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Substance P in the cerebrospinal fluid-contacting nucleus contributes to morphine physical dependence in rats

Xian-Fu Lu[a,b,*,1], Yuan-Yuan Li[b,c,1], Chun-Guang Wang[b], Jin-Qiu Wei[b], Ying Ye[a,b], Li-Cai Zhang[a,b,*], Jun-Li Cao[b]

[a] Department of Anesthesiology, The First Clinical College, China Medical University, Shenyang, Liaoning 110001, China
[b] Jiangsu Province Key Laboratory of Anesthesiology, Xuzhou Medical College, Xuzhou, Jiangsu 221002, China
[c] Department of Anesthesiology, Shanghai Ninth People's Hospital Affiliated to shanghai JiaoTong University School of Medicine, Shanghai 200011, China

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ABSTRACT

The cerebrospinal fluid-contacting nucleus (CSF-CN), distributes and localizes in the ventral periaqueductal central gray (PAG) of the brainstem, which may influence actual composition of the cerebrospinal fluid (CSF) for non-synaptic signal transmission via releasing or absorbing bioactive substances. Many experiments have demonstrated that substance P (SP), a substance that is shown to be up-regulated in CSF-CN, plays an important role in the development of inflammatory pain and neuropathic pain. Thus in the present study, we hypothesize that SP in CSF-CN might contribute to morphine dependence in rats, inhibiting SP with (D-Pro2, D-Phe7, D-Trp9)-SP intracerebroventricular (i.c.v.) injection reduce chronic morphine dependence and withdrawal. Rats were repeatedly injected with morphine in five escalating doses for morphine physical dependence. Morphine withdrawal-like behavioral signs and morphine analgesia behaviors were monitored after naloxone administration following i.c.v. injection of (D-Pro2, D-Phe7, D-Trp9)-SP. And SP-expression of CSF-CN was evaluated with dual-label immunofluorescent technique on morphine withdrawal in rats. After i.c.v. treatment with (D-Pro2, D-Phe7, D-Trp9)-SP, the naloxone-precipitated withdrawal symptoms were significantly attenuated, paw withdrawal threshold/thermal withdrawal latency (PWT/TWL) were increased, and SP-expression in CSF-CN was significantly reduced than control group. SP, known a neurotransmitter/neuromodulator of nociception, has also been implicated in the signs of opioid withdrawal. This study provides the first evidence that SP in CSF-CN contributes to morphine physical dependence and withdrawal, which may provide an important and specific role in mediating the motivational aspects of opiates withdrawal via CSF – the parenchyma of the brain, and may represent a novel pharmacological route such as SP inhibitor i.c.v. injection for the control of drug abuse.

We reported that the distal cerebrospinal fluid contacting neurons (dCSF-CNs) are peculiar type of neurons whose bodies are in the parenchyma of the brain and processes extend into CSF in the cavity of the ventricle in the central nervous system (CNS) [18,42]. Thereby, these nerve cells may influence actual composition of CSF for nonsynaptic signal transmission via releasing or absorbing bioactive substances [33,34]. So they may play important roles in neuromodulation or neuroendocrinal regulation [18]. Through a variety of morphological methods, we found the dCSF-CNs, with their bodies mainly located in the ventral periaqueductal central gray (PAG) of the brainstem, and their processes penetrate the ependymal cells, and stretched into the CSF, were a distinct group from other neurons. After this anatomical characteristic, we named cerebrospinal fluid-contacting nucleus (CSF-CN) [35,42]. With special tracing method, we can be ale to identify the dCSF-CNs from the non-CSF-CNs in brain parenchyma [11,18–20,35,41,42]. Up to present, we have found that lesion on CSF-CN can attenuate behavioral signs of morphine withdrawal and the associated neurochemical alterations [26,27,41].

SP, known a neurotransmitter/neuromodulator of nociception, has also been implicated in the signs of opioid withdrawal. Many experiments have demonstrated an important role of SP in the development of morphine dependence and withdrawal [9,22,29–31,40,43–46]. SP was up-regulated in CSF-CN in the model of inflammatory pain [19,20]. Thus, we hypothesize that SP in CSF-CN contributes to morphine dependence in rats, and the

* Corresponding authors at: Jiangsu Province Key Laboratory of Anesthesiology, Xuzhou Medical College, Xuzhou, Jiangsu 221002, China. Tel.: +86 516 8558 2951; fax: +86 516 8558 2951.
E-mail addresses: lxf0001@126.com (X.-F. Lu), lczhang@xzmc.edu.cn (L.-C. Zhang).
[1] X.F. Lu and Y.Y. Li contributed equally to this work.

