Antinociceptive Effects of Oriental Medicine Kei-Kyoh-Zoh-Soh-Oh-Shin-Bu-toh in Mice and Rats

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Antinociceptive effects of peroral administration of an oriental medicine Kei-Kyoh-Zoh-Soh-Oh-Shin-Bu-toh (TJ-8023) were examined using rats and mice. TJ-8023 (100 mg·kg⁻¹·d⁻¹) inhibited the induction of adjuvant-induced hyperalgesia of rats in the paw-pressure test following prophylactic administration, and normalized the nociceptive threshold at a dose of 600 mg·kg⁻¹·d⁻¹, without effects on adjuvant-induced inflammation. Mice suffering from repeated cold stress showed a decrease in nociceptive threshold for tail-pressure stimulation. Such a hyperalgesia was reversed by a single (30 and 100 mg/kg) or repeated administration (100 and 300 mg·kg⁻¹·d⁻¹) of TJ-8023. The nociceptive threshold of non-stressed mice was not affected by TJ-8023 (100 mg/kg). Nociceptive responses of mice to cold-plate stimulation were also not affected by repeated administration of TJ-8023 (300, 600 and 1200 mg·kg⁻¹·d⁻¹). The present results demonstrate the antinociceptive action of TJ-8023, and suggest that it is more effective in easing a hyperalgesia in morbidity state than in suppressing a nociception in the normal one.

Keywords — analgesia; oriental medicine; Kei-Kyoh-Zoh-Soh-Oh-Shin-Bu-toh; Bushi; sodium diclofenac; hyperalgesia; adjuvant-induced inflammation; repeated cold stress; cold-plate test

Introduction

An oriental medicine Kei-Kyoh-Zoh-Soh-Oh-Shin-Bu-toh consists of seven crude drugs, Keishi (Kei; Chinese cinnamon bark), Syohkyoh (Kyoh; ginger rhizome), Kanzoh (Zoh; licorice root), Taisoh (Soh; jujube fruit), Maoh (Oh; mahuang stalk), Saishin (Shin; Asiasarum root) and Bushi (Bu; aconite root). This medicine is used clinically for chronic pains such as neuralgia, rheumatalgia, and low back pain,¹ but its analgesic action has not been assessed in animals. In the present experiments, therefore, antinociceptive effects of this medicine were examined by using several analgesic tests. Since one of the indications for this medicine is rheumatalgia, we used adjuvant-induced hyperalgesic rats, an animal model of human chronic arthritis such as rheumatoid arthritis with chronic pain.²,³ In addition, as this medicine is used for humans oversensitive to cold,¹ we examined its effects on hyperalgesia of the mouse exposed repeatedly to cold environment⁴ and on the nociceptive responses of the mouse to noxious cold stimulation.

Materials and Methods

Materials — Kei-Kyoh-Zoh-Soh-Oh-Shin-Bu-toh (TJ-8023) and poison-attenuated Bushi (Syuch Bushi) were gifts from Tsumura, Inc. (Tokyo). TJ-8023 consists of Keishi, Syohkyoh, Kanzoh, Taisoh, Maoh, Saishin and poison-attenuated Bushi in 3:1:2:3:2:2:1 ratio in dry weight. Sodium diclofenac was a gift from Ciba-Geigy Japan (Takarazuka). Mycobacterium tuberculosis H37Ra was purchased from Difco Laboratories (Detroit, U.S.A.), and sodium carboxymethylcellulose from Nacalai Tesque (Kyoto). The other drugs used were morphine hydrochloride (Takeda Chemical Ind., Osaka), pentazocine (Sankyo Co., Tokyo), indomethacin and aspirin.

Adjuvant-Induced Hyperalgesia — A suspension (0.07 ml) of heat-killed Mycobacterium tuberculosis (12 mg/ml) in paraffin oil was inoculated intradermally into the foot pad of the left hind-paw of male Sprague-Dawley rats weighing

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about 200 g on day 0. The rats were kept on a 12-h light/dark cycle (8:00 a.m./8:00 p.m.) at 24 °C with food and water ad libitum. The nociceptive threshold of inoculated hind-paw for mechanical stimulation was measured using a pressure analgesimeter (Ugo Basile, Milan, Italy) with a loading rate of 48 g/s, in which struggling behavior was used as a nociceptive response. The volume of the inoculated hind-paw (a glabrous region distal to the lateral malleolus) was determined plethysmometrically and served as an index of the degree of inflammation.

