Experimental Neurology 212 (2008) 507–514

Contents lists available at ScienceDirect

Experimental Neurology

journal homepage: www.elsevier.com/locate/yexnr

BDNF induces late-phase LTP of C-fiber evoked field potentials in rat spinal dorsal horn

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ARTICLE INFO

Article history:
Received 2 January 2008
Revised 24 April 2008
Accepted 28 April 2008
Available online 11 May 2008

Keywords:
Long-term potentiation
Brain-derived neurotrophic factor
NMDA receptor
Spinal dorsal horn
MAPK
NF-κB
Protein synthesis
Neuropathic pain
Electrophysiology

ABSTRACT

Several lines of evidence have shown that in some brain regions brain-derived neurotrophic factor (BDNF) is important for long-term potentiation (LTP), a synaptic model of memory storage. In the present work we evaluate the role of BDNF in LTP of C-fiber evoked field potentials in spinal dorsal horn, a synaptic model of pain memory. We found that spinal application of BDNF-induced LTP of C-fiber evoked field potentials with a long latency, lasting for >8 h, and the effect was blocked by either tyrosine kinase inhibitor (K252a) or BNDF scavenger (TrkB-Fc). The potentiation produced by BDNF was occluded by late-phase LTP (L-LTP) but not by early-phase LTP (E-LTP) induced by electrical stimulation. Pretreatment of K252a or TrkB-Fc selectively blocked spinal L-LTP induced by low-frequency stimulation (LFS) but not E-LTP. BDNF-induced LTP was completely abolished by the protein synthesis inhibitor (anisomycin), by N-methyl-D-aspartate (NMDA) receptor blocker (MK-801), by extracellular signal-regulated protein kinase (ERK) inhibitor (PD98059) or by p38 mitogen-activated protein kinase (MAPK) inhibitor (SB203580) but not by c-Jun N-terminal kinase (JNK) inhibitor (SP600125). Nuclear factor-kappaB (NF-κB) inhibitor (PDTC) also suppressed spinal BDNF-LTP. The results suggest that BDNF play a crucial role in protein synthesis-dependent L-LTP in spinal dorsal horn via activation of ERK, p38 MAPK and NF-κB signal pathways.

Introduction

Long-term potentiation (LTP), referring to a long-lasting enhancement in the efficacy of synaptic transmission, is considered as a synaptic model of memory storage (Bliss and Collingridge, 1993). Our previous works have shown that LTP of C-fiber evoked field potentials in spinal dorsal horn can also be induced by electrical stimulation of afferent C-fibers (Liu and Sandkühler, 1997), by natural noxious stimulation of peripheral tissues (Sandkühler and Liu, 1998), or by acute nerve injury (Zhang et al., 2004). Because C-fibers transfer nociceptive information, LTP at the synapses between C-fibers and spinal dorsal horn neurons is considered as an attractive cellular model of central sensitization underlying some forms of hyperalgesia (see review: Sandkühler et al., 2000; Sandkühler, 2007; Willis, 2002). This notion is supported by the studies showing that LTP inducing electrical stimulation produces long-lasting allodynia and hyperalgesia in human (Klein et al., 2004; Klein et al., 2006).

BDNF, a member of the neurotrophin family, plays an important role in regulating survival and differentiation of neuronal populations during development (see reviews: Wozniak, 1993; Farinas, 1999). In recent 10 years considerable data have demonstrated that BDNF is also crucially involved in synaptic plasticity in adult brain (see reviews: Bramham and Messaoudi, 2005; Soule et al., 2006). Application of BDNF can trigger a long-lasting increase in synaptic efficacy (BDNF-LTP) in hippocampus, dentate gyrus, visual cortex and insular cortex (Escobar et al., 2003; Kang and Schuman, 1995; Messaoudi et al., 2002). Activation of mitogen-activated protein kinases (MAPK) family members extracellular signal-regulated protein kinase (ERK) and p38 MAPK but not c-Jun N-terminal protein kinase (JNK) is involved in the induction of BDNF-LTP (Kanhema et al., 2006; Ying et al., 2002).

BDNF is constitutively synthesized in a subpopulation of unmyelinated primary afferents (Michael et al., 1997) and is released into the superficial layers of the spinal dorsal horn along with substance P (SP) and glutamate in an activity-dependent manner (Lever et al., 2001). Tropomyosin-related kinase B (TrkB), a BDNF receptor, is found throughout the spinal dorsal horn with particularly high density in the superficial laminae (Zhou et al., 1993). Behavioral studies have shown that intrathecal injection of BDNF produces a transient (Coull et al., 2005) or long-lasting hyperalgesia (Yajima et al., 2005) in naive animals. Treatment with anti-BDNF antiserum significantly attenuates the hyperalgesia produced by peripheral inflammation (Matayoshi et al., 2005). Intrathecal injection of TrkB-Fc, a BDNF scavenger, attenuates thermal hyperalgesia and tactile allodynia induced by sciatic nerve ligation (Yajima et al., 2005). It has been shown that BDNF mRNA and protein are up-regulated in several nerve injury models (Fukuoka et al., 2001; Li et al., 2006).