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inhibition of SP with (D-Pro2, D-Phe7, D-Trp9)-SP intracerebroventricular (i.c.v.) injection reduces chronic morphine dependence and withdrawal. By combining dual-label immunofluorescent technique and withdrawal-like behavioral signs test, we evaluate SP-expression of CSF-CN on morphine withdrawal in rats. This study provides the first evidence that SP in CSF-CN contributes to morphine physical dependence and withdrawal, which may provide an important and specific role in mediating the motivational aspects of opiates and represent a new pharmacological route such as via SP inhibitor i.c.v. injection for the control of drug abuse.

All experiments were approved by The Committee for the Ethical Use of Laboratory Animal, Xuzhou Medical College. The animals were maintained in climate and light-controlled ($23 \pm 1\,^{\circ}C$, 12/12 h dark/light cycle with light on at 08:00 h) and protected units for at least two days prior to the experiments. Testing sessions were carried out during the light phase, in a quiet and temperature-controlled (23–24 °C) area. Male Sprague–Dawley rats (270–290 g, Grade SPF) were randomized into two groups: Group B with (D-Pro2, D-Phe7, D-Trp9)-SP (Sigma, USA) i.c.v. injection; Group A, as control, with artificial cerebrospinal fluid (ACSF) i.c.v. injection ($n = 8$).

In animals chronically treated with morphine, rats were injected intraperitoneally (i.p.) three times daily (at 8:00, 14:00 and 20:00) for 5 days with increasing doses of the opiate as follows [8,25–27]: day 1 – 10, 10, and 10 mg/kg; day 2 – 10, 10, and 20 mg/kg; day 3 – 20, 20, and 40 mg/kg; day 4 – 40, 40, and 80 mg/kg; day 5 – 80, 80, and 100 mg/kg. At day 4, all animals were injected into one of the rats' lateral ventricles with 30% CB-HRP. At day 5, Group B was injected with (D-Pro2, D-Phe7, D-Trp9)-SP (1ug, 2-ul) i.c.v. injection, and Group A injected with the identical artificial cerebrospinal fluid (ACSF).

Rats were anesthetized with sodium pentobarbital (40 mg/kg, i.p.) and then immobilized in the Digital Lab Standard Stereotaxic Apparatus (Stoelting, USA). A 3 μl volume of 30% CB-HRP (Sigma, USA) was injected into one of the rats' lateral ventricles according to stereotaxic coordinates [1,18,24,42] (Brega: -1.2 ± 0.4 mm, deep: 3.2 ± 0.4 mm, right to median sagittal plane: 1.4 ± 0.2 mm). Forty-eight hours later, the animals were measured behaviorally with the morphine withdrawal-like behavioral signs, or were perfused for immunofluorescence [11,18].

For testing the morphine withdrawal-like behavioral signs, rats were placed in a plexiglass observation chamber to allow for acclimatization to the environment at 8:00 AM of day 6. Two hours later morphine withdrawal rats were injected with naloxone [5 mg/kg, subcutaneous injection (s.c.)], and withdrawal symptoms were monitored for an hour after naloxone administration. Two classes of withdrawal signs were measured [8,27]: counted signs and observed signs. The counted signs were made every 15 min for 1 h. During each period of 15 min, the number of bouts of wet dog shakes, teeth chatting, and irritability (jumping and attack) were counted and a withdrawal score for each sign was assigned as follows: 0 = no occurrence; 1 = 1 occurrence; 2 > 2 occurrences. Abnormal position was observed over periods of 2 min, with two points being given for the presence during each period. The scores of four periods showing the signs were added. Diarrhea was evaluated and given a score based on the severity of the response observed (0 = absent, 4 = mild and moderate, 8 = severe). The score of salivation was based on the severity of the response observed (0 = absent, 1 = mild and moderate, 2 = severe). The withdrawal score of body weight loss was determined by the weight difference (DW) before and 60 min after administration of the naloxone, which was assigned as follows: 0 = no change; 1 = DW < 2%; 5 = DW < 4%; 10 = DW < 6%; 15 = DW < 8%; 20 = DW > 8%.