Repeated Cold Stress-Induced Hyperalgesia — Male ddY mice (4 weeks of age at start of experiments) were used. In experiments where drugs were administered daily, procedures of repeated cold stress (RCS) were essentially according to the methods of Hata et al. Mice were exposed to cold environmental temperature of 4 °C from 5:00 p.m. to 10:00 a.m. and then alternately to room temperature of 24 °C and the cold one of 4 °C at 1 h intervals from 10:00 a.m. to 5:00 p.m. Such repeated cold stress was delivered for 5 d and ceased at 10:00 a.m. after the exposure to the sixth overnight cold stress (RCS-A). The nociceptive threshold of the tail for mechanical stimulation was measured using the same pressure analgesimeter as rats, at a pressure loading rate of 16 g/s, 1 h after drug administration between 4:20 p.m. and 5:00 p.m.

In experiments where mice were given a single administration of drug, animals were exposed to cold temperature of 4 °C from 4:30 p.m. to 10:00 a.m. and then alternately to room temperature (24 °C) and cold temperature (4 °C) at 30-min intervals from 10:30 a.m. to 4:00 p.m. Such repeated cold stress was delivered for 2 d and ceased at 10:00 a.m. after the exposure to the third overnight cold stress (RCS-B).

Cold-Plate Test — Male ddY mice (4 weeks of age at start of experiments) were used. Mice were placed on a copper plate maintained below −10 °C by a thermo-electric freezing unit (model MA-101, Komatsu Electronics, Tokyo), and the latency of licking or flexion of the hind-paw or jumping was measured. To avoid tissue damage, mice which showed no nociceptive responses within 60 s were removed from the cold plate.

Drug Administration — TJ-8023, poison-attenuated Bushi and sodium diclofenac were suspended in 0.5% sodium carboxymethylcellulose, and given perorally in a volume of 0.5 ml/100 g or 0.1 ml/10 g in rats and mice, respectively. Animals were deprived of food for at least 2 h before peroral administration. Morphine hydrochloride and pentazocine were dissolved in 0.9% saline, indomethacin was dissolved in 0.9% saline by adding a minimal amount of sodium hydroxide, and aspirin was dissolved in dimethyl sulfoxide and diluted by 0.9% saline. These four drugs were administered subcutaneously into mice in a volume of 0.1 ml/10 g.

Data Processing — Results are expressed as mean ±S.E.M. Statistical analysis was made using a two-way analysis of variance (ANOVA), multiple comparisons test (Bonferroni t test) or paired t-test; p < 0.05 was considered significant.

Results

Adjuvant-Induced Hyperalgesia

In the first series of experiments, to evaluate the prophylactic effects of TJ-8023 and its constituent, poison-attenuated Bushi, on adjuvant-induced hyperalgesia and inflammation, the drugs were repeatedly administered from the day 1 to 22. As shown in Fig. 1a, adjuvant inoculation into vehicle-control rats produced a rapid decrease in nociceptive threshold (74% of pre-inoculation) on day 1, and the decrease was relatively constant (56% to 65% of pre-inoculation) from day 4 to 22. TJ-8023 (100 mg·kg⁻¹·d⁻¹) slightly but significantly (p < 0.005) suppressed the decrease in nociceptive threshold. Poison-attenuated Bushi (100 mg·kg⁻¹·d⁻¹) was without significant effect (p > 0.025). Adjuvant-induced swelling of the hind-paw was not suppressed by both TJ-8023 and poison-attenuated Bushi at a peroral dose of 100 mg·kg⁻¹·d⁻¹ (Fig. 1b). Both TJ-8023 and poison-attenuated Bushi did not affect changes in body weight as compared with vehicle control (data not shown).

