Correspondence

Lack of Opioid System in the Antidepressant Actions of Ketamine

To the Editor:

The *N*-methyl-D-aspartate receptor antagonist ketamine can elicit rapid and sustained antidepressant effects in treatment-resistant patients with major depressive disorder. However, the precise molecular mechanisms underlying ketamine's antidepressant actions are currently unknown. Recently, Williams *et al.* (1) demonstrated the role of the opioid system in the rapid antidepressant effects of ketamine in patients with treatment-resistant major depressive disorder. In the small-sample, single-center crossover trial, the authors investigated the effects of pretreatment with the opioid receptor antagonist naltrexone (50 mg, 45 minutes before) on the antidepressant effects of ketamine (0.5 mg/kg, intravenous) in the patients. In ketamine-responsive patients with treatment-resistant depression, pretreatment with naltrexone profoundly attenuated ketamine's antidepressant effects, with none of the ketamine responders meeting the response criterion at day 1. Furthermore, there were no differences in ketamine-induced dissociation between two conditions. The authors conclude that opioid receptor activation is required for ketamine's acute antidepressant effects, although the dissociative effects of ketamine are not mediated by the opioid system (1). However, the sample size (n = 7) of ketamine-responsive patients is too small. In addition, there are currently no reports showing the role of opioid receptors in the antidepressant effects of ketamine in rodent models of depression. Therefore, the present study was undertaken to examine whether naltrexone can block the antidepressant effects of ketamine in chronic social defeat stress (CSDS) and lipopolysaccharide (LPS)-treated inflammation models of depression.

Male adult C57BL/6 mice (8 weeks of age, body weight 20–25 g; Japan SLC, Hamamatsu, Japan) and male adult CD1 mice (13–15 weeks of age, body weight >40 g; Japan SLC) were used. This study was approved by the Chiba University Institutional Animal Care and Use Committee. Susceptible mice after CSDS and LPS (0.5 mg/kg)-treated mice were used as reported previously (2–5). Saline (10 mL/kg) or naltrexone (10 mg/kg as hydrochloride; Sigma-Aldrich, St Louis, MO) was administered intraperitoneally 30 minutes before intraperitoneal administration of ketamine (10 mg/kg as hydrochloride; Daiichi Sankyo, Tokyo, Japan) or saline (10 mL/kg). Behavioral tests such as the locomotion test, tail suspension test, forced swimming test, and 1% sucrose preference test were performed (Figure 1A, 1F). The data shown are the mean ± SEM. Data were analyzed using one-way analysis of variance, followed post hoc Fisher's least significant difference test.

There were no changes of locomotion among the five groups (Figure 1B, G). In the CSDS model, ketamine significantly attenuated the increased immobility time in the tail suspension test and forced swimming test in the susceptible mice (Figure 1C, 1D). Furthermore, ketamine significantly attenuated the decreased sucrose preference in the 1% sucrose preference test in the susceptible mice (Figure 1E). However, naltrexone did not block the antidepressant effects of ketamine in a CSDS model (Figure 1C–E). Furthermore, naltrexone alone did not show antidepressant activity in this model (Figure 1C–E). Moreover, naltrexone did not block the antidepressant effects of ketamine in LPS-treated mice (Figure 1H). Collectively, these results suggest that opioid receptors do not play a role in the antidepressant effects of ketamine in CSDS and LPS models, and that, unlike ketamine, naltrexone does not have rapid-acting and sustained antidepressant effects in these models.

Ketamine [or (*R,S*)-ketamine] is a racemic mixture containing equal parts of (*R*)-ketamine (arketamine) and (*S*)-ketamine (esketamine). (*S*)-ketamine has an approximately fourfold greater affinity for the *N*-methyl-D-aspartate receptor than (*R*)-ketamine (6). In addition, (*S*)-ketamine is also two to three times more potent than (*R*)-ketamine at the mu and kappa subtypes of the opioid receptors, although ketamine has a relatively low affinity at these subtypes (7). Interestingly, (*R*)-ketamine showed greater potency and longer-lasting antidepressant effects than (*S*)-ketamine in different animal models of depression (2–6). If opioid receptors play a key role in the antidepressant effects of ketamine, (*S*)-ketamine must be more potent than (*R*)-ketamine in animal models. In the conditioned place preference test, (*S*)-ketamine has greater abuse liability than (*R*)-ketamine (2), suggesting that *N*-methyl-D-aspartate receptor inhibition may play a role in ketamine's abuse liability. Taken together, it is unlikely that opioid receptors may play a role in abuse liability of ketamine because ketamine is an antagonist at opioid receptor subtypes (7).

