



Research article

Effects of fluoxetine on changes of pain sensitivity in chronic stress model rats



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HIGHLIGHTS

- Fluoxetine facilitates hypoalgesia in thermal and inflammatory pain and induced mechanical hyperalgesia.
- Fluoxetine aggravates stress-induced analgesia on thermal and inflammatory pain but not on mechanical pain.
- 5-HT system may be involved in changes of pain sensitivity after chronic stress exposure.

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ABSTRACT

Exposure to stress could facilitate or inhibit pain responses (stress-induced hyperalgesia or hypoalgesia, respectively). Fluoxetine is a selective serotonin (5-HT) reuptake inhibitor antidepressant. There have been contradictory reports on whether fluoxetine produces antinociceptive effects. The purpose of this study was to elucidate changes in pain sensitivity after chronic stress exposure, and the effects of fluoxetine on these changes. We measured thermal, mechanical, and formalin-induced acute and inflammatory pain by using the tail-flick, von Frey, and formalin tests respectively. The results showed that rats exposed to chronic stress exhibited thermal and formalin-induced acute and inflammatory hypoalgesia and transient mechanical hyperalgesia. Furthermore, fluoxetine promoted hypoalgesia in thermal and inflammatory pain and induced mechanical hyperalgesia. Our results indicate that the 5-HT system could be involved in hypoalgesia of thermal and inflammatory pain and induce transient mechanical hyperalgesia after stress exposure.

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1. Introduction

Stress is a reaction to life-threatening conditions and is accompanied by changes in the physiological, neural, endocrine, and immunological systems. Multiple studies have demonstrated that chronic stress can cause depression and anxiety [1,2] as well as elicit reactions of hyperalgesia/allodynia [3,4] or hypoalgesia/analgesia [5]. Stress has complex effects on pain processing, and the parameters of stressor intensity that cause stress-induced hypoalgesia or hyperalgesia remain unknown. Different types of stressors could have distinct impacts on pain response. Fluoxetine is a selective serotonin reuptake inhibitor (SSRI) that is used to treat depressive

orders. Pain is reported by 60–90% of patients with depression [6]. Studies in animals and humans have shown that fluoxetine has antinociceptive effects [6]. However, other studies have failed to show antinociceptive effects of SSRIs [7]. Reports on the effects of fluoxetine on nociception after chronic stress exposure do not cover all types of pain. In this study, we observed changes in pain sensitivity (thermal, mechanical, and inflammatory pain) after chronic stress exposure and the influence of fluoxetine on nociceptive behaviors. We aimed to clarify the effects of fluoxetine on changes in pain sensitivity under conditions of chronic stress.

2. Materials and methods

2.1. Experimental animals

Male Sprague–Dawley rats (Animal Centre of the Second Affiliated Hospital, Harbin Medical University, Certificate No.09-2-1) weighing between 170 and 190 g were used in this study. The ani-

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mals were housed at $22 \pm 2^\circ\text{C}$ with a 12 h light and dark cycle (light between 8:00 and 20:00 h). Laboratory food and tap water were available ad libitum. All the experimental procedures were approved by the Institutional Animal Care and Use Committee of Harbin Medical University, PR China.

Rats were randomly and equally divided into the following 4 groups ($n = 8$ per group): (1) normal rats; (2) chronic unpredictable mild stress (CUMS) rats; (3) CUMS rats with saline; (4) CUMS rats with fluoxetine.

2.2. CUMS procedure

The CUMS procedures were performed according to previously reported CUMS protocols [8–10]. As shown in Fig. 1, all CUMS rats were exposed to one unpredictable stressor each day for 35 days. The stressors included: (1) food deprivation (24 h); (2) water deprivation (24 h); (3) swimming in 4°C cold water for 5 min; (4) restraint in PVC tubes (19 cm \times 7 cm; 2 h); (5) damp bedding overnight; (6) high platform: 2 h exposure to an elevated platform (10 cm \times 10 cm) mounted on a 160 cm high post; and (7) novel odor (rats were placed into a cage with bedding that contains other rat's odor for 24 h). These stressors were randomly scheduled over a 1-week period and repeated throughout the 5-week experiment.

2.3. Drug treatment

Rats in the CUMS with saline group were administered with vehicle. Rats in the CUMS with fluoxetine group were administered with fluoxetine hydrochloride (PATHEON FRANCE, China). Saline and fluoxetine were administered intraperitoneally (4 mg/kg) once daily from the 22th day of the CUMS procedure

2.4. Sucrose preference test (SPT)

Sucrose preference test (SPT) was performed on the 36th day (Fig. 1) according to published data [11]. Rats were given 1% sucrose solution for 24 h, followed by 23 h of water deprivation and 1 h exposure to two identical bottles filled with either sucrose solution or water. Sucrose preference was identified as the ratio of the volume of sucrose vs total volume of sucrose and water consumed during the 1-h test.