Our previous studies have demonstrated that activation of both NMDA- and SP-receptors is important for LTP induction in spinal dorsal horn (Liu and Sandkühler, 1995, 1997). Up to date, however, little is

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doi:10.1016/j.expneurol.2008.04.034

known about the role of BDNF in long-lasting synaptic plasticity in spinal dorsal horn. To test the hypothesis that BDNF may contribute to LTP in spinal dorsal horn, in this study the effect of BDNF on C-fiber evoked field potentials in spinal dorsal horn and the signal transduction pathways underlying the effect were investigated.

Materials and methods

Animals

Experiments were performed on adult male Sprague–Dawley rats (200–280 g body wt). The rats were housed in separated cages under a 12:12-h light/dark cycle with access to food and water ad libitum. The room temperature was kept around 24 °C and humidity 50–60%. All experimental procedures were approved by the local animal care committee.

Surgical preparation for electrophysiological recording

Anesthesia was induced and maintained with urethane (1.5 g/kg, i.p.) and verified by the stable mean arterial blood pressure and constant heart rate during noxious stimulation. The trachea was cannulated, and the animal breathed spontaneously. One carotid artery was cannulated to continuously monitor the mean arterial blood pressure, which was maintained from 80 to 120 mmHg. A laminectomy was performed to expose the lumbar enlargement of the spinal cord and the left sciatic nerve or sural nerve was dissected free for electrical stimulation with a bipolar platinum hook electrodes. The rats were placed in a stereotaxic frame and a small well was formed on the cord dorsum at the recording segments with 1.5% agar dissolved with 0.9% saline for drug application. The dura mater was incised longitudinally. All exposed nerve tissues were covered with warm paraffin oil in a pool made of skin flaps, except for the well where the drug was applied. The body temperature of the rats was maintained at 37–38 °C with a feedback-controlled heating blanket. At the end of the experiments, the animals were killed with an overdose of urethane.

Electrophysiological recording and nerve stimulation

The electrophysiological recording of C-fiber evoked field potentials has been described elsewhere (Liu and Sandkühler, 1995; Yang et al., 2005). Briefly, following electrical stimulation of the sciatic nerve, field potentials were recorded with a glass microelectrode (filled with 0.5 M Sodium acetate, impedance 0.5–1 MΩ), which was driven by an electronically controlled microstepping motor (Narishige Scientific Instrument Laboratory) at a depth of 100–500 μm from the surface of the spinal cord in lumbar enlargement (L4 and L5 segments). An A/D converter (ADC-42, PICO) was used to digitize and store data in a Pentium computer. Single square pulses (0.5 ms duration, delivered every 1 min) delivered to the sciatic nerve were used as test stimuli. The strength of stimulation was adjusted to 1.5–2 times of threshold for C-fiber responses. Either high-frequency