In the second series of experiments, drug administration was started on post-inoculation day
Fig. 1. Prophylactic Effects of TJ-8023 and Poison-Attenuated Bushi on Adjuvant-Induced Hyperalgesia (a) and Swelling (b) of the Rat Hind-Paw

Rats were intradermally given adjuvant on day 0 indicated by an open inverse triangle, and then perorally given TJ-8023 100 mg·kg⁻¹·d⁻¹ (●), poison-attenuated Bushi 100 mg·kg⁻¹·d⁻¹ (■) or vehicle (○) on days indicated by closed inverse triangles. (a) Nocteceptive threshold was determined by the paw-pressure method 1 and 2 h after drug administration, and their average was referred as nociceptive threshold. Three kinds of treatment produced significantly different effects (F(2,105) = 12.0034, p < 0.0001, ANOVA). The effects of vehicle were significantly different from those of TJ-8023 (p < 0.005) but not from those of poison-attenuated Bushi (p > 0.025) when assayed by Bonferroni t test (two comparisons). a) p < 0.025 as compared with vehicle control on each day (Bonferroni t test, two comparisons). The number of animals in each group was 6, and values are mean ± S.E.M.

Fig. 2. Effects of Repeated Administrations of TJ-8023 and Sodium Diclofenac on (a) the Nociceptive Threshold and (b) Volume of the Hind-Paw of Rats Inoculated with Adjuvant

Rats were given adjuvant inoculation on day 0. TJ-8023 (□) 120 or (■) 600 mg·kg⁻¹·d⁻¹, (●) sodium diclofenac 2.5 mg·kg⁻¹·d⁻¹, or (○) vehicle were perorally administered on days indicated by closed inverse triangles. (a) Nociceptive threshold was determined by the paw-pressure method 1 h after drug administration, and subsequently (b) the volume of the hind-paw was determined plethysmometrically. The number of animals in each group was 10, and values are mean ± S.E.M. (a) Four kinds of treatment produced significantly different effects (F(3,180) = 7.6439, p = 0.001, ANOVA). The effects of vehicle were significantly different from those TJ-8023 600 mg·kg⁻¹·d⁻¹ (p < 0.016) and sodium diclofenac (p < 0.0001) but not those of TJ-8023 120 mg·kg⁻¹·d⁻¹ (p > 0.016) as compared with vehicle control (Bonferroni t test, three comparisons). (b) The swelling of the hind-paw was not significantly different among four groups (F(3,180) = 2.21937, p > 0.05). a) p < 0.016 as compared with vehicle control on each day (Bonferroni t test, three comparisons).
Table I. Effects of TJ-8023 and Diclofenac on the Body Weight of Adjuvant-Inoculated Rats

<table>
<thead>
<tr>
<th>Drug (mg·kg⁻¹·d⁻¹)</th>
<th>n</th>
<th>Day 17</th>
<th>Day 19</th>
<th>Day 22</th>
<th>Day 25</th>
<th>Day 30</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>10</td>
<td>99.6±0.8</td>
<td>100.8±0.9</td>
<td>100.0±1.6</td>
<td>101.5±1.7</td>
<td>100.2±2.0</td>
<td></td>
</tr>
<tr>
<td>TJ-8023</td>
<td>120</td>
<td>100.0±0.9</td>
<td>100.9±1.0</td>
<td>102.0±1.6</td>
<td>101.9±1.8</td>
<td>102.7±2.4</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>600</td>
<td>101.4±0.5</td>
<td>101.8±0.6</td>
<td>102.0±0.7</td>
<td>103.4±0.9</td>
<td>101.0±1.5</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>2.5</td>
<td>103.3±1.3 d)</td>
<td>103.7±1.5</td>
<td>105.4±1.7 d)</td>
<td>109.4±2.2 d)</td>
<td>109.8±2.5 d)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

a) Percent of mean body weight on day 16 (16 d after inoculation).  
b) The values from day 17 to 25 were compared with vehicle values by ANOVA.  
c) Not significant.  
d) p < 0.016 (Bonferroni t test, three comparisons).

During administration (from day 17 to 25) as compared with the vehicle group, and decreased to the level of the vehicle group after cessation of administration (Table I).

