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Esketamine Anesthetizes Mice With a Similar Potency to Racemic Ketamine

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Abstract

Esketamine, the right-handed optical isomer of racemic ketamine, has recently become widely used for anesthesia and analgesia as a replacement for racemic ketamine. However, there are limited studies comparing the anesthetic and analgesic effects of esketamine and racemic ketamine in mice. This research was conducted to analyze the dose-dependent anesthetic and analgesic efficacy of esketamine in mice and to compare its potency with that of the racemate. We tested the anesthetic effects of different doses of esketamine and compared its potency with that of the racemate using righting reflex tests. Then, the acetic acid-induced pain model and formalin-induced pain model were used to investigate the analgesic effect. Compared with racemic ketamine, an equivalent dose of esketamine at 100 mg/kg was required to induce stable anesthesia. In contrast, 5 mg/kg esketamine was sufficient to provide analgesic effects similar to those of 10 mg/kg ketamine. Together, esketamine had a similar potency to racemic ketamine for anesthesia and a stronger potency for analgesia in mice.

Keywords

ketamine, esketamine, anesthesia, analgesia

Introduction

Ketamine is a non-competitive antagonist of N-methyl-d-aspartate receptors (NMDARs), which were first synthesized in 1962 to alleviate the serious psychotomimetic side effects of phencyclidine (PCP) but retain its anesthetic effects.[1] Apart from its potent anesthetic and analgesic effects, ketamine can maintain airway reflexes and respiration and increase sympathetic activity; therefore, it is a preferable anesthetic option when resuscitation equipment is limited.[2] Since it was approved by the Food and Drug Administration (FDA) for anesthesia in 1970, ketamine has played an important role in specialist anesthesia and pain management.[2,3]

Ketamine is a racemate containing 2 optical isomers, esketamine and R(-)-ketamine. Esketamine, the right-handed optical isomer of racemic ketamine, is also widely used for anesthesia and analgesia.[4] In clinical anesthesia, esketamine, especially in combination with midazolam and/or propofol, can be used to preserve spontaneous ventilation during short procedures.[5,6] For pain management, esketamine is commonly used to treat various kinds of chronic pain syndromes.[7,8] It is also applied to control perioperative pain and reduce consumption of postoperative analgesics.[9,10] However, most studies have focused on racemic ketamine, and the anesthetic and analgesic effects of esketamine have been reported only in

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some limited clinical studies. The minimum doses of racemic ketamine to induce anesthesia and analgesia in mice are 100 mg/kg and 10 mg/kg, respectively, but the minimum doses of esketamine in mice have not been reported.[11,12] Although researchers have shown that esketamine has a higher affinity for NMDARs than racemate and R(-)-ketamine,[13] which may reduce the dose of esketamine required to produce equal anesthesia and analgesia in mice, the dose dependency of esketamine remains unknown.

In the present study, we investigated the doses of esketamine that produce anesthesia in mice and compared its anesthetic potency with that of the racemate using righting reflex tests. We also tested the analgesic effects of different doses of esketamine using an acetic acid-induced pain model and a formalin-induced pain model.

Materials and Methods

Animals

Male C57BL/6J mice at 12 to 18 weeks of age and weighing 25*g*–32*g* (purchased from SiPeiFu Biotechnology Co., Ltd., China) were used in this study. The animal experiments were approved by the Animal Care Committee of the Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine (Shanghai, China) and was carried out in compliance with the ARRIVE guidelines. All of the mice were housed with *ad libitum* access to water and food. They were maintained under controlled temperature with a 12-hour light/dark cycle (7 AM–7 PM). All experiments were performed between 9 AM and 5 PM

Anesthesia

Esketamine (Hengrui Pharmaceuticals Co., Ltd., China; 25 mg/mL) was dissolved in a sterile saline solution before intraperitoneal injection at 10 mL/kg body weight. Mice were randomly divided into 7 groups (n = 8 per group): 33.3, 50, 75, 90, 100, 120, and 150 mg/kg esketamine. The doses of racemic ketamine used for anesthesia in previous literature ranged from 75 to 150 mg/kg.[14-16] Considering the higher affinity of esketamine for NMDARs, we set the minimum dose at 33.3 mg/kg.