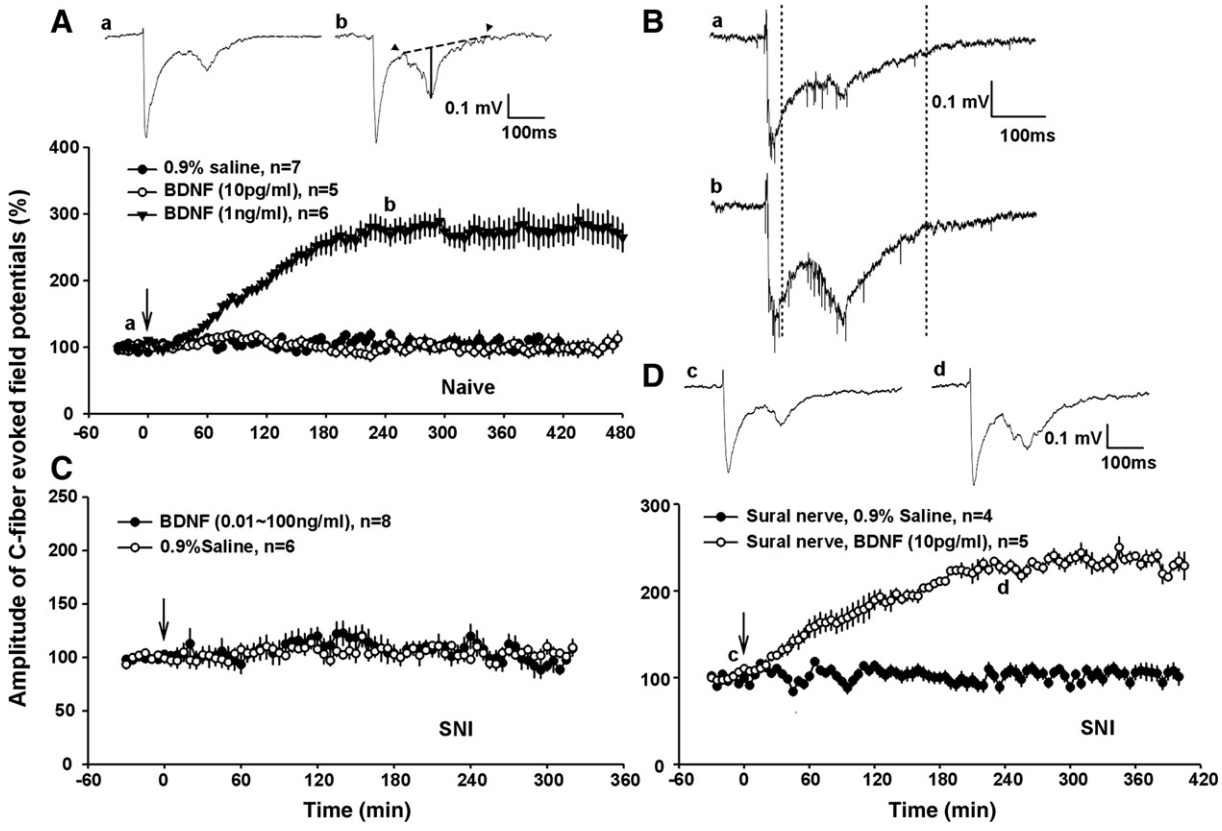

Fig. 1. Spinal application of rhBDNF induces LTP of C-fiber evoked field potentials in spinal dorsal horn. (A) BDNF at 1 ng/ml (filled triangles) but not at 10 pg/ml (open circles) induced LTP of C-fiber evoked field potentials in intact rats. Mean responses of C-fiber evoked field potentials before drug application served as baseline. Data represent mean amplitudes of 5 consecutively recorded potentials. Summary data, expressed as means ± SE, were plotted vs. time. At top two representative original recordings before (a) and 4 h after (b) BDNF (1 ng/ml) are shown. Amplitude of C-fiber evoked field potential as shown in b (vertical line) is determined automatically by parameter extraction software. Baseline, indicated by dotted line, is determined by 2 highest points within the time range defined manually on either side of C-fiber responses (arrowheads). (B) Simultaneous recording of C-fiber evoked action potential discharges and C-fiber evoked field potentials before (a) and after (b) BDNF (1 ng/ml) are shown. The action potentials, which occur between the two vertical dotted lines (30 and 300 ms after test stimulation, conduction velocities ranged 0.36–3.6 m/s), were considered as C-fiber responses. In those experiments, a bandwidth of 0.1–10 kHz was used. (C) BDNF (from 10 pg/ml to 100 ng/ml, filled circles) or saline (open circles) had no effect on C-fiber responses evoked by stimulation of the sciatic nerve in SNI rats. (D) BDNF (10 pg/ml, open circles) induced LTP of C-fiber responses evoked by stimulation of the sural nerve in SNI rats. Two representative original recordings before (c) and 4 h after (d) BDNF (10 pg/ml) are shown on top. The downward arrows in A, C and D indicate the onset of spinal application of BDNF or saline.

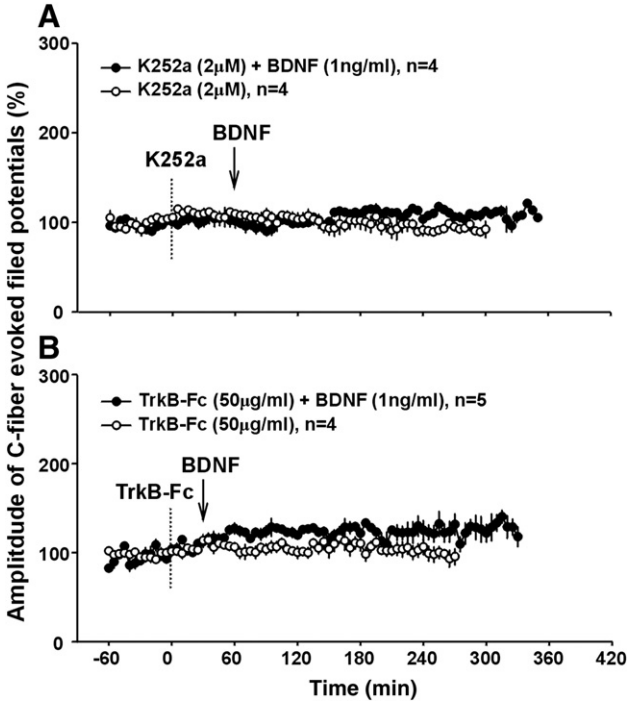

Fig. 2. Potentiation induced by BDNF is completely blocked by TrkB-Fc or K252a. (A) Application of K252a (2 μM) 1 h before BDNF (1 ng/ml) suppressed LTP induced by BDNF (filled circles), and the same dose K252a alone had no effect on the baseline C-fiber responses (open circles). (B) Superfusion of TrkB-Fc (50 μg/ml) before BDNF (1 ng/ml) abolished BDNF-induced potentiation of C-fiber evoked field potentials (filled circles), whereas TrkB-Fc at the same concentration did not affect the basal synaptic transmission (open circles).

stimulation (HFS: 100 Hz, 40 V, 0.5 ms, 100 pulses given in 4 trains of 1-s duration at 10-s intervals) or low-frequency stimulation (LFS: 2 Hz, 2 min) was used to induce LTP of C-fiber evoked field potentials.

Spared nerve injury

The spared nerve injury (SNI) was done following the procedures described by Decosterd and Woolf (2000). Briefly, the rats were anesthetized with chloral hydrate (10%). The skin of the rat's left thigh was shaved and sterilized, and an incision was made to expose the left sciatic nerve and its three terminal branches: the sural, common peroneal and tibial nerves. The common peroneal nerve and the tibial nerve were tightly ligated and transected a 2–4 mm length of each nerve distal to the ligation. Great care was taken to avoid any lesion of the sural nerve. The wound was closed in two layers.

