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THE INDUCTION OF LONG-TERM POTENTIATION IN SPINAL DORSAL HORN AFTER PERIPHERAL NOCICEPTIVE STIMULATION AND CONTRIBUTION OF SPINAL TRPV1 IN RATS

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Abstract—During chronic pain states, peripheral nociceptive stimulation can induce long-term potentiation (LTP) in the spinal dorsal horn, but it is not clear how quickly spinal LTP develops after peripheral noxious stimulation. Furthermore, transient receptor potential vanilloid type 1 (TRPV1) receptors are abundant in spinal cord dorsal horn, especially in the superficial layers, and are thought to be involved in synaptic plasticity. In this study, we investigated the time frame of LTP induction after inflammatory insult and electrical stimulation and the involvement of TRPV1 receptors. By using extracellular recordings of C-fiber-evoked field potentials in the superficial spinal dorsal horn and teased fiber recording *in vivo*, we found that subcutaneous injection of complete Freund's adjuvant (CFA) or 5% formalin induced low-frequency, irregular discharges of C-fibers and LTP of the C-fiber-evoked field potentials in the spinal dorsal horn within 3 h. Topical application of the TRPV1 receptor antagonist capsazepine onto the spinal cord inhibited the induction of spinal LTP by CFA or formalin. Furthermore, capsazepine and another TRPV1 antagonist, (E)-3-(4-t-butylphenyl)-*N*-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)acrylamide, partially or completely blocked the LTP induced by conditioning stimulation with high- and low-frequency electrical stimulation. These results suggest that acute peripheral inflammatory stimulation by CFA or 5% formalin can induce spinal LTP very early after stimulation onset and that TRPV1 receptors in the spinal dorsal horn might contribute to this LTP induction. © 2014 Published by Elsevier Ltd. on behalf of IBRO.

Key words: long-term potentiation, transient receptor potential vanilloid type 1, spinal dorsal horn, inflammatory pain, complete Freund's adjuvant.

INTRODUCTION

Long-term potentiation (LTP) is a long-lasting and activity-dependent increase in synaptic transmission. It is one mechanism by which central sensitization leads to amplified nociception in the spinal cord (Randic, 1996; Sandkuhler, 2000). Here, the term ''spinal LTP'' refers to a long-lasting increase in the field potentials evoked by afferent stimulation and recorded in the spinal dorsal horn. In normal rats, spinal LTP can be induced by high-frequency (~100 Hz) stimulation of afferent nerve fibers (Liu and Sandkuhler, 1995, 1997) as well as by low-frequency stimulation (Ikeda et al., 2006) that mimics the discharges of peripheral inflammation or nerve injury. Usually, spinal LTP is regarded as a mechanism of central sensitization. For example, we reported that the induction of spinal LTP was facilitated in rats with spinal nerve ligation-induced neuropathic pain compared with that in normal rats (Xing et al., 2007). Spinal LTP also develops in acute pain situations. For example, it can be induced after subcutaneous injections of irritants such as capsaicin or formalin (Ikeda et al., 2006).

Transient receptor potential vanilloid type 1 (TRPV1) receptors in the brain have been shown to modulate synaptic plasticity. For example, in mouse hippocampus, TRPV1 activation induces long-term depression (LTD) in interneurons (Alter and Gereau, 2008; Gibson et al., 2008), and in amygdala, capsaicin induces TRPV1-dependent LTP (Zschenderlein et al., 2011). Further more, in behavioral and electrophysiological experiments, intrathecal injection of TRPV1 antagonists capsazepine and (E)-3-(4-t-butylphenyl)-*N*-(2,3-dihydrobenzo[b][1,4] dioxin-6-yl)acrylamide (AMG 9810) (Gavva et al., 2005) significantly inhibited thermal hyperalgesia and mechanical allodynia, as well as Aδ- and C-fiber-evoked responses of wide-dynamic-range neurons (Luo et al., 2008; Yu et al., 2008).

TRPV1 receptors are expressed not only in peripheral nociceptive ganglion neurons and their nerve fibers (Guo et al., 1999; Valtschanoff et al., 2001), but also in the spinal dorsal horn. They are located in laminae I and II, primarily in presynaptic neurons (Guo et al., 1999; Farquhar-Smith et al., 2000; Valtschanoff et al., 2001;

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Abbreviations: AMG 9810, (E)-3-(4-t-butylphenyl)-*N*-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)acrylamide; CFA, complete Freund's adjuvant; CV, conduction velocity; DRG, dorsal root ganglion; LTD, long-term depression; LTP, long-term potentiation; TRPV1, transient receptor potential vanilloid type 1.