To test effects of SP inhibitors (D-Pro2, D-Phe7, D-Trp9)-SP on the pain threshold and the initial analgesic response to morphine, Paw Withdrawal Threshold (PWT, to assess mechanical allodynia) was measured by ElectroVonFrey (IITC Life Science, USA) [5,10], and Thermal Withdrawal Latency (TWL, to assess thermal hyperalgesia) was measured by Plantar Test Hargreaves Method (IITC Life Science, USA) on 0 d (baseline), 1 d, 3 d, 5 d (before drug injection), and 6 d (1 h after naloxone injection) [7,12].

In order to determine the expression of SP in CSF-CN, one in every four sections of ACSF-injected ($n = 4$) or (D-Pro2, D-Phe7, D-Trp9)-SP-injected animals ($n = 4$) were processed as following:

All the animals were deeply anesthetized with intraperitoneal pentobarbital sodium (50 mg/kg) and transcardially perfused with 150 ml of phosphate-buffered saline (0.01 mol/L PBS, pH 7.4), followed without interruption by 4% paraformaldehyde in 0.2 M phosphate buffer (PB, 400 ml, pH 7.4). The brain was removed immediately, post-fixed for 4–6 h in the final perfusate at 4 °C, and then transferred to 0.01 mol/L PBS containing 20% sucrose for cryoprotection. The brain was stored overnight at 4 °C and then sectioned with a cryostat (Leica CM1900, Germany) at 40 μm in the transfer plane of CSF-CN. Frozen sections (40 μm) were cut and collected in PBS. Following three washes in PBS, tissue sections were incubated in an antibody cocktail consisting of goat anti-Cholera Toxin antiserum (1:1000; 9540-1004, AbD serotec, UK) and rabbit anti-SP antiserum (1:100; BA0126, BOSTER) in PBS with 0.3% Triton X-100 (PBST) for 48–72 h at 4 °C. The antibodies to Cholera Toxin and SP were visualized with a 2-h incubation in a cocktail containing donkey anti-goat IgG-Rhodamine (1:200; sc-2094, Santa Crutz, USA) and donkey anti-rabbit IgG-FITC (1:200; sc-2090, Santa Crutz, USA) in PBST. And controls without using primary antibodies were used for antibody specificity controls. As control for SP-expression in the natural morphine withdrawal rats do not treated with naloxone or SP inhibitor. As normal controls for test groups, additional sections from normal animals non-injected with morphine were processed, no significant staining was detected (not shown). Finally sections were rinsed, mounted, cover-slipped and stored at −20 °C in the dark. Tissue sections were examined using laser scanning confocal microscopy (TCS SP2, Leica, Germany) to identify dCSF-CNs and SP. Red shows the single-labeled dCSF-CNs, green shows SP-labeling positive neurons, and yellow shows CB-HRP/SP dual-labeled neurons. The number of labeled neurons was counted in every four sections of two groups.

For statistical analysis, GraphPad Prism v 5.0 (GraphPad Software, USA) was used. Results were presented as mean ± SEM. (n = number of animals). The data were analyzed by Student's t-test. Values of $P < 0.05$ were considered to be statistically significant.

On the process of setting the morphine dependence model, the experimental animals showed stagnant response. Their body weight did not increase or declined. But when Animals' naloxone-stimulating withdrawal reactions were judged, or in another word when animals grit their teeth, do wet dog shake, jump, salivate, the rat' weight usually decreased significantly. The withdrawal symptoms of Group B were significantly decreased in comparison to the withdrawal group ($P < 0.05$) (Fig. 1).

There were no significant pain thresholds changes in morphine dependence rat. (D-Pro2, D-Phe7, D-Trp9)-SP (i.c.v. injection) did not affect the motor functions, but significantly attenuated naloxone-precipitated withdrawal symptoms and increased PWT and TWL, which means i.c.v.-injected SP inhibitor can revise mechanical allodynia and thermal hyperalgesia following morphine exposure and withdrawal (Fig. 2).