Behavioral tests

Mechanical sensitivity was assessed using von Frey hairs with the up-down method, as described previously (Chaplan et al., 1994; Liu et al., 2007). Briefly, three rats were placed in the separate transparent Plexiglas chambers positioned on a wire mesh floor. Five minutes were allowed for habituation. Each stimulus consisted of a 6–8 s application of the von Frey hair to the lateral surface of the paw for SNI rats with 5 min interval between stimuli. Quick withdrawal or licking of the paw in response to the stimulus was considered a positive response. Only the rats exhibiting significant decrease in paw withdrawal threshold after SNI were selected for electrophysiological experiments.

Compounds and drug treatment

Recombinant human BDNF (rhBDNF, Promega) and TrkB-Fc (R&D Systems) were first dissolved as a concentrated stock solution in 0.1% BSA, aliquoted in small volumes and stored at -80 °C. Pyrrolidine dithiocarbamate (PDTC, Sigma) and dizocilpine maleate (MK-801, Sigma) were directly dissolved in 0.9% saline to a final concentration before each experiment. K252a (Sigma), PD98059 (Sigma), SB203580 (Promega), SP600125 (Calbiochem) and anisomycin (Sigma) were first dissolved in DMSO to make a stock concentration of 50 mM, which was diluted with 0.9% saline to make final concentrations immediately before administration. Maximum final DMSO concentration in the diluted working solution was 0.2%. Our previous study has shown that spinal application of 0.5% DMSO does not affect C-fiber evoked field potentials (Xin et al., 2006). The drugs (200 μl in volume) were warmed before superfusion on the spinal cord surface.

Statistical analysis

The amplitude of C-fiber evoked field potentials was determined off-line by parameter extraction, which was implemented by ADC-42 (Fig. 1Ab). In each experiment, responses to five consecutive test stimuli were averaged. The mean amplitudes of C-fiber responses before drug or saline application were served as baseline. All data are expressed as means±SE. For statistical analysis, data within animals were compared using the nonparametric Wilcoxon signed-rank test, and those between animals were compared using the Mann–Whitney *U* test. $P<0.05$ was considered significant.

Results

Spinal application of BDNF induces LTP of C-fiber evoked field potentials in spinal dorsal horn with a long latency

To test whether extraneous BDNF produce long-lasting synaptic plasticity in spinal dorsal horn, rhBDNF was applied directly onto the spinal dorsal surface at the recording segments 30 min after stable recording of C-fiber evoked field potentials. As shown in Fig. 1A, BDNF at 1 ng/ml but not at 10 pg/ml (in 200 μl volume) induced LTP of C-fiber evoked field potentials with a long latency in all six rats tested. The amplitude of C-fiber responses were significantly elevated above baseline at 65 min (145.9±3.9%, $n=6$; $P<0.05$), climbed gradually to a stable plateau (268.5±17.2%) at 3–4 h after BDNF application, and persisted without decrement until the end of each experiment. In six other rats spinal application of saline, which was used to dissolve the BDNF, did not affect the baseline of C-fiber responses, as observed within 6 h (Fig. 1A). The data suggest that exogenous BDNF is sufficient to induce LTP of C-fiber evoked field potentials in spinal dorsal horn.

To examine whether BDNF is capable of inducing long-lasting change in the excitability of single spinal dorsal horn neuron, C-fiber

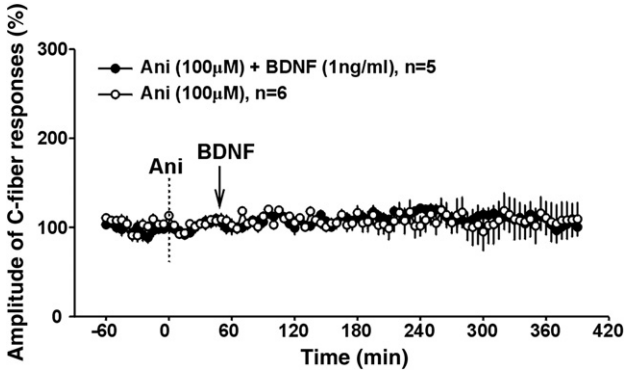

Fig. 3. Inhibition of protein synthesis prevents BDNF-LTP. Spinal application of protein synthesis inhibitor anisomycin (Ani, 200 μM, filled circles) had no effect on the baseline of C-fiber evoked field potentials (open circles), but completely blocked BDNF-LTP When applied 50 min before BDNF.