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Hwang and Valtschanoff, 2003; Matta and Ahern, 2011). Previously, we showed that TRPV1 expression increased in both dorsal root ganglion (DRG) neurons and superficial layers of the spinal dorsal horn after complete Freund's adjuvant (CFA) was injected into the plantar skin of rats (Luo et al., 2004). Furthermore, CFA, which is commonly used in models of inflammatory pain, induced pain in the rats that persisted for 28 days.

In the current study we investigated whether peripheral injection of CFA into planter skin can induce spinal LTP and over what time period. Moreover, we examined whether TRPV1 in the spinal dorsal horn participates in the LTP induced after CFA injection.

EXPERIMENTAL PROCEDURES

Animals

Male Sprague–Dawley rats weighing 250–350 g were provided by the Department of Experimental Animal Sciences, Peking University Health Science Center. The animals were housed in plastic cages (up to four per cage) with soft bedding under a natural diurnal cycle at room temperature. They were provided with water and food *ad libitum* and were housed for at least 7 days before experiments. All protocols were approved by the Animal Use and Care Committee of the Peking University Health Science Center.

In vivo recordings of C-fiber-evoked field potentials

Surgical procedures were carried out as described previously (Xing et al., 2007). Rats were initially anesthetized with urethane (1.5 g/kg, i.p.). A tracheotomy was performed to maintain an open, low-resistance airway. A cannula was inserted into the right jugular vein for continuous infusion of Tyrode's solution (in mM: NaCl 137, KCl 2.7, $CaCl_2$ 1.4, $MgCl_2$ 1.0, $NaHCO_3$ 6.0, NaH_2PO_4 2.1, D-(+)-glucose 6.5; pH 7.4) at a rate of 1.0–1.5 ml/h.

The lumbar enlargement of the spinal cord was exposed by a laminectomy between vertebrae T_{12} and L_1. The vertebral column was tightly fixed in a frame with clamps. A small well was built with 3% agar on the dorsal spinal cord at the recording segment to allow application of drugs or vehicles. A pair of bipolar silver hook electrodes was placed under the sciatic nerve immediately proximal to the trifurcation for electrical stimulation. During recording, the animals were paralyzed with i.v. injection of curare (2.0 mg/kg) and artificially ventilated. During the experiment, continuous anesthesia and paralysis were maintained with urethane (0.10–0.17 g/kg/h) and curare (0.21 mg/kg/h). The body temperature of the rats was maintained at 36.5–37.5 °C via a feedback-controlled under-body heating pad. After the surgery, the whole experiment could last up to 10 h.

C-fiber-evoked field potentials were recorded in the spinal dorsal horn according to a previously published method (Liu and Sandkuhler, 1995, 1997; Xing et al., 2007). Briefly, the C-fiber-evoked field potentials with long latency (90–130 ms, corresponding to conduction velocities less than 2 m/s) and high thresholds (7–13 V, 0.5 ms) were recorded at a depth of 100–500 μm from the dorsal surface of L_4–L_5 spinal cord with parylene-coated tungsten microelectrodes (impedance 1–3 MΩ, FHC, Bowdoinham, ME, USA) driven by a micro-stepping motor. According to a previous report (Liu and Sandkuhler, 1997), the amplitude of the field potential was not diminished but rather increased by spinalization, indicating that the supraspinal loop did not contribute to the field potentials. A bandwidth of 0.1–300 Hz was used to remove artifacts without altering the C-fiber-evoked field potentials. The signals were amplified, filtered, displayed on an oscilloscope, and fed to a Pentium computer via a CED 1401 interface for off-line analysis with Spike 2 software (Cambridge Electronic Design, Cambridge, UK).

Single pulses of 0.5 ms at intensities of 10–20 V were applied to the sciatic nerve every 5 min for at least 30 min and were used as control. The mean amplitude of the control potentials (100%) was obtained from an average of six individual test potentials. To induce LTP of the C-fiber-evoked field potentials, we applied different types of conditioning stimulation to the sciatic nerve: CFA (100 μl, subcutaneous intraplantar injection), formalin (5%, 100 μl, subcutaneous intraplantar injection), high-frequency electrical stimulation (100 Hz, 40 V, 0.5 ms, 400 pulses given in four trains of 1 s duration at 10 s intervals), or low-frequency electrical stimulation (2 Hz, 30 V, 0.5 ms, 240 pulses given in 2 min) to the sciatic nerve. After the conditioning stimulation, the C-fiber-evoked field potentials were recorded again for another 2–3 h with the same test stimulation delivered to the sciatic nerve. The amplitude of the field potential induced by each conditioning stimulus was normalized and expressed as the percentage of the control value. LTP in the spinal cord was defined as an increase in the field potential of at least 20% after induction that lasted for at least 1.5 h. To test the role of the TRPV1 receptors, we applied a TRPV1 antagonist (capsazepine or AMG 9810) topically 20 min before the conditioning stimulus.

