant, including nonfinancial support (e.g., travel to advisory meeting); receiving study medications from AstraZeneca, Novartis, and Pfizer; being a Data and Safety Monitoring Board member for the National Institute on Drug Abuse (EMMES Corporation) and a member of the American Society of Clinical Pharmacology Alcohol Clinical Trials Initiative supported by Alkermes, Amygdala, Ethypharm, Lilly, Lundbeck, Otsuka, Pfizer, and Indivior. All other authors report no biomedical financial interests or potential conflicts of interest.

ClinicalTrials.gov: Kappa-PET Imaging and Naltrexone in Alcohol Drinking Behaviors; https://clinicaltrials.gov/ct2/show/NCT01625611; NCT01625611.

ARTICLE INFORMATION

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Received Feb 22, 2019; revised May 23, 2019; accepted May 28, 2019.

Supplementary material cited in this article is available online at https://doi.org/10.1016/j.biopsych.2019.05.021.

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