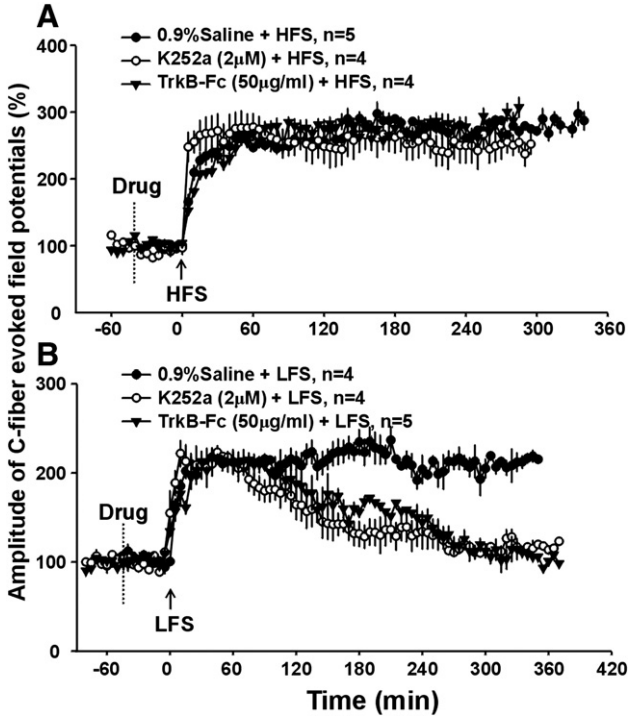

Fig. 4. Inhibition of TrkB signaling reverses LTP induced by LFS, but does not affect LTP induced by HFS. (A) Spinal appication of K252a (2 μM, filled triangles) or TrkB-Fc (50 μg/ml, open circles) did not affect LTP induced by HFS. (B) Pretreatment with K252a (open circles) or TrkB-Fc (triangles) did not affect E-LTP but abolished L-LTP induced by LFS. The downward arrows indicate the onset of drug application and the upward arrows the time-points when LFS or HFS was delivered to the sciatic nerve.

evoked field potentials and C-fiber evoked action potential discharges in wide dynamic range neurons were simultaneously recorded for >5 h with the same microelectrode in 3 rats (Figs. 1B a and b). We found that the number of C-fiber evoked action potentials was significantly increased after application of BDNF.

In eight rats with SNI performed 5–7 days before recording of C-fiber responses evoked by stimulation of the sciatic nerve, we found that different dosages of hrBDNF (10 pg/ml, $n=2$; 1 ng/ml, $n=3$; 100 ng/ml, $n=3$) did not affect C-fiber responses, therefore, the data were pooled together (Fig. 1C). As in SNI model common peroneal and tibial nerves were injured, and the sural nerve, which is much smaller, remained intact, the negative results may be resulted from the differential effects of BDNF on the synapses made by injured and uninjured afferents (Schoffnegger et al., 2008). To test this, C-fiber responses evoked by stimulation of the sural nerve were recorded for 30 min in other five SNI rats, and then BDNF at 10 pg/ml, which was unable to produce LTP in naïve animals (Fig. 1A, open circle), was applied onto spinal dorsal surface at recording segments. In these experiments BDNF did induce spinal LTP of C-fiber evoked field potentials (Fig. 1D), which was almost identical to that which was recorded when sciatic nerve was stimulated in intact rats. The results suggested that BDNF might induce LTP only at the synapses made by intact afferents after nerve injury. The result that potentiation at the synapses made by the sural nerve cannot be detected when test stimuli are delivered to the sciatic nerve may be due to that C-fibers in the sural nerve might contribute little to the C-fiber responses evoked by stimulation of the sciatic nerve.

Spinal BDNF-LTP is blocked by inhibition of TrkB signaling

To test whether the effect of BDNF on C-fiber evoked field potentials is receptor-specific, we next explored the role of TrkB receptor activation in BDNF-LTP pharmacologically, using either K252a, a tyrosine kinase inhibitor, or TrkB-Fc, a TrkB-immunoglobulin G fusion protein that scavenges BDNF. Superfusion of either K252a (2 μM) for 1 h or TrkB-Fc (50 μg/ml) for 30 min before application of BDNF completely prevented BDNF-LTP ($P>0.05$, $n=5$, Fig. 2), while application of K252a ($n=4$) or TrkB-Fc ($n=4$) alone had no effect on baseline of C-fiber responses.