To explore differences in anesthetic effects between esketamine and the racemate, we also tested the anesthetic dose of racemic ketamine. Ketamine (Hengrui Pharmaceuticals Co., Ltd., China; 50 mg/mL) was dissolved in a sterile saline solution before intraperitoneal injection at 10 mL/kg body weight and doses of 80, 90, and 100 mg/kg (n = 5 in 90 mg/kg ketamine group and 8 in the other groups).

Anesthetic effects were evaluated by the absence or presence of the righting reflex, which was assessed by placing the mouse in the supine position and observing whether it was capable of turning prone. Many animal experiments have used loss of the righting reflex (LORR) as a behavioral indicator of general anesthesia since LORR was found to be closely related to loss of consciousness (LOC) in humans.[17] A warming blanket was used to maintain the body temperature and the experimental process was recorded by video. The investigators were blinded to the experimental groups during scoring. The induction time was defined as the time from esketamine injection to complete LORR, and the duration was defined as the time from LORR reflex to recovery of the righting reflex. All mice subjected to the experiment were included for the statistical analysis.

Acetic Acid-Induced Pain Model

Mice were randomly divided into 5 groups (n = 7 per group): saline solution, 2.5 mg/kg esketamine, 5 mg/kg esketamine, 10 mg/kg esketamine, and 20 mg/kg esketamine. We based our choices for esketamine dosages on preliminary experiments in mice and previous studies.[12,18,19] Pain was induced by intraperitoneal injection of .6% acetic acid at 10 mL/kg body weight. Positive responses were characterized by the presence of abdominal contractions, which consisted of backwards stretching of the hind limb, substantial twisting of the body, or whole-body stretching. Saline and different doses of esketamine were intraperitoneally injected at 10 mL/kg body weight 30 minutes before acetic acid injection. The experimental process was recorded by video. The number of writhing episodes was counted over 30 minutes after acetic acid injection and the investigators were blinded to the experimental groups during scoring. The percentage of analgesia (% analgesia) was then calculated by the following equation: % analgesia = [100 × (mean writhes in control group - mean writhes in drug treated group)]/mean of writhes in control group. All mice subjected to the experiment were included for the analysis.

Formalin-Induced Pain Model

Mice were randomly divided into 4 groups (n = 7 per group): saline solution, 2.5 mg/kg esketamine, 5 mg/kg esketamine, and 10 mg/kg esketamine. Then, 5% formalin was injected into the intraplantar surface of the left hind paw to induce acute pain. Saline and different doses of esketamine were intraperitoneally injected at 10 mL/kg body weight 30 minutes before formalin injection. The experimental process was recorded by video. The time spent licking the injected paw was recorded in the first 5 minutes (phase 1, neurogenic) and 5 to 60 minutes (phase 2, inflammatory) after formalin injection and the investigators were blinded to the experimental groups during scoring. All mice subjected to the experiment were included for the analysis.

Statistical Analysis

Data are presented as the mean ± standard error of the mean (SEM). All analyses were carried out with GraphPad Prism 9.0