Repeted Cold Stress-Induced Hyperalgesia

In the first series of experiments, to evaluate the prophylactic effects of TJ-8023 on hyperalgesia induced by RCS, mice were exposed to cold environment for 60 min every two hours in the daytime (RCS-A) and TJ-8023 was daily administered. As seen in Fig. 3, mice given RCS-A showed a gradual decrease in nociceptive threshold over 5 d, and a gradual recovery after cessation of RCS-A. TJ-8023 at a peroral dose of 300 mg·kg⁻¹·d⁻¹ was perorally administered 1 h before the tail-pressure test from day 0 to 5 as indicated by closed triangles, and RCS control mice (□) were given no drug. Values represent mean percentage of pre-stress threshold and S.E.M. The number of animals was 8, 7 or 8 in control, TJ-8023 (100 mg·kg⁻¹·d⁻¹) or TJ-8023 (300 mg·kg⁻¹·d⁻¹) group, respectively. Three kinds of treatment produced significantly different effects between day 1 and 5 (F (2,100) = 9.1299, p < 0.001, ANOVA). The effects of RCS control were significantly different from those of TJ-8023 at a dose of 300 mg·kg⁻¹·d⁻¹ (p < 0.0001) but not at a dose of 100 mg·kg⁻¹·d⁻¹ (0.025 < p < 0.05) as compared with control (Bonferroni t test, two comparisons). a) p < 0.025 as compared with control on each day (Bonferroni t test, two comparisons).

In the second series of experiments, to evaluate the effects of two types of RCS on nociceptive threshold in the tail-pressure test.

RCS-A (▲): mice were exposed to cold temperature for 60 min every two hours in the daytime (from 10:00 a.m. to 5:00 p.m.) for 5 d indicated by an open bar. RCS-B (●): mice were exposed to cold temperature for 30 min every hour in the daytime during the initial two days. Both groups of mice were exposed to cold temperature in the nighttime, that is from 5:00 p.m. (RCS-A) or 4:30 p.m. (RCS-B) to 10:00 a.m., for 5 d. Non-stress control (□): mice were exposed to no cold temperature. Values were mean and S.E.M. from 10 (▲, ●) or 6 (□) experiments. a) p < 0.016 as compared with control and b) p < 0.016 as compared with RCS-A on each day (Bonferroni t test, three comparisons).
examining the time course of drug effect after a single administration, and it is advantageous that nociceptive threshold is constant during the experiment. Therefore, we examined the conditions of RCS to decrease nociceptive threshold more rapidly and to give a constant decreased threshold in the daytime without further RCS. As seen in Fig. 4, RCS-A gradually decreased nociceptive threshold over 5 d, after which nociceptive threshold was $61.4 \pm 3.1\%$ of pre-RCS level. On the other hand, 30-min interval RCS (RCS-B) rapidly decreased nociceptive threshold for 2 d, after which nociceptive threshold was $66.0 \pm 5.2\%$ of pre-RCS level. Thereafter, the threshold was constant for 3 d so long as the mouse was given only overnight cold-stress. In the following experiments, therefore, we used RCS-B for 2 d and examined the effects of single administration of TJ-8023 on the third day.

Although the nociceptive threshold of RCS-B mice given vehicle was relatively constant for at least three hours examined here, TJ-8023 at peroral doses of 30 and 100 mg/kg significantly ($p < 0.01$ each comparison) increased the nociceptive threshold in a dose-dependent manner (Fig. 5). TJ-8023 at the higher dose did not alter the nociceptive threshold of mice given no RCS (Fig. 5). RCS-induced hyperalgesia was slightly but not significantly ($0.01 < p < 0.05$) alleviated by sodium diclofenac at a dose of 5 mg/kg, which was significantly smaller than those of TJ-8023 at both doses of 30 mg/kg ($p < 0.01$) and 100 mg/kg ($p < 0.01$).