2.5. Tail flick test

Tail-flick test was performed every week. Tail-flick test was used to assess the nociceptive response to acute thermal noxious stimuli [12]. The animals were restrained in a cage with their tails hanging freely. The lower 5-cm portion of the tail was placed over a burning light. Tail-flick latency was defined as the time between turning the burning light on and tail-flick out. In order to avoid the influence of different test times, tail-flick tests were performed at the same time every week (Fig. 1).

2.6. von Frey test

The mechanical paw-withdrawal thresholds were tested every week by using the up-and-down method described by Chaplan et al. [13]. The rats were enclosed in a transparent plastic box with a metal wire mesh floor. Ten von Frey filaments were chosen (von Frey numbers: 3.61, 3.84, 4.08, 4.17, 4.31, 4.56, 4.74, 4.93, 5.07, and 5.18, equivalent to: 0.4, 0.6, 1.0, 1.4, 2.0, 4.0, 6.0, 8.0, 10, and 15.0 g, respectively). The test was initiated with the 2.0 g hair. Depending on whether rats presented positive (paw withdrawal) or negative responses (no withdrawal), we chose the next weaker or stronger stimulus. Counting of 6 consecutive data points did not begin until the response threshold was first crossed. These 6 data points were

converted to a 50% mechanical withdrawal threshold (50% MWT) by using the formula provided by Chaplan. In order to avoid the influence of different test times, von Frey tests were performed at the same time every week (Fig. 1).

2.7. Formalin test

As shown in Fig. 1, in the 6th week, inflammatory pain thresholds were measured using the formalin test described by Cervantes-Duran [14]. Each rat was placed in an open transparent plastic chamber with mirrors to observe spontaneous activity of the injected paw. The rat received a 50- μl subcutaneous injection of diluted (5%) formalin to the unilateral hind paw pad. The animals were returned to the chambers and nociceptive behavior was observed immediately after formalin injection. Licking time during 0–5 min for Phase I (the acute phase) and 20–40 min for Phase II (the inflammatory phase) were recorded.

2.8. Statistical analysis

Analysis of data was performed using SPSS 19.0. All data were presented as mean \pm S.E.M. One-way repeated measures ANOVA followed by Bonferroni's post-hoc test was used to determine differences in body weight and thermal pain thresholds between normal and CUMS rats. One-way ANOVA followed by Bonferroni's post-hoc test was used to determine whether fluoxetine had effects on body weight, sucrose preference, thermal pain thresholds, and the licking time in CUMS rats. The Friedman repeated measures analysis of variance was used to determine differences in mechanical pain thresholds between normal and CUMS rats. Kruskal–Wallis one-way analysis of variance was used to determine the effects of fluoxetine on mechanical thresholds. Statistical significance was determined as $p < 0.05$.

3. Results

3.1. Fluoxetine did not affect slowing of weight increase in chronic stress rats but improved sucrose consumption

At the beginning of the experiment, there was no significant difference in body weight between the two groups. Rats in the CUMS group exhibited a slowdown in body weight gain from the 17th day to the end of the CUMS procedure, compared with rats in the control group (Fig. 2A; 17th day: 257.07 ± 25.6 g vs. 323.1 ± 27.86 g; 35th day: 337.15 ± 20.7 g vs. 440.7 ± 32.47 g), which was not ameliorated by fluoxetine treatment (Fig. 2B; 6th week: 351.7 ± 21.9 g vs. 347.15 ± 20.1 g). Thus, fluoxetine did not affect the slowdown in weight gain of rats in the CUMS group.

Compared with rats in the control group, rats in the CUMS group exhibited a significant reduction in sucrose preference after 5 weeks of stress exposure (Fig. 3C, $59.95\% \pm 8.6\%$ vs. $78.6\% \pm 8.1\%$). We verified that these stressors reduced sucrose preference. Fluoxetine treatment improved the sucrose consumption of rats ($78.3 \pm 10.5\%$) in the CUMS group compared with those treated with saline.

3.2. Effects of fluoxetine on changes in the thermal pain threshold in a rat model of chronic stress

We performed tail-flick tests every week to study changes in thermal pain during stress treatment. As shown in Fig. 3A, chronic stress exposure elevated tail-flick latency at the 4th week (6.9 ± 0.8 s vs. 5.36 ± 0.56 s) and the 5th week (6.5 ± 0.5 s vs. 5.27 ± 0.43 s), indicating that CUMS rats were less sensitive to thermal stimuli than normal rats were. Administration of fluoxetine produced a significant increase in tail-flick latency in CUMS

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