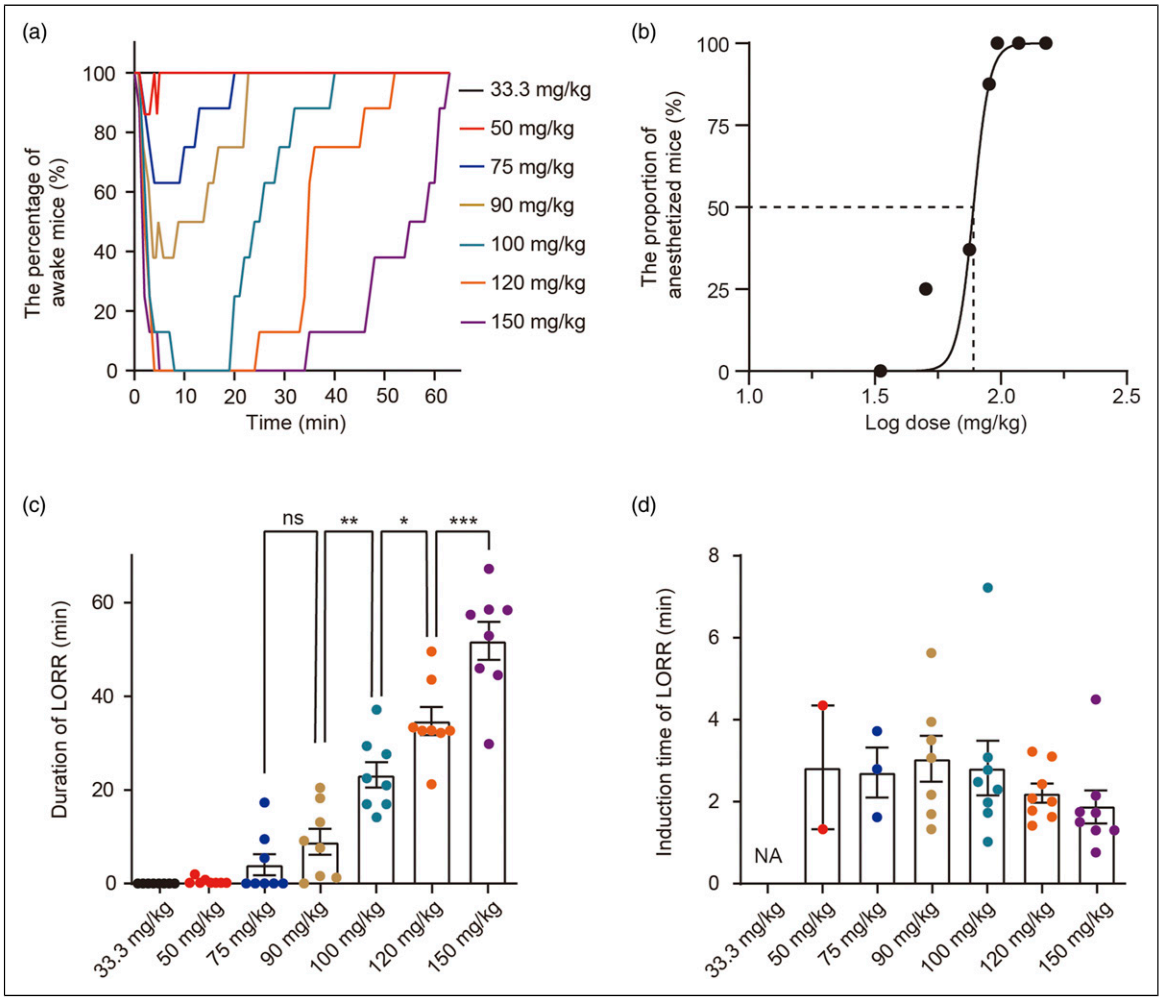

Figure 1. 100 mg/kg is required for esketamine to induce stable anesthesia in mice. (a) Time course of esketamine-induced LORR in mice. Different doses of esketamine were applied in each group. n = 8. (b) Dose–response curve for esketamine-induced anesthesia. The ED50 was 77.86 mg/kg, with a 95% confidence interval from 71.77 to 84.45 mg/kg. n = 8. Least-squares non-linear regression analysis. (c) Quantitation of the average duration of LORR induced by treatment with different doses of esketamine. Drugs were administered by intraperitoneal injection. Data are presented as the mean ± s.e.m.; n = 8. *$P < .05$, **$P < .01$ and ***$P < .001$. One-way ANOVA followed by Tukey's post hoc test. (d) Quantitation of the average induction time of LORR by treatment with different doses of esketamine. Data are presented as the mean ± s.e.m.; n = 8, data from mice with unsuccessful anesthesia induction were excluded. One-way ANOVA.

(GraphPad Software, San Diego, CA). The ED_{50} values and the 95% confidence intervals (CIs) were calculated using a least-squares non-linear regression analysis. The significance of differences between means was determined by one-way ANOVA followed by Tukey's post hoc test, and $P < .05$ was considered significant.

