Biological Psychiatry: Celebrating 50 Years

Kappa Opioid Receptors and Mu Opioid Receptors as Combined Targets for Medication Development for Alcoholism

Yan Zhou and Mary Jeanne Kreek

After chronic alcohol exposure, kappa opioid receptor (KOR) activation prompts negative mood states and symptoms that are involved in negative reinforcing aspects of alcohol addiction. Stress or "classic" KOR agonist has been found to induce alcohol-seeking behavior and promote alcohol relapse–like drinking. In this issue of *Biological Psychiatry*, a new publication from de Laat *et al.* (1) studied non-treatment-seeking heavy drinkers who met the DSM-IV criteria for alcohol dependence. First, using positron emission tomography with the selective KOR radioligand [^{11}C]LY2795050, de Laat *et al.* (1) found that alcohol-dependent individuals with higher KOR availability experienced a higher craving level during a laboratory-based alcohol drinking test compared with the ones with lower KOR availability. Specifically, higher KOR availability in the amygdala, pallidum, striatum, cingulate cortex, prefrontal cortex, and hippocampus was found to be associated with higher craving. These exciting data are consistent with the above-mentioned "negative reinforcing hypothesis" and have provided, for the first time, evidence that the KOR may play a role in alcohol craving in humans, confirming early studies in rodent models (2). de Laat *et al.* (1) suggest that because KOR has tonic inhibition of dopamine release in the central nervous system, individuals with alcoholism who have higher KOR availability/activity could have lowered basal dopamine tone, which could be involved in higher craving and alcohol consumption. In rodents, activation of KOR/endogenous dynorphin transmission is a key mediator of stress-induced dysphoria, aversion, and anxiety-like and depression-like behaviors, and also acts as a counter-regulator on dopamine and mu opioid receptor (MOR) activations (3). The selective blockade of KOR attenuates excessive drinking and stress-induced alcohol seeking in mice and rats (2,4). These findings not only provide support for the critical involvement of the KOR/dynorphin activity in the process of alcohol addiction but also strongly suggest that KOR antagonists may offer a strategy to treat alcohol dependency, especially in patients with high levels of stress, like those with posttraumatic stress disorder.

de Laat *et al.* (1) proposed the potential molecular mechanisms for high radiotracer binding for KOR because it may be related to low levels of dynorphin, the competing endogenous KOR ligand for [^{11}C]LY2975050. There is a compensatory increase in basal KOR expression and availability levels that is likely due to a relative dynorphin deficiency. Therefore, the current results also support the "relative dynorphin deficiency" hypothesis in alcoholism (3). Indeed, pharmacological studies in rodents have demonstrated that KOR agonists decrease alcohol drinking and reward. However, classic KOR agonists yield dysphoria, depression, and sedation in humans, and these side effects limit the potential of their clinical use. We recently examined the pharmacological effects of the highly potent KOR agonist nalfurafine on alcohol drinking in mice; nalfurafine is the first and only currently clinically approved KOR agonist (in Japan) for treatment of pruritus, with a lack of side effects (e.g., dysphoria, sedation, or depression), as reported in a recent postmarket survey of nalfurafine safety in more than 3700 patients in Japan (5). We found that nalfurafine dose-dependently reduced alcohol consumption in an excessive drinking paradigm (an appropriate animal model for high alcohol consumption) with few side effects; repeated administrations of nalfurafine decreased alcohol consumption without showing any tolerance (6). Therefore, the clinically used KOR agonist nalfurafine may have some potential for treating alcohol addiction.