CB-HRP labeling positive dCSF-CNs, the neuron whose somas and dendrites filled with red, mainly distributed symmetrically in the ventral PAG of the brainstem. The cell bodies of dCSF-CNs were in the brain parenchyma and the processes extended into CSF. SP-expressing in CSF-CN was significantly increased after i.p. naloxone

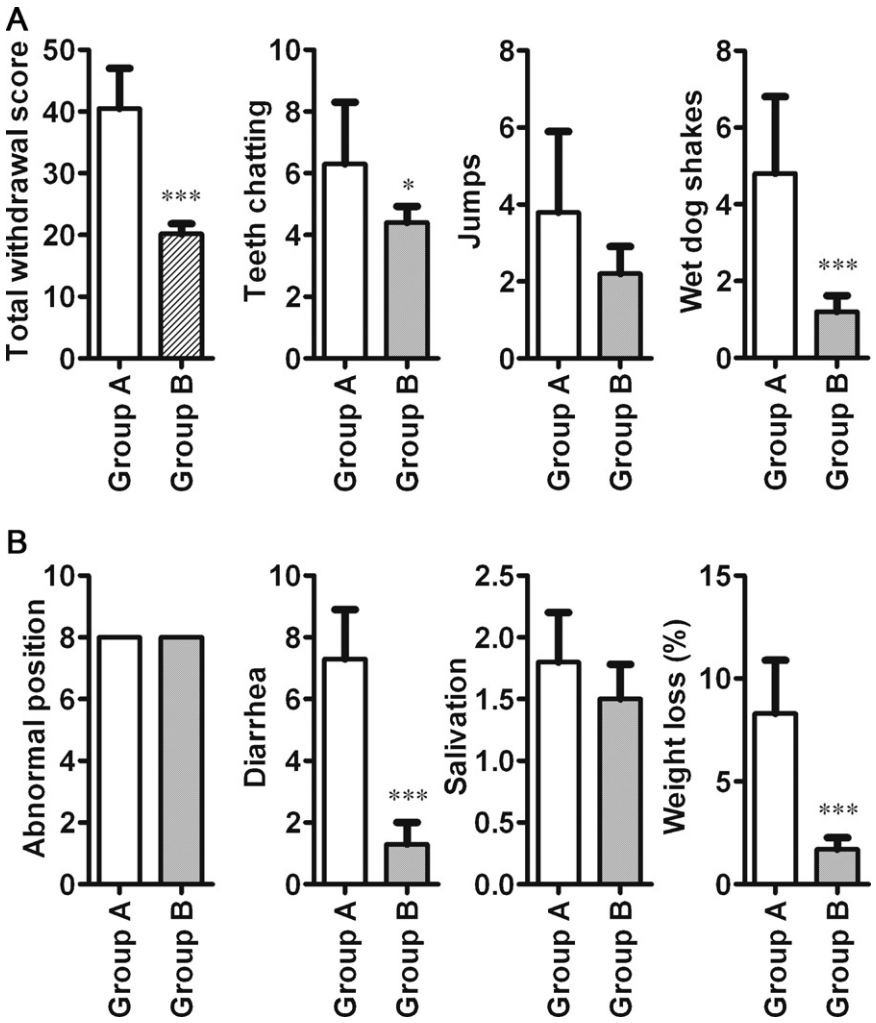

Fig. 1. SP inhibitor, (D-Pro2, D-Phe7, D-Trp9)-SP, attenuates behavioral signs of naloxone-precipitated morphine withdrawal. Total withdrawal scores (A) were calculated from the individual signs. $^{*}p < 0.05$, $^{***}P < 0.001$ shows Group B significantly, compared to the control group (Group A).

injection. Compared with Group A, the number of CB-HRP/SP dual-labeled neurons in group B significantly reduced by i.c.v. treatment (D-Pro2, D-Phe7, D-Trp9)-SP, which is positively relevant to the morphine withdrawal behavior signs (Fig. 3).

The present study has shown several findings. Firstly, SP in CSF-CN was activated by chronic morphine treatment. Secondly, SP inhibitor (D-Pro2, D-Phe7, D-Trp9)-SP reduced naloxne precipitation withdrawal signs. Pain threshold was up-regulated by SP inhibitor. The analgesic responses changes include that PWT and TWL were increased significantly, that mechanical allodynia and thermal hyperalgesia was attenuated obviously on morphine dependence in Group A. Thirdly, SP-expression in CSF-CN was reduced after i.c.v. administration of SP inhibitor, (D-Pro2, D-Phe7, D-Trp9)-SP, which was up-regulated by naloxone injection on morphine withdrawal. These results provide the first evidence that SP in CSF-CN contributes to morphine physical dependence and withdrawal, and provide a novel pharmacological route for preventing or reversing opioid dependence. We can do this by i.c.v. injection of SP inhibitor, and we can also achieve this by selectively destroying Neurokinin 1 (NK-1) receptor (SP receptor) in CSF-CN by means of a targeted cytotoxin, SP-saporin, a substance that would cause lesion on CSF-CN while injecting into the cerebrospinal fluid in future [36].

