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Research article

Acute single dose of ketamine relieves mechanical allodynia and consequent depression-like behaviors in a rat model

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HIGHLIGHTS

- Inflammatory pain can induce depression-like behaviors in rats.
- Ketamine relieves inflammatory pain and depression-like behaviors of rats.
- Ketamine downregulates inflammatory cytokines and IDO/KYN pathway in rat hippocampus.

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ABSTRACT

Both chronic pain and depression are debilitating diseases, which often coexist in clinic. However, current analgesics and antidepressants exhibit limited efficacy for this comorbidity. The present study aimed to investigate the effect of ketamine on the comorbidity of inflammatory pain and consequent depression-like behaviors in a rat model established by intraplantar administration of complete Freunds adjuvant (CFA). The mechanical withdrawal threshold, thermal withdrawal latency, open field test, forced swimming test, and sucrose preference test were evaluated after the CFA injection and ketamine treatment. The hippocampus was harvested to determine the levels of interleukin (IL)-6, IL-1β, indoleamine 2,3-dioxygenase (IDO), kynurenine (KYN), 5-hydroxytryptamine (5-HT), and tryptophan (TRP). The inflammatory pain-induced depression-like behaviors presented on 7 days and lasted to at least 14 days after the CFA injection. Single dose of ketamine at 20 mg/kg relieved both the mechanical allodynia and the associated depression-like behaviors as demonstrated by the attenuated mechanical withdrawal threshold, reduced immobility time in the forced swim test, and increased sucrose preference after ketamine treatment. The total distance had no significant change after the CFA injection or ketamine treatment in the open field test. Simultaneously, ketamine reduced the levels of IL-6, IL-1β, IDO, and KYN/TRP ratio and increased the 5-HT/TRP ratio in the hippocampus. In conclusion, acute single dose of ketamine can rapidly attenuate mechanical allodynia and consequent depression-like behaviors and down-regulate hippocampal proinflammatory responses and IDO/KYN signal pathway in rats.

1. Introduction

Chronic pain and depression show high rates of comorbidity in clinic, and patients with this comorbidity report more and sever pain symptoms as well as longer duration of pain, which complicates the treatment procedure [1]. Depression affects 30%–100% of patients with chronic pain and the prevalence rate is several times higher than that in the general population [2,3]. By contrast, the prevalence of chronic pain is reported to be 51.8%–59.1% in patients treated for depression [4,5]. Although current available analgesics and antidepressants are often used in combination for the treatment of this comorbidity, the clinical remission is limited. Therefore, there is an urgent need to develop novel drugs

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with better curative efficacy for patients with pain and depression comorbidity.

A great number of studies have demonstrated the important role of hippocampal proinflammatory responses in the pathogenesis of both chronic pain and depression [6–8]. Moreover, proinflammatory cytokines have potency to activate indoleamine 2,3-dioxygenase (IDO), and the activated IDO may deplete tryptophan (TRP) and reduce 5-hydroxytryptamine (5-HT) in the hippocampus, which exerts a key action in the pathophysiology of pain and depression comorbidity [9,10].

Ketamine is a common used analgesic for acute pain management in clinical practice and animal studies, and its long-acting analgesia effects have been explored recently [11–13]. Moreover, clinical randomized controlled studies have shown robust and sustained antidepressant effects after an intravenous infusion of single sub-anesthetic dose of ketamine in depressed patients [14,15], therefore subsequent preclinical trials are performed to investigate the underlying mechanisms [16,17].

Our previous animal study [18] has demonstrated that ketamine's antidepressant effects for chronic unpredictable mild stress (CUMS)-induced depression-like behaviors are associated with its anti-inflammatory actions in the hippocampus. However, whether ketamine can produce a treatment effect for the comorbidity of chronic pain and depression-like behaviors remains unclear, which was investigated in the present study as well as the determination of the hippocampal levels of interleukin (IL)-6, IL-1β, IDO, kynurenine (KYN), 5-HT, and TRP after intraplantar administration of complete Freunds adjuvant (CFA).

2. Materials and methods

2.1. Animals

The present study was approved by the Ethics Committee of Jinling Hospital, and was performed in accordance with the Guide for the Care and Use of Laboratory Animals from the National Institutes of Health, USA. Male adult SD rats, weighing 230–260 g, were purchased from the Jingling Hospital, Nanjing, China. The rats were housed 5 per cage with food and water available *ad libitum* and were maintained on a 12 h light/dark cycle (lights on at 7:00 a.m.), and were allowed 7 days to acclimate to the surroundings before the beginning of experiments.