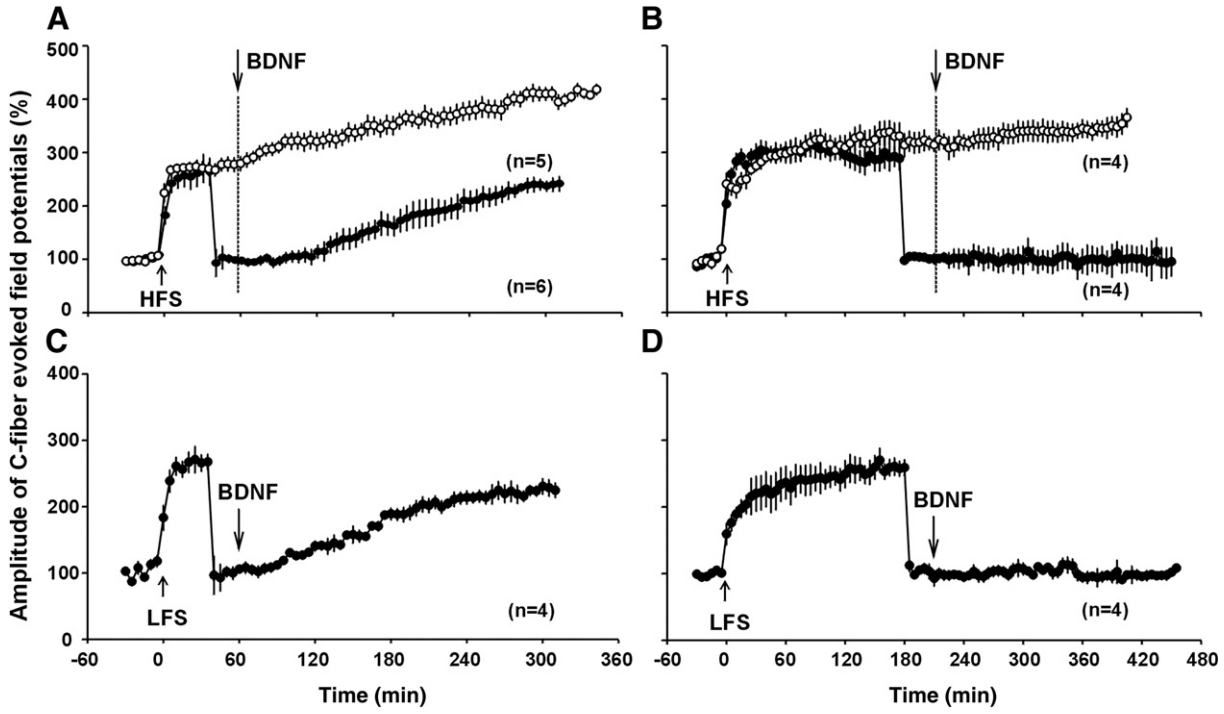

Fig. 5. Spinal BDNF-LTP is occluded by L-LTP but not E-LTP induced by electrical stimulation. (A and B) BDNF produced a further potentiation only at 1 h but not 3.5 h after LTP induced by high-frequency stimulation (HFS, 100 Hz, 40 V, 0.5 ms, 100 pulses given in 4 trains of 1-s duration at 10-s intervals) no matter the intensities of test stimuli were reduced to reset the baseline of C-fiber evoked responses (filled circles) or not (open circles). (C and D) BDNF failed to produce further potentiation 3.5 h but not 1 h after LTP induced by low-frequency stimulation (LFS, 2 Hz for 2 min).

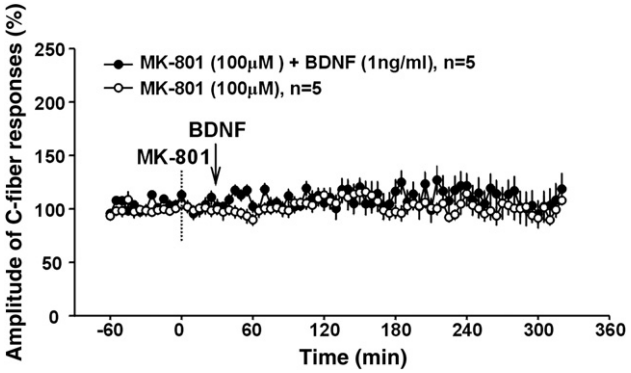

Fig. 6. BDNF-LTP is blocked by MK-801. Superfusion of spinal cord with NMDA receptor antagonist MK-801 (100 μM), which had little effect on the amplitude of C-fiber-evoked potentials (open circles), completely blocked LTP induced by BDNF in all rats tested (filled circles).

Spinal BDNF-LTP is blocked by inhibition of protein synthesis

De novo protein synthesis is required for L-LTP but not E-LTP in both hippocampus (Frey et al., 1988) and spinal dorsal horn (Hu et al., 2003). As our results showed that exogenous BDNF induced spinal LTP with a long latency (Fig. 1A), we presumed that BDNF might directly induce L-LTP. To test this hypothesis, we examined whether spinal BDNF-LTP is protein synthesis-dependent. In the presence of anisomycin (200 μM), a protein synthesis inhibitor, BDNF failed to produce any change in C-fiber evoked field potentials (Fig. 3). At 5 h after application of BDNF, the mean amplitude of C-fiber responses was 114.4±7.1%, which was significantly different from that recorded in the rats with the BDNF alone (293.6±6.0%, $n=5$; $P<0.05$, Fig. 1A). The same dose of anisomycin alone had no effect on baseline responses.

Blockade of TrkB signaling attenuates spinal LTP induced by low-frequency stimulation but not by high-frequency stimulation

LTP of C-fiber evoked field potentials in spinal dorsal horn can be induced by either HFS or LFS (Liu and Sandkühler, 1997; Ikeda et al., 2006). To ascertain the possible involvement of TrkB signaling in spinal LTP produced by electrical stimulation, either K252a (2 μM) or TrkB-Fc (50 μg/ml) was applied onto spinal dorsal surface at recording segments 30~40 min before electrical stimulation. The results showed that LTP induced by HFS was not different from that recorded in the saline group (Fig. 4A, $P>0.05$). In contrast, both K252a and TrkB-Fc inhibited LTP induced by LFS. As shown in Fig. 4B, in the presence of K252a, the potentiation was 204.8±15.6% ($n=4$) at 30 min after LFS, which was not different from that recorded in saline treated group (208.3±5.8%, $n=4$, $P>0.05$). While the amplitudes of C-fiber responses were gradually descended afterwards, and at 5 h after LFS, the potetiation reduced to 114.1±2.0%, which was no longer different from baseline ($P>0.05$). In the rats treated with TrkB-Fc, potentiation reached 213±12.6% at 30 min after LFS, and then reduced subsequently. At 5 h after LTP induction, the mean C-fiber responses decreased to 112.5±7.7%, which was not different from baseline ($n=5$, $P>0.05$). The results indicate the TrkB signaling is required for LTP induced by LFS but not for that induced by HFS.