### Cold-Plate Test

It has been known that immersion of a hand in cold water produces a pain in man. However, in preliminary experiments, immersion of the mouse tail in the ice-cold water could not elicit a

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**TABLE II. Effect of Analgesic Drugs on Cold Stimulation-Induced Nociceptive Responses in Mice**

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Dose (mg/kg, s.c.)</th>
<th>n</th>
<th>Vehicle</th>
<th>Drug $a)$</th>
<th>D/V (%) $b)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>5</td>
<td>10</td>
<td>21.4±2.4</td>
<td>34.8±3.9</td>
<td>163 $c)$</td>
</tr>
<tr>
<td>Pentazocine</td>
<td>20</td>
<td>10</td>
<td>23.2±1.8</td>
<td>28.7±1.3</td>
<td>124 $c)$</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>40</td>
<td>10</td>
<td>24.9±4.2</td>
<td>22.4±4.2</td>
<td>90</td>
</tr>
<tr>
<td>Aspirin</td>
<td>800</td>
<td>10</td>
<td>17.6±3.2</td>
<td>18.4±2.2</td>
<td>105</td>
</tr>
</tbody>
</table>

$a)$ 30 min after drug administration.  
$b)$ (drug)/(vehicle) × 100.  
$c)$ $p < 0.05$ (paired $t$-test).
TABLE III. Effects of TJ-8023 on Cold Stimulation-Induced Nociceptive Responses in Mice

<table>
<thead>
<tr>
<th>Treatment (^a)</th>
<th>(n)</th>
<th>Pre-drug (day 0)</th>
<th>Post-drug (day 7) (^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>10</td>
<td>22.9 ± 2.0</td>
<td>22.8 ± 2.1</td>
</tr>
<tr>
<td>TJ-8023 (mg·kg(^{-1})·d(^{-1}))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>300</td>
<td>10</td>
<td>27.8 ± 2.3</td>
<td>25.4 ± 3.6</td>
</tr>
<tr>
<td>600</td>
<td>10</td>
<td>24.5 ± 2.0</td>
<td>24.8 ± 3.0</td>
</tr>
<tr>
<td>1200</td>
<td>10</td>
<td>27.7 ± 1.8</td>
<td>22.1 ± 2.8</td>
</tr>
</tbody>
</table>

\(^a\) TJ-8023 and vehicle were daily administered p.o. for 7 d. \(^b\) Nociceptive latency was determined 30 min after the last administration.

withdrawal reflex, such as a tail-flick response, in a few minutes. Furthermore, when the mouse was placed on a copper plate maintained at a few degrees below zero, pseudoaffective responses were not always observed within a minute. However, when the temperature of the plate was lowered below \(-10^\circ\)C, mice showed pseudoaffective responses such as licking or flexion of the hind-paw and in some mice jumping, which were used as a nociceptive response in the present experiments.

In the first instance, to evaluate the cold-plate test as an analgesic test, we examined the effects of some analgesics on nociceptive responses of the mouse. Morphine hydrochloride (5 mg/kg) and pentazocine (20 mg/kg) significantly \((p < 0.05\) each, paired \(t\)-test) prolonged the latency of response 30 min after s.c. administration, but indomethacin (40 mg/kg) and aspirin (800 mg/kg) were without effect (Table II).

Table III shows the effects of TJ-8023 on the cold-plate response of the mouse. TJ-8023 did not alter the nociceptive latency after daily administration for 7 d at any doses examined (300, 600 and 1200 mg·kg\(^{-1}\)·d\(^{-1}\)).

Discussion

TJ-8023 at a dose of 100 mg·kg\(^{-1}\)·d\(^{-1}\) prevented the decrease in nociceptive threshold of adjuvant-inoculated rats. Although a higher dose was required, TJ-8023 also reversed the decreased threshold. Thus, the analgesic action of TJ-8023 on human chronic pain could be confirmed by an antinociceptive test using the rat with adjuvant-induced chronic hyperalgesia. The effectiveness of TJ-8023 during administration is also supported by findings that 5 d after cessation of the TJ-8023 administration, the nociceptive threshold decreased to the level similar to the control. The increase in body weight of rats given either TJ-8023 or sodium diclofenac may be due to their antinociceptive action because rats suffering from chronic adjuvant-induced inflammation show weight loss, which is inhibited by elimination of rostral transmission of nociceptive information by the section of the ventrolateral funiculus of the spinal cord.\(^6\)