Teased fiber recording of primary afferent discharges *in vivo*

The surgical procedure was similar to that described above, but the L_4 or L_5 dorsal root was exposed in a lower lumbar laminectomy and covered with warmed paraffin oil (37 °C) in a pool formed by skin flaps. The teased fiber recording method was used to record the primary afferent discharges entering the spinal cord along the dorsal root. Most of the dorsal muscles supplied by the dorsal ramus of the L_4 or L_5 spinal nerve were removed during the laminectomy.

Fine axon bundles (microfilaments) were teased from the dorsal root with specially honed No. 5 jewelers forceps (Fine Science Tools, Switzerland). The microfilament was cut between the DRG and the spinal cord and the cut end was placed on a platinum recording electrode referenced to a nearby indifferent electrode. Electrical stimulation is then applied 25–30 mm distal to the recording electrode. Each microfilament was observed passively for $\geqslant$30 s.

If we noted any spontaneous action potentials during this period, we extended observation and recorded the frequency and pattern of the firing. Shocks of gradually increasing intensity were delivered via the bipolar silver hook electrode. We then determined the response latency for every individually identifiable fiber (invariant waveform, discrete all-or-nothing threshold, and fixed latency of response) that was recruited as the intensity of stimulation was gradually increased. Conduction velocity was calculated from the latency of response and the distance between the recording electrode and stimulating electrodes. We classified fibers according to their conduction velocities (CVs): myelinated A fibers if the CV was greater than 2.0 m/s, unmyelinated C-fibers if the CV was less than 2.0 m/s (Leem et al., 1993; Chen and Levine, 2001; Djouhri and Lawson, 2004). We did not differentiate between Aβ- and Aδ-fibers.

Drugs

CFA (Sigma–Aldrich) was used as directed by the manufacturer. Formalin (37% formaldehyde) was dissolved in 0.9% NaCl to a 5% solution. The TRPV1 antagonist capsazepine (Sigma–Aldrich) was dissolved in vehicle (5% methanol, 5% Tween 80, 90% saline) at 2 μg in 40 μl. The TRPV1 antagonist AMG 9810 (Tocris Cookson) was dissolved in the same vehicle at 50 μg in 100 μl.

No rat received multiple treatments. For an individual experiment, we used only one method (high-frequency stimulation, low-frequency stimulation, formalin injection, or CFA injection) to induce spinal LTP and administered only one kind of treatment (capsazepine or AMG 9810).

Statistical analysis

All data are expressed as mean ± standard error of the mean (SEM) Changes in values over time were analyzed with a one-way analysis of variance (ANOVA) followed by Dunnett's post hoc test. Parametric statistics were used after confirmation that the data were normally distributed. Statistical significance was set at $p < 0.05$.

RESULTS

Subcutaneous injection of 5% formalin or CFA induces spinal LTP of C-fiber-evoked field potentials

To investigate how rapidly spinal LTP develops after CFA or 5% formalin injection, we recorded C-fiber-evoked field potentials in the superficial spinal cord dorsal horn. When normal saline was injected into the glabrous skin of the ipsilateral hind paw, the amplitude of C-fiber-evoked field potentials did not change significantly during a 3-h recording period (Fig. 1A). In contrast, injection of 5% formalin into the paw induced a slow-onset LTP (Fig. 1B). The mean amplitude of the field potentials after formalin was 154.1 ± 7.3% of the baseline ($p < 0.01$). Similarly, LTP developed during the 3 h after CFA injection (Fig. 1C). The mean amplitude of the C-fiber-evoked field potentials reached 157.8 ± 7.9% of baseline ($p < 0.01$).

During the 3-h observation period after formalin (Fig. 1D) or CFA (Fig. 1E) injection, the C-fiber spontaneous discharges were irregular and at low frequencies of 1–5.3 Hz. As reported previously (Xiao and Bennett, 2007), we also recorded long-lasting and low-frequency C-fiber discharges 7 days after CFA injection (data not shown).