Spinal BDNF-LTP is occluded by L-LTP but not E-LTP induced by electrical stimulation

If two forms of LTP utilize a common mechanism for expression, the generation of one should occlude (inhibit) the other (Bramham and Messaoudi, 2005). Accordingly, a series of occlusion experiments was performed to determine whether the spinal LTP induced by electrical stimulation, including HFS and LFS, can inhibit BDNF-LTP. At first we tested if E-LTP produced by HFS or LFS inhibits BDNF-LTP. To do this, 40 min after LTP induction by HFS or LFS, the test stimulus

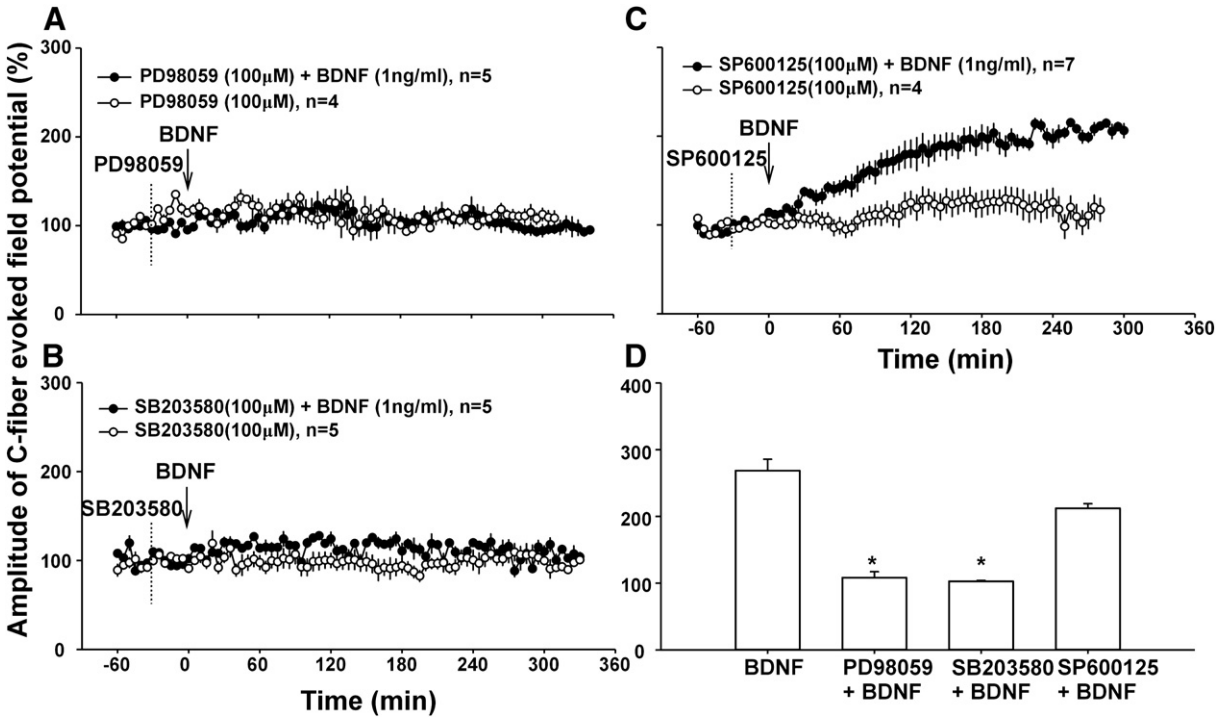

Fig. 7. Spinal BDNF-LTP is blocked by inhibition of ERK and p38 MAPK but not by inhibition of JNK. (A–C) spinal application of the MEK inhibitor (PD98059, 100 μM) or p38 MAPK inhibitor (SB203580, 100 μM) but not JNK inhibitor (SP600125, 100 μM) completely blocked BDNF-LTP (filled circles). The same dosages of inhibitors had no effect on the baseline of C-fiber responses (open circles). (D) The mean amplitudes of C-fiber evoked field potentials recorded at 200 min after BDNF infusion in 4 groups of rats are shown. The value in BDNF group is from Fig. 1A (filled circles). * $P<0.05$, significantly different from BDNF group.

intensities were lowered to reset the amplitudes of C-fiber responses to the control baseline, and then BDNF was applied onto the spinal dorsal surface. The data showed exogenous BDNF could still enhance the amplitudes of C-fiber evoked field potentials ($P<0.05$, Figs. 5A and C). The kinetics and the magnitude of the potentiation were not different from those recorded in the control ($P>0.05$, see Fig. 1A). In the second series of experiments, BDNF was applied at 3.5 h after LTP induction by HFS (Fig. 5B) or LFS (Fig. 5D), which by all accounts falls within the period of protein synthesis-dependent L-LTP, no change in the amplitudes of C-fiber evoked field potentials was observed ($P>0.05$). To test whether reset of baseline affect the results of occlusion test, we performed the experiments, in which the intensities of test stimuli were not changed and found that BDNF can increase C-fiber responses 1 h but not 3.5 h after LTP induced HFS (Figs. 5A and B, open circles), which is similar to that recorded when intensities of test stimuli were reduced. Taken together, spinal BDNF-LTP is selectively occluded by L-LTP but not E-LTP induced by electrical stimulation.