The brain dynorphin/KOR systems have been found to be activated in several neuronal regions in humans and rodents after excessive alcohol drinking, which could produce sedation, dysphoria-like, anxiety-like, or depression-like behavior that may promote excessive drinking (2,4). For example, several groups have shown that there are increases in the KOR activity and dynorphin messenger RNA levels observed in rodent extended amygdala after chronic alcohol consumption (2). Our recent finding that the highly potent KOR agonist nalfurafine at low doses (3–10 μg/kg) decreased, rather than increased, drinking seems to conflict with studies using the classic KOR agonists, such as U50,488H, at doses of 1–3 mg/kg. In contrast, nalfurafine at clinically effective doses does not produce such side effects in humans or rodents (5,6). Alternatively, nalfurafine could compete to bind the KOR with excessive dynorphin, which may be responsible for decreasing excessive alcohol consumption. In the current study, de Laat *et al.* (1) addressed the potential limit of our understanding on the KOR system: "In healthy control subjects, a strict balance exists between dynorphin concentrations and kappa receptor expression, . . . 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." Therefore, further studies investigating both dynorphin and KOR in specific brain regions would be interesting and are needed.

Alcohol stimulates dopamine release in the striatum, and nalfurafine may prevent the dopamine surge induced by

SEE CORRESPONDING ARTICLE ON PAGE 864

https://doi.org/10.1016/j.biopsych.2019.08.011
ISSN: 0006-3223

alcohol drinking. Alternatively, nalfurafine may activate the hypothalamic-pituitary-adrenal axis, and the enhanced hypothalamic-pituitary-adrenal axis activity may prevent alcohol relapse drinking and craving, as demonstrated in humans (7). With few side effects, such as sedation and anxiety-like and depression-like behavior, nalfurafine's effects on dopamine and the hypothalamic-pituitary-adrenal axis could be responsible, at least in part, for the observed reduction of excessive alcohol drinking in mice (6).

Second, in this new study, de Laat *et al.* (1) further confirm a reduction in both alcohol consumption and craving during a controlled laboratory drinking session after a week of open-label naltrexone (100 mg/day). Alcohol increases MOR-mediated transmission, and binding of endogenous β-endorphin to MOR is, in part, responsible for alcohol's positive reinforcing and motivational properties, which is involved in excessive alcohol consumption and relapse episodes. Naltrexone (an MOR antagonist with a high affinity at the MOR and a KOR partial agonist) decreases alcohol craving and relapse in humans with alcoholism (8). Preclinical studies have consistently shown that naltrexone decreases the alcohol-rewarding effect and reduces alcohol intake, consistent with many clinical reports (2).

Third, using KOR positron emission tomography imaging, de Laat *et al.* (1) extended their earlier study on the potential role of KOR in people with alcoholism and found that the decrease of alcohol drinking after 1 week of naltrexone treatment was associated with basal KOR availability in the cingulate cortex, prefrontal cortex, striatum, pallidum, and hippocampus. Therefore, the findings indicate that KOR availability is involved in the alcohol consumption response to naltrexone treatment in humans. Individuals with higher KOR activity may respond less to naltrexone treatment, as de Laat *et al.* (1) suggested a potential influence of the KOR activity (or KOR/dynorphin balance after alcohol) on successful outcome of naltrexone treatment. Of interest, the new finding provides new insight into the complicated balance between the pharmacological effects of KOR and MOR, but further studies are needed to fully understand the molecular mechanisms. As the investigators point out, therapeutic approaches targeting the KOR have the potential to achieve greater efficacy in reducing excessive drinking than naltrexone alone.

Neurobiological studies have demonstrated that both the MOR and KOR pathways—among multiple actions of alcohol in the central nervous system—are profoundly altered by alcohol consumption, and we have recently hypothesized that by targeting on both the MOR and KOR, the combination of MOR antagonists and KOR agonists would enhance efficacy over the single-compound approach on reducing excessive drinking and preventing relapse (2). Indeed, we found that naltrexone combined with the clinically used nalfurafine is more effective than either drug alone in both male and female mice—the combination of low-dose naltrexone with nalfurafine displayed synergistic effects on reducing excessive and relapse-like drinking, and each compound alone at low doses had no effect (6). In support of this idea, the effective medication nalmefene is a MOR antagonist with KOR partial agonism (9), and it possibly synergistically reduces alcohol consumption by targeting both the MOR and the KOR. Nalmefene is now approved in Europe for reducing alcohol consumption in alcohol-dependent patients (10).