A variety of peptides, such as SP and calcitonin gene-related peptide (CGRP), modulate drug abuse after they are released from synaptic vesicles into ventricular systems [2,6,9,13,14,22,29–32,43]. After release, these transmitters may also influence actual composition of CSF for non-synaptic signal transmission [2], or interact with their receptors, which typically lead to neural depolarization via synaptic signal transmission. Thus, SP may produce a persistent depolarization of the membrane, leading to an augmentation of the discharge and long-term potentiation [2,13,14]. Morphine dependence and withdrawal were attributed to neural plasticity and cell memory [16,23,28,38,39]. The mechanisms of cellular memory response to NK-1 receptor largely depend on a receptor-mediated second messenger system [21]. SP and NK1 receptor are coupled to the Extracellular Receptor Kinase/Mitogen-activated protein kinase (ERK/MAPK) activation by morphine [3,4,6]. Whereas the physical response to opiate withdrawal was reduced in SP receptor knockout animals [22]. Therefore, SP release between parenchyma and ventricular system provides a well-defined model for studying modulatory components involved in morphine dependence.

The dCSF-CNs, whose body located in the parenchyma of the brain and process extend into the CSF in the cavity of the ventricle, were centered in the localization where CSF-CN located [18,42]. Intercellular communication in the brain can be divided into two types: wiring transmission-via synaptic contacts, and volume transmission-by the diffusion of chemical messengers via the intercellular space or CSF [2,34]. The dCSF-CNs, with its long

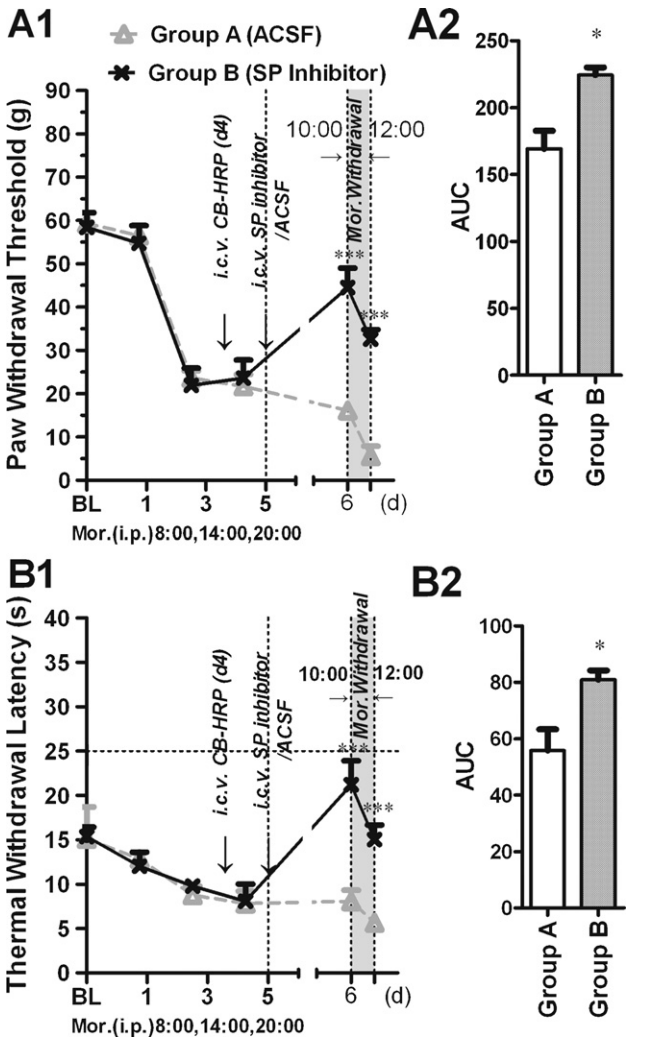

Fig. 2. Chronic treatment of morphine causes mechanical allodynia and thermal hyperalgesia. SP inhibitor, (D-Pro2, D-Phe7, D-Trp9)-SP, increases pain threshold. PWT and TWL of Group B are revised by i.c.v. injection (D-Pro2, D-Phe7, D-Trp9)-SP following morphine exposure and withdrawal. $^{*}p < 0.05$, $^{***}P < 0.001$ shows Group B significantly, compared to Group A.