Clinically achievable concentrations of ketamine interact with mu and kappa, but not delta, opioid receptors, in a competition fashion (7). In addition, ketamine produces functional antagonism of opioid receptor–mediated cellular signaling (7). Collectively, it seems that ketamine may be an antagonist at the mu and kappa subtypes (7). Given the antagonism of ketamine at opioid receptors, it seems that the lack of antagonism of ketamine's antidepressant effects by naltrexone is reasonable. Furthermore, we did not find antidepressant effects of naltrexone in CSDS and LPS models, although ketamine showed rapid and sustained antidepressant effects in the same models. Therefore, it is unlikely that opioid receptor antagonists have ketamine-like robust antidepressant effects because naltrexone is an antagonist at three subtypes (mu, kappa, and delta).

Kappa opioid receptors located within the mesolimbic system are essential for regulating mood and affective disorders (8). A previous report showed that buprenorphine (antagonist at kappa opioid receptors, and partial agonist at mu opioid receptors) showed antidepressant effects in an unpredictable chronic mild stress model (9). Furthermore, the study, using knockout mice, suggests the key role of kappa opioid receptors in the antidepressant effects of buprenorphine (9). A multicenter, randomized, double-blind,

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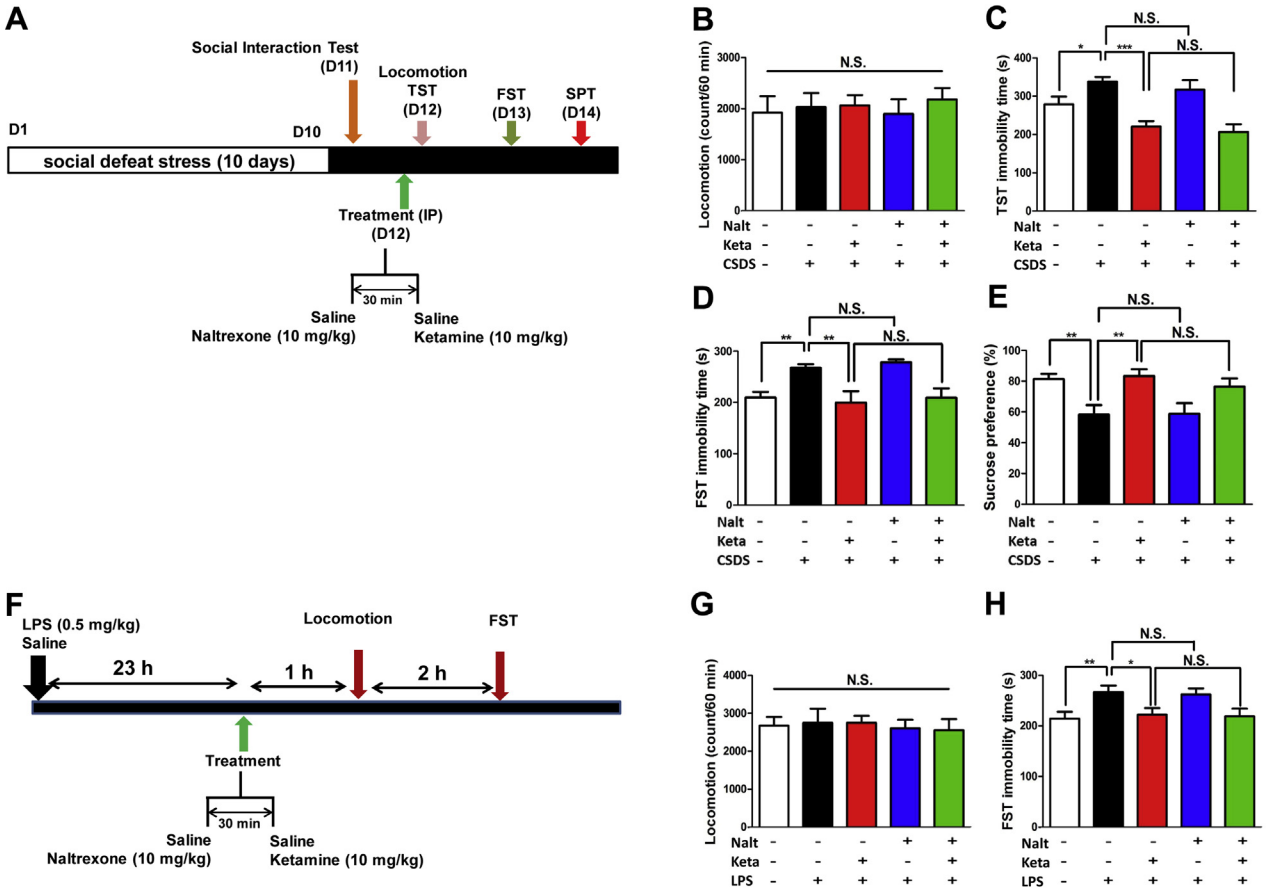