Results

Esketamine and Racemic Ketamine Have Similar Potencies to Anesthetize Mice

To test the dose-dependent anesthetic effects of esketamine, we recorded the induction time and the duration of LORR as a measurement of anesthesia after i.p. administration of a series of doses of esketamine (33.3, 50, 75, 90, 100, 120, 150 mg/kg). Treatment with 50 mg/kg esketamine induced only very brief LORR in 25% of mice (2 of 8) and 75 mg/kg esketamine induced LORR in 37.5% of mice (3 of 8). Until 100 mg/kg or higher doses, esketamine induced LORR in all mice (Figure 1a and 2b). The dose–response curve for LORR by injection of esketamine is shown in Figure 1b. The ED_{50} was 77.86 mg/kg (95% CI, 71.77–84.45 mg/kg). The average duration of LORR was only about 23 minutes at 100 mg/kg ketamine, and it increased to about 35 minutes and 52 minutes at 120 and 150 mg/kg ketamine, respectively, indicating that esketamine maintained anesthesia in a dose-dependent manner (Figure 1c). However, increasing the dose of esketamine might not influence the induction process of anesthesia since the induction times appeared to be similar (Figure 1d).

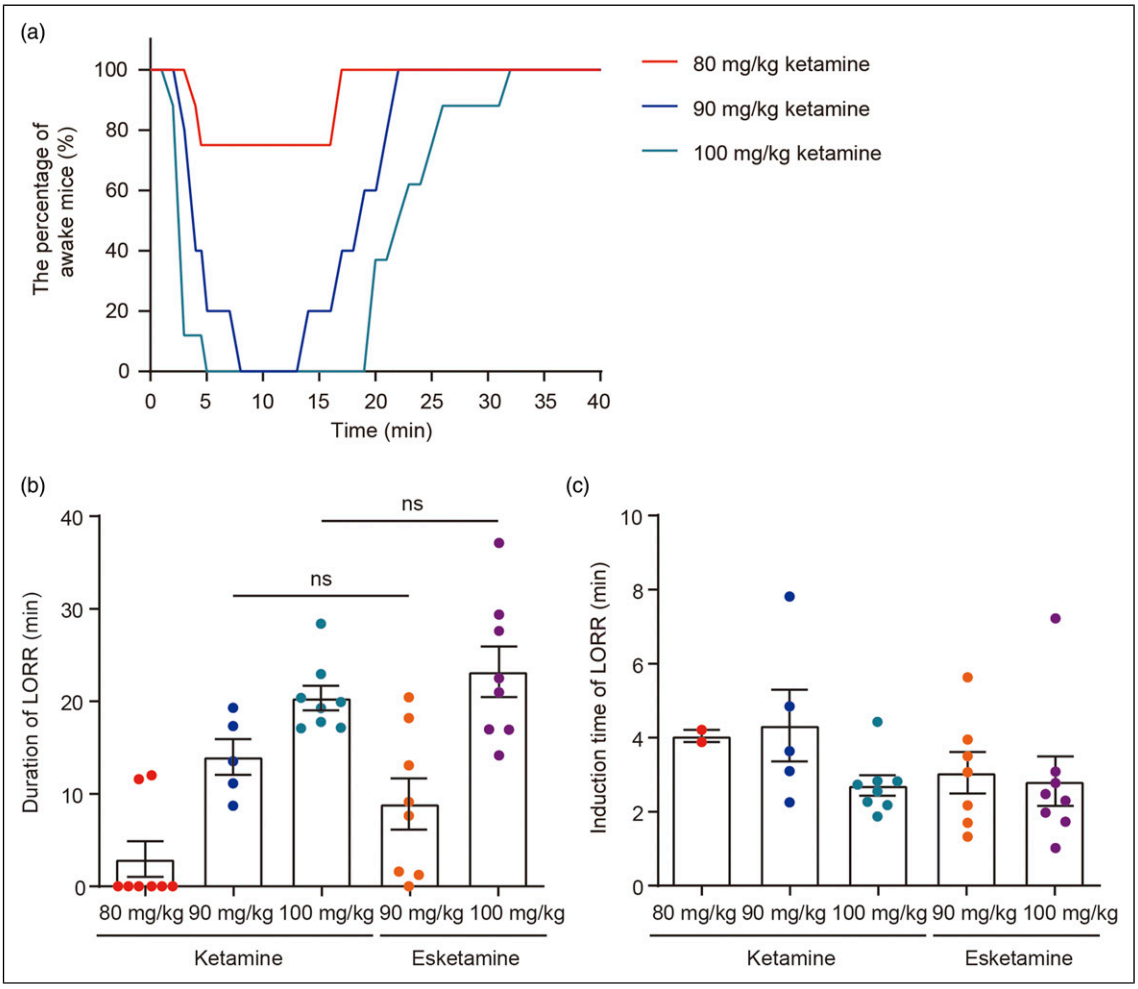

Figure 2. Esketamine has a similar anesthetic potency as racemic ketamine. (a) Time course of racemic ketamine-induced LORR in mice. n = 5 in 90 mg/kg ketamine group and 8 in the other groups. (b) Quantitation of the average duration of LORR induced by treatment with racemic ketamine and esketamine. Drugs were administered by intraperitoneal injection. Data are presented as the mean ± s.e.m.; n = 5 in 90 mg/kg ketamine group and 8 in the other groups. One-way ANOVA followed by Tukey's post hoc test. (c) Quantitation of the average induction time of LORR by treatment with racemic ketamine and esketamine. Data are