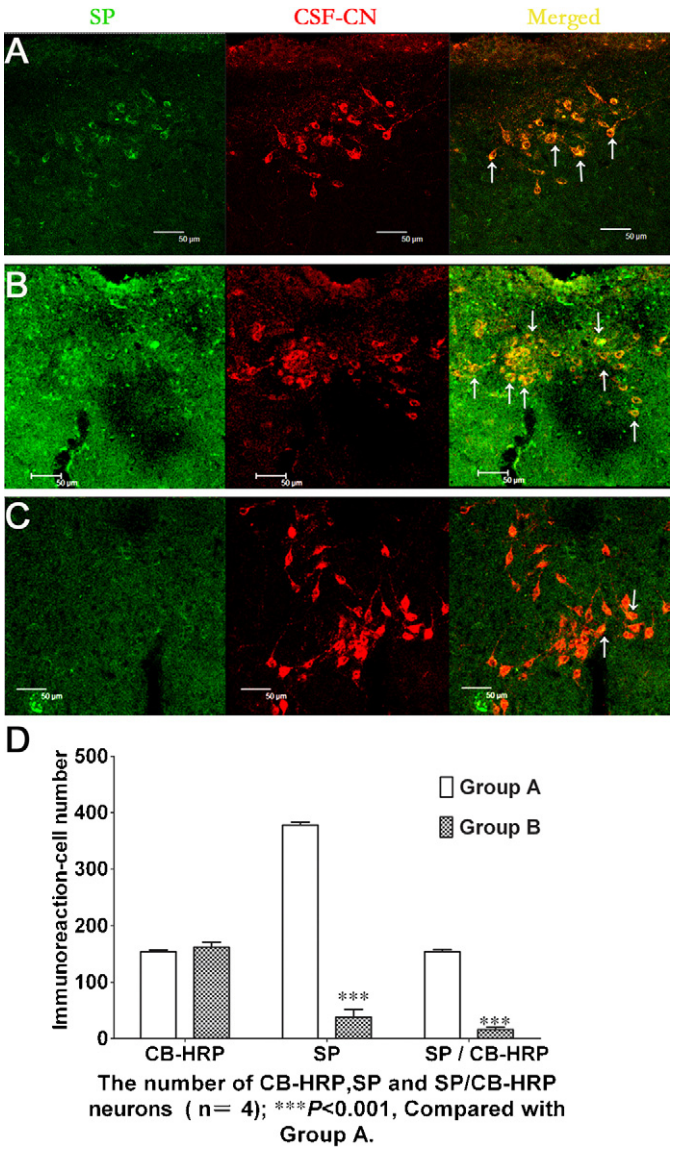

Fig. 3. SP-expression in CSF-CN (double-staining for SP-arrowheads). Photomicrograph (A) depicts SP-expression in the natural morphine withdrawal rats. Photomicrograph (B) shows SP-expression in Group A, which is significantly higher than Group B (C). Graph (D) depicts the numbers of neurons labeled with SP or CB-HRP in every four sections of two groups. Scale bars represent 50 μm (A–C are at the same magnification).

ecphyma extending into CSF and vascular system [17], enable a passage through the blood–brain barrier and the blood–cerebrospinal fluid barrier, and a recruitment of the bioactive materials (such as SP) in blood plasma and cerebrospinal fluid [19].

Morphine treatment of rats was shown to affect the SP production in several CNS tissues [15,37]. Following naloxone injection in morphine-maintaining animals, the SP concentration was significantly enhanced in the midbrain and hypothalamus. This elevation occurred at a time correlated with the peak of the behavioral morphine withdrawal syndrome [22]. In our study, we used CB-HRP tracking technique combined with double-labeled immunofluorescent technique to observe the enhanced SP in CSF-CN after naloxone precipitated withdrawal reaction, which matched with the prior result.

As mentioned above, intrathecal or i.c.v. pharmacological interventions in CSF-CN is mild in comparison with other aggressive vocalizations produced by activation or deactivation of NK-1 receptor. Even so, the development of hyperalgesia is significantly attenuated by SP inhibitor. Thus, SP in CSF-CN contributes to morphine physical dependence and withdrawal, lesion on the SP receptor with SP-saporin. Study on CSF-CN may be conducive to reveal some roles of neuromodulation or neuroendocrinal regulation in the future.

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