TRPV1 antagonist inhibits formalin- or CFA-induced spinal LTP

To test the possible role of TRPV1 receptors in the induction of spinal LTP in the dorsal horn, we applied capsazepine, a TRPV1 antagonist, directly onto the spinal cord 20 min before peripheral injection of 5% formalin or CFA. Capsazepine completely blocked formalin- and CFA-induced LTP of the C-fiber-evoked field potentials in the spinal cord. In the presence of capsazepine, the amplitude of the C-fiber-evoked field potentials remained at 104.3 ± 2.7% of baseline after formalin injection ($p > 0.05$; Fig. 2A) and at 111.0 ± 13.4% of baseline after CFA injection ($p > 0.05$; Fig. 2B). These results suggest that spinal TRPV1 receptors contribute to the induction of spinal LTP by subcutaneous injection of 5% formalin or CFA.

TRPV1 antagonists inhibit spinal LTP induced by high-frequency stimulation of the sciatic nerve

Experimentally, spinal LTP is usually induced by high-frequency stimulation (100 Hz) of the sciatic nerve. We first tested whether TRPV1 receptors in the spinal dorsal horn are involved in the induction of LTP by high-frequency stimulation of the sciatic nerve. When vehicle was applied to the nerve, high-frequency stimulation induced LTP of the C-fiber-evoked field potentials in the spinal dorsal horn. The mean amplitude of the C-fiber-evoked field potentials after induction was 186.9 ± 8.3% of the baseline ($p < 0.01$; Fig. 3A). When spinal TRPV1 receptors were blocked with capsazepine, LTP was decreased, and the mean amplitude of C-fiber-evoked field potentials reached only 138.3 ± 9.9% of baseline ($p < 0.01$; Fig. 3B). Additionally, enhancement of the amplitude was less pronounced in the capsazepine group than in the vehicle group (Fig. 5A).

AMG 9810, another TRPV1 antagonist, also inhibited high-frequency-stimulation-induced LTP. In the AMG 9810 vehicle group, the mean amplitude of the C-fiber-evoked field potentials after induction was 166.3 ± 7.1% of baseline ($p < 0.01$; Fig. 3C). However, when AMG 9810 was applied, the mean amplitude of the C-fiber-evoked field potentials after induction was 94.1 ± 10.5% of baseline ($p > 0.05$; Fig. 3D), indicating that LTP induction is inhibited by blockade of spinal TRPV1 receptors.

TRPV1 antagonists inhibit spinal LTP induced by low-frequency stimulation of the sciatic nerve

Because we observed continuous low-frequency discharges in the peripheral fibers, we used low-frequency stimulation of the sciatic nerve as a conditioning stimulus. As shown in Fig. 4, low-frequency