presented as the mean ± s.e.m.; n = 5 in 90 mg/kg ketamine group and 8 in the other groups, data from mice with unsuccessful anesthesia induction were excluded. One-way ANOVA. Data for esketamine are shown in Figure 1 and are shown again here for a better comparison with racemic ketamine.

In comparison, we found that 80 mg/kg racemic ketamine induced anesthesia in only 25% of the mice. Additionally, 90 mg/kg and 100 mg/kg racemic ketamine induced anesthesia in all mice (Figure 2a). Moreover, racemic ketamine and esketamine induced anesthesia with comparable induction time and led to similar durations of LORR at 90 and 100 mg/kg (Figures 2b and 2c). The results above showed that esketamine had a similar potency to racemic ketamine as an anesthetic.

A Dose of 5 mg/kg of Esketamine Produces an Analgesic Effect

We then measured the analgesic effects of esketamine at a series of doses using the acetic acid-induced pain model and formalin-induced pain model (saline, 2.5, 5, 10, 20 mg/kg). For the acetic acid-induced pain model, treatment with 5, 10 or 20 mg/kg esketamine significantly decreased the number of writhing episodes, whereas 2.5 mg/kg esketamine failed to produce such effects (Figure 3a). In addition, esketamine seemed to exert its analegesic effect in a dose-dependent manner. As the dose–response curve for analgesia shown in Figure 3e, the percentage of analgesia increased from 32.8% at 5 mg/kg to 76.9% at 20 mg/kg. The ED_{50} was 10.51 mg/kg (95% CI, 8.26–13.70 mg/kg).

Similarly, 5 or 10 mg/kg esketamine reduced licking time to similar levels for the formalin-induced pain model, and 2.5 mg/kg esketamine failed to produce such effects (Figure 3b). Interestingly, esketamine significantly inhibited the antinociceptive responses in phase 2 but not in phase 1 (Figures