2.2. Experimental paradigm

2.2.1. Experiment 1

To determine whether the CFA injection induces hyperalgesia and depression-like behaviors: We used 2 groups of rats (n = 10) in this experiment. Hind paw monoarthritis was induced by the injection of CFA into a right tibiotarsal joint cavity under brief isoflurane anesthesia. The body weight, circumference of the right ankle, mechanical withdrawal threshold (MWT), and thermal withdrawal latency (TWL) were examined, respectively, on days 1 and 7 before and days 1, 2, 5, 7, and 14 after the CFA injection. The forced swimming test (FST) was performed on days 1, 7, and 14 after the CFA injection. The sucrose preference test (SPT) and the open field test (OFT) were performed on day 1 before and days 7 and 14 after the CFA injection. Saline group: saline (50 μl) was injected into the right tibiotarsal joint cavity; CFA group: CFA (50 μl, Sigma Aldrich, St. Louis, MO) was injected into the right tibiotarsal joint cavity.

2.2.2. Experiment 2

To evaluate the effect of ketamine on pain and pain-related depression-like behaviors: Four groups of rats (n = 8) were used in this experiment. All the rats were injected with CFA into a right tibiotarsal joint cavity under brief isoflurane anesthesia. Saline or ketamine (20 mg/kg, Hengrui Pharmaceutical Company, Jiangsu, China) in the same volume of 1 ml was intraperitoneally injected on day 14. The MWT, immobility time in the FST, and total distance in the OFT were measured 1 h and 24 h after the treatment. The SPT of a 24-h period was preformed immediately after the treatment. Saline or ketamine 1 h group: rats were sacrificed 1 h after the treatment; and saline or ketamine 24 h group: rats were sacrificed 24 h after the treatment. Hippocampus was harvested after decapitation to detect the levels of IL-6, IL-1β, IDO, KYN, and 5-HT.

2.3. MWT

Mechanical allodynia was evaluated via determining MWT by using Electro VonFrey Aneshesiometer. After 30 min of adaptation time, gentle incremental pressure (maximum 200 g) by a rigid von-Frey hair was applied perpendicularly onto the plantar surface of the right hind paw until the paw was withdrawn. Five trials for each paw were conducted at intervals of 5-min and the force (g) applied was recorded. The maximum and the minimum values were discarded and the average of the left 3 measures represented MWT.

2.4. TWL

Thermal hyperalgesia was measured by determining TWL. A radiant thermal stimulator was focused onto the plantar surface of the hind paw through the glass plate. The nociceptive end point in the radiant heat test was the characteristic lifting or licking of the hind paw, and the time to the end point was considered as the TWL. A cutoff time of 20 s was used to avoid tissue damage. There were 5 trials per rat and 5-min intervals between trials. The mean TWL was obtained from the latter 3 stimuli.

2.5. OFT

OFT was carried out in a Plexiglas square box (100 × 100 cm) with walls 40 cm in height. Behaviors were observed for a 10-min period. The total distance was automatically recorded and analyzed by the computerized tracking system.

2.6. FST

FST was performed according to the method of Li et al. [16]. The immobility time during the last 5-min of a 6-min test was recorded by manual scoring. Immobility was defined as that the rat remains floating in the water without struggling and makes only those movements necessary to keep its head above water.

2.7. SPT

Sucrose solution (1%) was offered in a rat's home cage. Sucrose and tap water intakes were separately measured by weighing each bottle before and after the test (a 24-h period). The sum of sucrose and tap water intake was calculated as the total water intake. The sucrose preference was expressed as the percent of sucrose solution intake relative to the total water intake.

2.8. Hippocampal IL-6, IL-1β, IDO, KYN, and 5-HT quantification

The hippocampus was dissected after decapitation under a deep anesthesia with intraperitoneal injection of 60 mg/kg phenobarbital. The hippocampus samples were stored at −80 °C until assaying. IL-6, IL-1β, IDO, TRP, KYN, and 5-HT levels were determined using enzyme linked immunosorbent assay kits (Jiancheng Biologic Project Company, Nanjing, China) following the manufacturer's instructions.