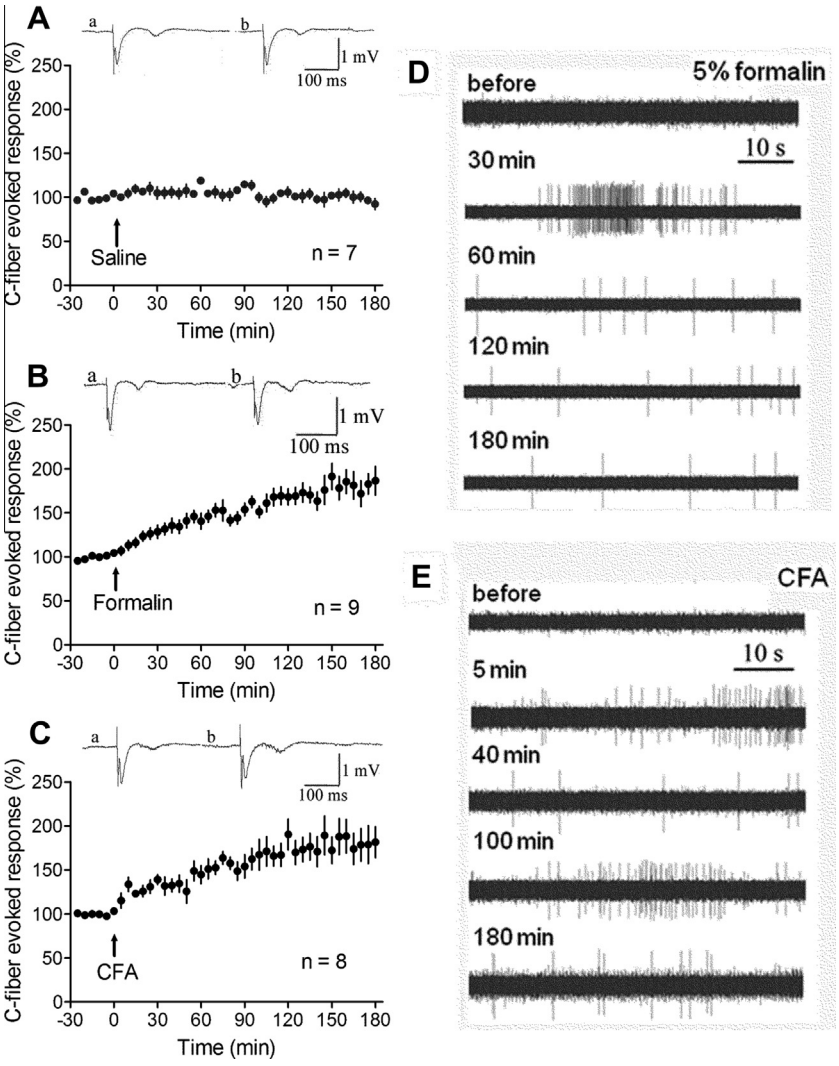

Fig. 1. Spinal LTP of the C-fiber-evoked field potentials induced by subcutaneous injection of 5% formalin or CFA. (A) Amplitude of the C-fiber-evoked field potentials did not change significantly in the 3-h period after injection of normal saline into the glabrous skin of the ipsilateral hind paw. (B, C) LTP (increase in amplitude of the C-fiber-evoked field potentials) was induced within 3 h after subcutaneous injection of 5% formalin (B) or CFA (C) into the glabrous skin of the ipsilateral hind paw. Two individual potentials recorded in a rat are shown in insets. (D, E) Examples of low-frequency, irregular discharges of C-fibers within 3 h after formalin (D) or CFA (E) injection. n = 8–9 per group.

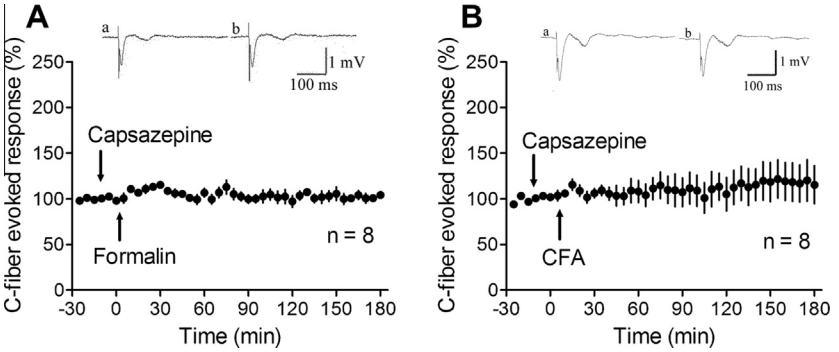

Fig. 2. TRPV1 antagonist capsazepine (2 μg) inhibits spinal LTP induced by 5% formalin (A) or CFA (B). Insets: Representative recordings of the C-fiber-evoked field potentials in the spinal cord of a rat. n = 8 per group.

stimulation also induced LTP of the C-fiber-evoked field potentials in intact animals. The mean amplitude of the C-fiber-evoked field potentials after induction reached 180.7 ± 10.1% of baseline after low-frequency stimulation ($p < 0.01$; Fig. 4A). However, topical application of capsazepine onto the spinal cord