In conclusion, single-receptor pharmacotherapies have been recently found to have modest therapeutic value, suggesting a need for better efficacy. Our recent study in mice has provided promising in vivo data demonstrating that the clinically used KOR agonist nalfurafine, in combination with low-dose naltrexone, may offer a novel strategy to treat excessive alcohol consumption and relapse (6). From the clinical development standpoint, this strategy benefits from the fact that the combinations are effective at low doses of each compound, which may provide a low risk of aversive effects. This KOR positron emission tomography imaging study in humans provides further support of this new strategy by targeting both KORs and MORs as combined targets for the development of therapies for alcoholism (1).

Acknowledgments and Disclosures

The authors report no biomedical financial interests or potential conflicts of interest.

Article Information

From the Laboratory of the Biology of Addictive Diseases, The Rockefeller University, New York, New York.

Address correspondence to Mary Jeanne Kreek, M.D., Laboratory of the Biology of Addictive Diseases, The Rockefeller University, 11230 York Avenue, New York, NY 10065; E-mail: kreek@mail.rockefeller.edu.

Received Aug 15, 2019; accepted Aug 19, 2019.

References

1. de Laat B, Goldberg A, Shi J, Tetrault JM, Nabulsi N, Zheng M-Q, *et al.* (2019): The kappa opioid receptor is associated with naltrexone-induced reduction of drinking and craving. Biol Psychiatry 86:864–871.
2. Zhou Y, Kreek MJ (2018): Involvement of activated brain stress responsive systems in excessive and "relapse" alcohol drinking in rodent models: Implications for therapeutics. J Pharmacol Exp Ther 366:9–20.
3. Kreek MJ, Koob GF (1998): Drug dependence: Stress and dysregulation of brain reward pathways. Drug Alcohol Depend 51:23–47.
4. Walker B, Koob G (2008): Pharmacological evidence for a motivational role of kappa-opioid systems in ethanol dependence. Neuropsychopharmacology 33:643–652.
5. Kozono H, Yoshitani H, Nakano R (2018): Post-marketing surveillance study of the safety and efficacy of nalfurafine hydrochloride (Remitch® capsules 2.5 μg) in 3,762 hemodialysis patients with intractable pruritus. Int J Nephrol Renovasc Dis 11:9–24.
6. Zhou Y, Kreek MJ (2019): Combination of clinically utilized kappa-opioid receptor agonist nalfurafine with low-dose naltrexone reduces excessive alcohol drinking in male and female mice. Alcohol Clin Exp Res 43:1077–1090.
7. O'Malley SS, Krishnan-Sarin S, Farren C, Sinha R, Kreek MJ (2002): Naltrexone decreases craving and alcohol self-administration in alcohol-dependent subjects and activates the hypothalamic-pituitary-adrenocortical axis. Psychopharmacology 160:19–29.
8. O'Malley SS, Jaffe A, Chang G, Schottenfeld RS, Meyer RE, Rounsaville BJ (1992): Naltrexone and coping skills therapy for alcohol dependence: A controlled study. Arch Gen Psychiatry 49:881–887.
9. Bart G, Schluger JH, Borg L, Ho A, Bidlack JM, Kreek MJ (2005): Nalmefene induced elevation in serum prolactin in normal human volunteers: Partial kappa opioid agonist activity? Neuropsychopharmacology 30:2254–2262.
10. Mason BJ, Ritvo EC, Morgan RO, Salvato FR, Goldberg G, Welch B, *et al.* (1994): A double-blind, placebo-controlled pilot study to evaluate the efficacy and safety of oral nalmefene HCl for alcohol dependence. Alcohol Clin Exp Res 18:1162–1167.