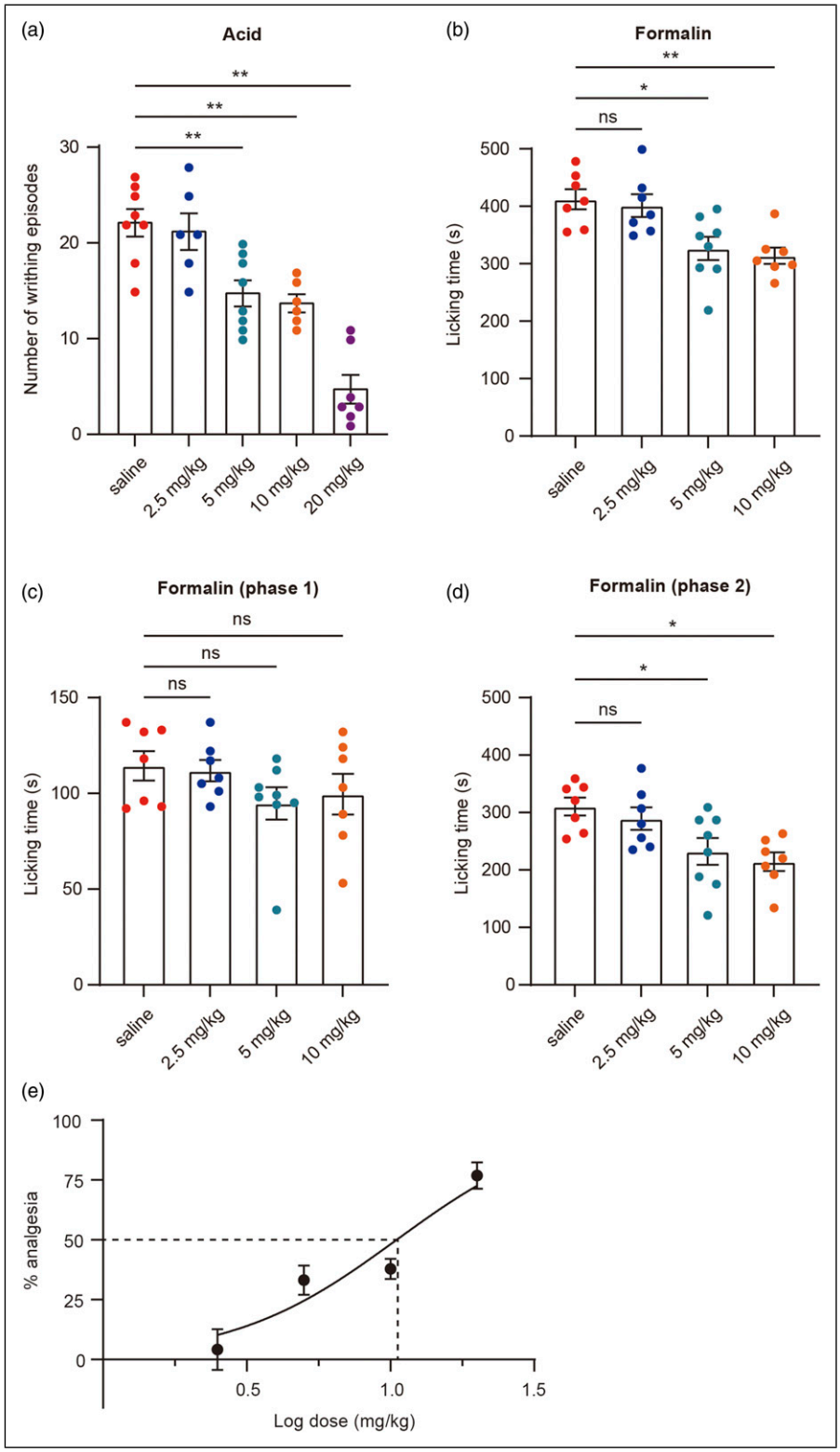

Figure 3. A dose of 5 mg/kg is sufficient for esketamine to induce analgesia in mice. (a) quantitation of the average number of writhing episodes in the acetic acid-induced pain model under treatment with different doses of esketamine. Drugs were administered by intraperitoneal injection. Data are presented as the mean ± s.e.m.; n = 6 to 8. **P* < .05 and ***P* < .01. One-way ANOVA followed by Tukey's post hoc test. (b, c and d) Quantitation of average licking time in the total (b), phase 1 (c), and phase 2 (d) formalin-induced pain models under treatment with different doses of esketamine. Drugs were administered by intraperitoneal injection. Data are presented as the mean ± s.e.m.; n = 7 to 8. **P* < .05 and ***P* < .01. One-way ANOVA followed by Tukey's post hoc test. (e) Dose–response curve for the analgesic effects of esketamine in the acetic acid-induced writhing test. The ED_{50} was 10.51 mg/kg, with a 95% confidence interval from 8.26 to 13.70 mg/kg. Data are expressed as percentage of analgesia ± s.e.m.; n = 6 to 8. Least-squares non-linear regression analysis. Potency of esketamine compared to its racemate.