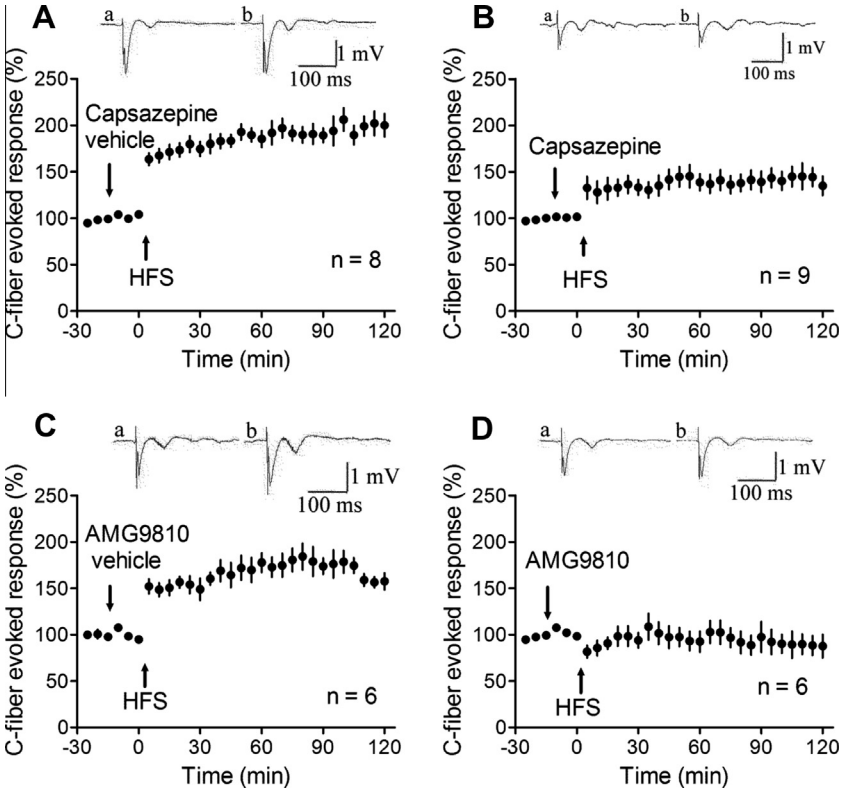

Fig. 3. TRPV1 antagonists inhibit spinal LTP induced by high-frequency stimulation (HFS). (A) Capsazepine vehicle group. High-frequency stimulation induced LTP of the C-fiber-evoked field potentials. (B) Capsazepine group. Topical application of capsazepine (2 μg) inhibited the induction of LTP induced by high-frequency stimulation. (C) AMG 9810 vehicle group. High-frequency stimulation induced LTP of the C-fiber-evoked field potentials. (D) AMG 9810 group. Topical application of AMG 9810 (50 μg) inhibited the induction of LTP by high-frequency stimulation. Insets: Representative examples of two individual potentials recorded in a rat. n = 8, 9, 6, and 6 in A, B, C, and D, respectively.

completely inhibited induction of LTP. The mean amplitude of the C-fiber-evoked field potentials after induction was 109.0 ± 2.7% of baseline ($p < 0.05$; Fig. 4B). In addition, the enhancement in amplitude was decreased in the capsazepine group compared with that in the vehicle group (Fig. 5B).

AMG 9810 similarly blocked the LTP induced by low-frequency stimulation (Fig. 4C, D). After induction by low-frequency stimulation, the mean amplitude of the C-fiber-evoked field potentials was 188.5 ± 16.1% of baseline ($p < 0.01$; Fig. 4C) in the presence of vehicle but only 105.3 ± 5.3% of baseline in the presence of AMG 9810 ($p > 0.05$; Fig. 4D). Topical application of capsazepine, AMG 9810, or their vehicles alone had no obvious effect on the amplitude of the C-fiber-evoked field potentials in the spinal dorsal horn in the absence of low-frequency stimulation (data not shown). These results suggest that the induction of LTP induced by low-frequency stimulation can be inhibited by TRPV1 receptor antagonists.

DISCUSSION

In the present study, we found that LTP of the C-fiber-evoked field potentials in the spinal dorsal horn could be induced within 3 h after subcutaneous, intraplantar injection of 5% formalin or CFA. The LTP could also be induced by high- or low-frequency stimulation of the sciatic nerve. Blockade of spinal TRPV1 receptors prevented LTP induction, indicating that these receptors are involved in the spinal LTP.

LTP in the spinal dorsal horn as a form of central sensitization can be induced by high- and low-frequency stimulation of the sciatic nerve

LTP has become an experimental paradigm for studying synaptic plasticity and a synaptic model for storage of information throughout the central nervous system (Sandkuhler et al., 2000). Spinal LTP is now regarded as a mechanism of central sensitization by which chronic pain states are maintained (Sandkuhler et al., 2000; Rygh et al., 2002; Klein et al., 2004).