Figure 1. Effects of pretreatment with naltrexone on the antidepressant actions of ketamine. **(A)** Schedule of a chronic social defeat stress (CSDS) model, treatment, and behavioral tests. CSDS was performed from day 1 (D1) to D10, and the social interaction test was performed on day 11. On D12, saline (10 mL/kg) or naltrexone (Nalt) (10 mg/kg) was administered intraperitoneally in the susceptible mice 30 min before intraperitoneal (IP) administration of saline (10 mL/kg) or ketamine (Keta) (10 mg/kg). Locomotion test (LMT) and tail suspension test (TST) were performed 1 and 3 hours after a single injection of saline or Keta, respectively. The forced swimming test (FST) and 1% sucrose preference test (SPT) were performed 1 and 3 days after a single injection, respectively. **(B)** Locomotion (D12; one-way analysis of variance [ANOVA] [$F_{4,35} = 0.185$, $p = .945$]). **(C)** TST (D12; one-way ANOVA [$F_{4,35} = 9.473$, $p = .000$]). **(D)** FST (D13; one-way ANOVA [$F_{4,35} = 6.672$, $p = .000$]). **(E)** SPT (D14; one-way ANOVA [$F_{4,35} = 5.146$, $p = .002$]). In panels **(B–E)**, the values represent the mean ± SEM ($n = 8$). $^{*}p < .05$, $^{**}p < .01$, and $^{***}p < .001$ compared with saline-treated susceptible mice. **(F)** The schedule of the inflammation model and behavioral tests after treatment. Twenty-three hours after IP administration of saline (10 mL/kg) or lipopolysaccharide (LPS) (0.5 mg/kg), saline (10 mL/kg) + saline (10 mL/kg), saline (10 mL/kg) + Keta (10 mg/kg), Nalt (10 mg/kg) + saline (10 mL/kg), or Nalt (10 mg/kg) + Keta (10 mg/kg) were administered intraperitoneally. The LMT and FST were performed 1 and 3 hours after injection, respectively. **(G)** Locomotion for the LPS model (one-way ANOVA [$F_{4,35} = 0.112$, $p = .997$]). **(H)** FST for the LPS model ($F_{4,35} = 3.627$, $p = .014$). The values represent the mean ± SEM ($n = 8$). $^{*}p < .05$ and $^{**}p < .01$ compared with saline + LPS–treated mice. N.S., not significant.

placebo-controlled study showed that the combination of buprenorphine and samidorphan (a potent mu opioid receptor antagonist) is a novel and promising candidate for treatment of treatment-resistant major depressive disorder (10). Taken together, it is likely that kappa opioid antagonists would be potential therapeutic drugs for depression, although kappa opioid antagonists do not have ketamine-like robust antidepressant actions.

In conclusion, the current data suggest that the opioid system may not play a role in the antidepressant effects of ketamine in mice with a depression-like phenotype. Nonetheless, further detailed preclinical study and clinical study using a larger sample size will be needed to confirm the hypothesis that the opioid system plays a role in the antidepressant effects of ketamine.

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Article Information

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