The anti-inflammatory analgesic sodium diclofenac suppressed inflammation (swelling of the hind-paw) as well as hyperalgesia induced by adjuvant inoculation. In contrast, TJ-8023 did not suppress inflammation at doses effective in alleviating adjuvant-induced hyperalgesia. Therefore, the antinociceptive effect of TJ-8023 may not be due to an anti-inflammatory action. In addition, the antinociceptive effects of TJ-8023 (600 mg·kg\(^{-1}\)·d\(^{-1}\)) on adjuvant-induced hyperalgesia was smaller than those of sodium diclofenac (2.5 mg·kg\(^{-1}\)·d\(^{-1}\)), while the antinociceptive effects on RCS-induced hyperalgesia of TJ-8023 even at a dose of 30 mg/kg was greater than those of sodium diclofenac (5 mg/kg). These findings taken together suggest that the mechanism of TJ-8023 antinociception is different from that of sodium diclofenac.

Exposure to stressful situations such as electrical footshock, swimming, immobilization and rotation has been shown to reduce reactivity.
of animals to noxious stimulation.\textsuperscript{7–13} On the contrary, RCS produced a remarkable decrease in nociceptive threshold of the mouse. RCS-induced hyperalgesia has been demonstrated using several antinociceptive methods.\textsuperscript{4} Thus, although the precise mechanisms of the induction of RCS hyperalgesia are still unknown,\textsuperscript{14} RCS mice may be useful as an animal model for a kind of hyperalgesia. In the present experiments, a single injection of TJ-8023 at doses of 30 and 100 mg/kg suppressed RCS-induced hyperalgesia in a dose-dependent manner. Clinical dosage of TJ-8023 is 3.5 g/d, and assuming body weight to be 60 kg, it corresponds to about 58 mg/kg. Thus, it should be noted that the effective doses of TJ-8023 in the RCS hyperalgesic test are comparable to the clinical dose. The dose of 100 mg/kg, which was potent in RCS-induced hyperalgesia, was without effect on the nociceptive threshold of non-stressed mice. Thus, TJ-8023 may be particularly effective in a relief of the hypernociception in a morbid state.

The cold-plate test, in the present experiments, was sensitive to morphine and pentazocine, but not to indomethacin and aspirin. These findings are consistent with results gotten from humans that the opiates dipipanone and codeine suppress cold-induced pain\textsuperscript{15–17} and that aspirin gives little or no analgesia.\textsuperscript{16,17} TJ-8023 could not alter the nociceptive responses to cold-plate stimulation, suggesting that TJ-8023 is not potent to suppress cold-induced pain.

Three out of seven constituents of TJ-8023: Bushi, Syokyo and Maoh, have been shown to have antinociceptive action. Bushi\textsuperscript{18} and its alkaloids, such as aconitine and mesaconitine\textsuperscript{19} have been claimed to have potent antinociceptive actions. In the present experiments, however, poison-attenuated Bushi at a peroral dose of 100 mg·kg\textsuperscript{-1}·d\textsuperscript{-1} did not inhibit the adjuvant-induced hyperalgesia, although a significant inhibition was produced by TJ-8023 at the same dose. As 100 mg of TJ-8023 contains only about 7 mg of poison-attenuated bushi, the latter may not be exclusively responsible for the antinociceptive action of the former. In this context, poison-attenuating processes of Bushi were reported to decrease also its antinociceptive effects.\textsuperscript{19} Syokyo contains oils such as shogaol at concentrations less than 1%. Recently, we found that shogaol at peroral doses between 5 and 80 mg/kg inhibited the RCS-induced hyperalgesia in a dose dependent manner (unpublished observations). Therefore, although 100 mg of TJ-8023 contains less than 5 mg of shogaol, Syokyo might in part contribute to the TJ-8023 antinociception. Maoh contains ephedrine as a main alkaloid at concentrations less than 1%, which has been demonstrated to have antinociceptive action following subcutaneous dosage of 10 mg/kg in guinea-pigs.\textsuperscript{20} Thus, at present, the main antinociceptive principles is unclear. These constituents might synergistically produce the antinociceptive action of TJ-8023.

In conclusion, we have demonstrated that the oriental medicine TJ-8023 (Kei-Kyoh-Zoh-Soh-Oh-Shin-Bu-toh) has an antinociceptive effect and that it is more effective in alleviating a hyperalgesia in the morbid state than in suppressing a nociception in the normal one.

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