It has been shown that conditioning stimulation with high-intensity, high-frequency burst-like stimulation of the sciatic nerve can induce LTP of the C-fiber-evoked field potentials in the spinal dorsal horn in normal rats (Liu and Sandkuhler, 1995, 1997; Liu and Sandkuhler, 1998; Sandkuhler and Liu, 1998). Later, it was found that low-frequency stimulation could also induce spinal LTP (Ikeda et al., 2006). During inflammatory pain induced by peripheral injection of capsaicin or 5% formalin, the peripheral discharges are usually low-frequency (Puig and Sorkin, 1996). In a relatively long time period after peripheral nerve injury (for example, 2 days after spinal nerve ligation in a neuropathic pain model), the discharge rate was also low-frequency (Sun et al., 2005). Apparently, the low-frequency stimulation

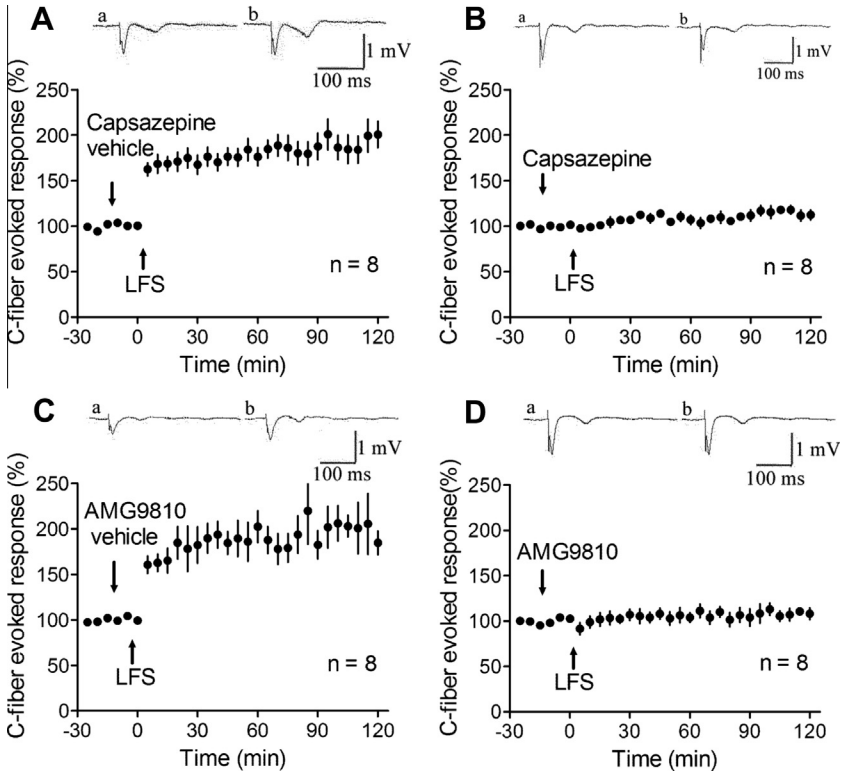

Fig. 4. TRPV1 antagonists inhibit LTP induced by low-frequency stimulation (LFS). (A) Capsazepine vehicle group. Low-frequency stimulation induced LTP of the C-fiber-evoked field potentials. (B) Capsazepine group. Topical application of capsazepine (2 μg) inhibited the induction of LTP by low-frequency stimulation. (C) AMG 9810 vehicle group. Low-frequency stimulation induced LTP of the C-fiber-evoked field potentials. (D) AMG 9810 group. Topical application of AMG 9810 (50 μg) completely inhibited the induction of LTP by low-frequency stimulation. Insets: Representative examples of two individual potentials recorded in a rat. $n = 8$ per group.

of the sciatic nerve could resemble the low-frequency afferent barrage. In the present study, consistent with a previous report (Ikeda et al., 2006), we found that low-frequency stimulation of the sciatic nerve (Fig. 4A, C), in addition to high-frequency stimulation (Fig. 3A, C), could induce spinal LTP.

Intradermal injection of 5% formalin or CFA leads to rapid LTP induction in the spinal dorsal horn

Injections of formalin or CFA are commonly used in inflammatory pain models. In the formalin test, spontaneous pain occurs almost immediately after formalin injection. In the CFA model, rats shows mechanical allodynia and thermal hyperalgesia as early as 2, 6, and 12 h after injection of CFA (Lee et al., 2004; Chen et al., 2007), and lasts for as long as 21–28 days (Luo et al., 2004; Yu et al., 2008).

It is already known that spinal LTP occurs under neuropathic pain conditions and that inhibition of LTP can alleviate neuropathic pain (Xing et al., 2007). Here we found that inflammatory pain induced by 5% formalin or CFA also induces LTP. More interestingly, the spinal LTP could be induced very rapidly, within 3 h after formalin or CFA injection (Fig. 1B, C). These results suggest that spinal LTP, as a form of central sensitization, occurs not only in chronic pain but also in acute pain.