3c and 3d), indicating that esketamine had better analgesic effects on inflammatory pain than trauma or chemical stimulation-induced pain.

Discussion

Esketamine, the right-handed optical isomer of racemic ketamine, has attracted increasing attention in both preclinical studies and clinical applications. As the right-handed optical isomer of racemic ketamine, esketamine has a higher affinity for NMDARs than the racemate.[13] Therefore, esketamine has been predicted to be twice as potent as racemic ketamine, and esketamine may lead to similar effects as racemic ketamine at only half of its dose.[20] Additionally, 2 mg/kg esketamine has been reported to lead to anesthetic effects similar to those of 4 mg/kg ketamine in humans.[21] However, ketamine is usually dosed at 1–2 mg/kg in humans for anesthesia,[4] and 4 mg/kg is a saturated dose for ketamine that might complicate the results of the experiment described above. Whether esketamine is more potent than ketamine for inducing stable anesthesia remains unknown.

To answer this question, we measured the dose response curve of esketamine for its potency to induce anesthesia in mice and found that 100 mg/kg was the lowest dose for esketamine that could induce stable anesthesia in all mice, which was similar to that of racemic ketamine. Furthermore, equivalent doses of racemic ketamine and esketamine at 90 and 100 mg/kg produced similar induction time and duration of LORR in mice. These results strongly support that esketamine and racemic ketamine share comparable potency to induce anesthesia, which is inconsistent with a previous conjecture that lower doses of esketamine may lead to impacts similar to those of racemic ketamine.[20] Therefore, the higher affinity of esketamine for NMDARs fails to increase the anesthetic potency of esketamine. The underlying reasons remain to be investigated. Theoretically, 2 possibilities might contribute to this controversy: (1) the anesthetic effect of esketamine does not only depend on its affinity for NMDARs; and (2) the pharmacokinetic property of esketamine compromises its anesthetic effects. However, our data strongly support that similar dose of esketamine and racemic ketamine are required to induce comparable anesthetic effects in mice.

However, when we tested the antinociceptive effect of esketamine, we found that 5 mg/kg esketamine was sufficient to induce robust analgesia in 2 mouse pain models with dose dependency. Interestingly, previous studies indicated that intraperitoneal injection of 10 mg/kg racemic ketamine failed to produce sustained analgesia in mice.[12,22,23] The effective doses of esketamine and ketamine differed by more than 2 times, which was consistent with a previous report.[24] Actually, NMDARs are widely expressed in pain transduction pathways including the brain, spinal cord, and dorsal root ganglia and there is substantial evidence that NMDAR activation is involved in the pain transmission procedure.[20,25] Esketamine can not only directly block the pathway, but also inhibit the sensitization of central nervous system, which is caused by persistent activation and phosphorylation of NMDARs and results in allodynia or hyperalgesia.[25] There has been research reporting that esketamine bonds to the PCP binding site of NMDARs with twice the affinity of R-ketamine,[26] which may explain why esketamine is more potently analgesic than racemic ketamine.

Besides its direct analgesic effect, esketamine can be used to relieve depression and the esketamine nasal spray was approved for treatment-resistant depression by FDA in 2019.[27] Interestingly, this effect on emotion regulation seems to affect pain perception, especially for chronic pain. Based on its antidepressant efficacy, it has been proposed that its long-term benefits also originate from changes in the emotional dimensions of pain (i.e., relieving pain-related aversion), rather than just those in the sensory dimension of pain.[28] This may explain why esketamine can provide pain relief in chronic pain patients up to 4 weeks after infusion, after the antinociceptive effect has largely worn off.[29] Follow-up studies are needed to explore the effects of esketamine on chronic pain and associated aversion. Taken together, we believe that esketamine is a promising analgesic drug that deserves further exploration.

This study detailed the anesthetic and analgesic effects of esketamine in mice and compared them with those of the racemate. The different relative potencies of esketamine to ketamine for anesthesia and analgesia suggest that different underlying mechanisms may account for the different effects of ketamine. Further research is needed to explore the reasons for the different potencies of esketamine and racemate in their anesthetic and analgesic effects, as the results may guide subsequent basic research.

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Declaration of Conflicting Interests

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