In the present study, we found that formalin or CFA injection caused low-frequency, irregular firings in peripheral fibers (Fig. 1D, E). We speculate that these low-frequency discharges in the peripheral fibers induce spinal LTP. It is well known that in the later stage of the CFA pain model, from day 2 to day 14 (Xiao and Bennett, 2007), rats exhibit persistent low-frequency spontaneous discharges in C-fiber primary afferent neurons. However, it was not known how soon after CFA injection the spontaneous discharges of C-fibers began. In our study, irregular, low-frequency discharges of C-fibers could be observed as early as 3 h after CFA injection (Fig. 1E). What is more, these low-frequency discharges could induce spinal LTP. When we applied low-frequency stimulation onto the sciatic nerve to mimic the peripheral spontaneous discharges, spinal LTP was produced (Fig. 4A, C). Our findings are supported by a study from Ikeda et al. (Ikeda et al., 2006), who used rat formalin and capsaicin models of inflammatory pain to demonstrate that natural, low-frequency, irregular and asynchronous discharges in nociceptive C-fibers induce spinal LTP.

Spinal TRPV1 participates in the induction of LTP by CFA or formalin injection and conditioning stimulus

In our previous studies, we found that TRPV1 expression increased in the spinal dorsal horn from day 1 to day 21 after subcutaneous plantar CFA injection. The increased TRPV1 was distributed mainly in the primary afferent nerve fibers in the superficial layers of the spinal dorsal horn (Luo et al., 2004). We also found that intrathecal administration of TRPV1 antagonist AMG 9810 after

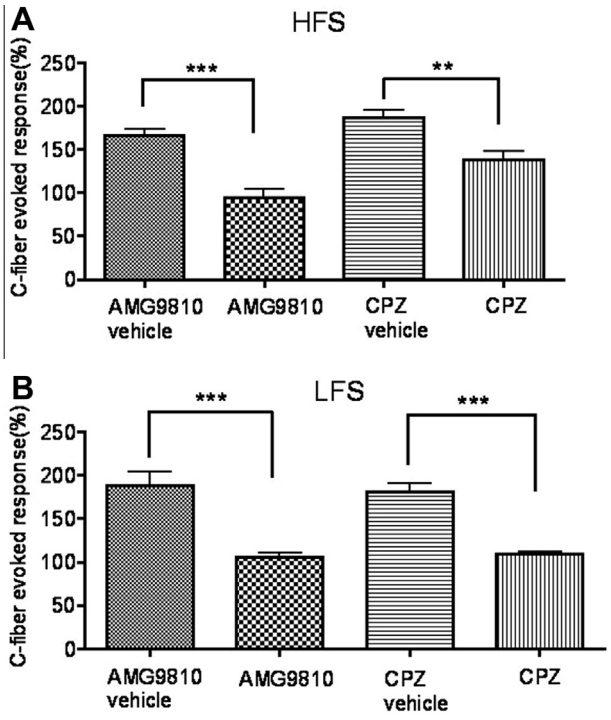

Fig. 5. TRPV1 receptor antagonists capsazepine and AMG 9810 significantly inhibit the LTP induced by high-frequency stimulation (HFS; A; $^{**}p < 0.01$, $^{***}p < 0.001$) and low-frequency stimulation (LFS; B; $^{**}p < 0.01$, $^{***}p < 0.001$) in the spinal dorsal horn.

CFA injection significantly reduced thermal hyperalgesia and mechanical allodynia (Yu et al., 2008). Spinal application of capsazepine also inhibited Aδ- and C-fiber-evoked responses of wide-dynamic-range neurons in the spinal cord (Luo et al., 2008). These results suggest an important role of the spinal TRPV1 receptors in inflammatory pain.

In summary, we found that inflammatory pain produced by intraplantar injection of 5% formalin or CFA induced low-frequency, irregular discharges of C-fibers in rats. Within a very short period of time (3 h) after formalin or CFA injection, spinal LTP of the C-fiber-evoked field potentials developed. These results suggest that spinal LTP develops rapidly after an inflammatory insult. Based on our results, we speculate that acute inflammatory pain also causes spinal central sensitization or that this kind of acute inflammatory stimulation could initiate central sensitization to transform acute pain to chronic pain. Our data also showed that spinal TRPV1 participates in spinal LTP induction. It is well known that peripheral TRPV1 is pivotal in inflammatory pain; our results suggest that spinal TRPV1 might also be important.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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