Spinal BDNF-LTP is blocked by NMDA receptor antagonist MK-801

BDNF-LTP at CA3-CA1 synapses in hippocampal slices does not require NMDA receptor activation (Messaoudi et al., 2002). To test whether NMDA receptor activation is required for the induction of BDNF-LTP in spinal dorsal horn *in vivo*, a competitive NMDA receptor antagonist MK-801 (100 μM) was added onto the surface of the recording site at 30 min before BDNF. As shown in Fig. 6, 3 h after BDNF the mean amplitude of C-fiber evoked field potentials was 116.3 ± 11.1% ($n=5$; $P>0.05$), while the same dose of MK-801 alone did not affect the baseline of C-fiber evoked potentials ($n=5$; $P>0.05$). In pilot experiments we found that MK-801 at 1 μM blocked BDNF-LTP in six out of nine rats tested (data not shown).

Activation of ERK and p38 MAPK but not JNK is required for the induction of spinal BDNF-LTP

Our previous work showed that activation of ERK but not p38 MAPK or JNK is needed for the induction of HFS-LTP in intact rats (Liu et al., 2007; Xin et al., 2006). To investigate the roles of MAPK family numbers in the induction of BDNF-LTP, PD98059 (a selective MAPK kinase (MEK) inhibitor), SB203580 (a p38 MAPK inhibitor) or SP600125 (a JNK inhibitor) was applied directly onto spinal cord surface (all at 100 μM) 30 min before spinal application of BDNF. The results showed that pretreatment with either PD98059 ($n=5$, Fig. 7A) or SB203580 ($n=5$, Fig. 7B), which did not affect the baseline of C-fiber responses, completely blocked BDNF-LTP. In contrast, spinal application of SP600125 did not affect BDNF-LTP (Fig. 7C). In this group, the mean amplitude of C-fiber responses at 220 min after BDNF increased to 212.2 ± 7.0% ($n=5$, $P<0.05$), which was not statistically indistinguishable from that recorded in BDNF alone group ($P>0.05$, Fig. 1A).

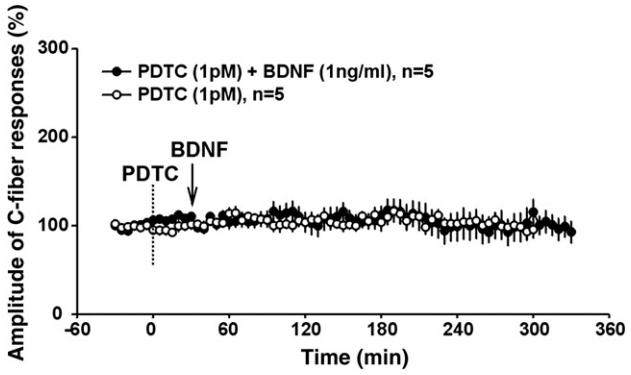

Fig. 8. NF-κB is required for LTP induction by BDNF. Pretreatment with specific NF-κB inhibitor PDTC (10 pM) prevented LTP induced by BDNF (filled circles) but did not affect the baseline responses of C-fiber evoked field potential (open circles).

NF-kB inhibitor PDTC blocks BDNF-LTP

To examine whether NF-κB signaling pathway is involved in LTP induced by BDNF, PDTC, a specific inhibitor of NF-κB, was applied onto the recording segments following ≥30 min stable recording of C-fiber evoked field potentials. As shown in Fig. 8, PDTC (1 pM) completely abolished the potentiation induced by BDNF (1 ng/ml) applied at 30 min after PDTC application. The mean amplitude of C-fiber responses at 220 min after BDNF was 103.6 ± 14.8%, which was not different from the baseline ($n=5$; $P>0.05$). The same dosage of PDTC had no effect on basal synaptic transmission.

Discussion

In the present work we found that spinal application of rhBDNF induced LTP of C-fiber evoked field potentials with a long latency in adult rats. The spinal BDNF-LTP was prevented completely by either TrkB blocker or BDNF scavenger. Inhibition of protein synthesis blocked BDNF-LTP and BDNF-LTP occluded with L-LTP but not E-LTP produced by electrical stimulation. Activation of NMDA receptor, NF-κB, ERK and p38 MAPK but not JNK were needed for the induction of spinal BDNF-LTP.

Exogenous BDNF induces late-phase LTP

BDNF-LTP was first shown at CA3-CA1 synapses in hippocampal slices (Kang and Schuman, 1995) and was subsequently reported *in vivo* in the dentate gyrus, in visual cortex and in insular cortex (Escobar et al., 2003; Jiang et al., 2001; Messaoudi et al., 1998). The minimal concentration of exogenous BDNF for LTP induction in hippocampal slices is 50 ng/ml. The present study further demonstrated that in spinal dorsal horn rhBDNF at 1 ng/ml was sufficient for induction of LTP of C-fiber evoked field potentials.

We found that BDNF-LTP was occluded by L-LTP but not by E-LTP induced by either HFS or LFS and that BDNF-LTP was completely prevented by protein synthesis inhibitor, indicating that exogenous BDNF may directly contribute to L-LTP in spinal dorsal horn.

BDNF is capable of increasing protein synthesis both globally and locally (Bramham and Messaoudi, 2005). Recently, it has been shown that several hundred proteins are up-regulated in a synaptoneurosome preparation derived from cultured cortical neurons treated with BDNF (Liao et al., 2007). According to synaptic tagging theory, proteins that are necessary for L-LTP are synthesized in early-phase and captured by synapses nearby (Frey and Morris, 1997). As BDNF increases the synthesis of a wide variety of synaptic proteins, at least some of them may contribute to L-LTP. So, it is not surprising that exogenous BDNF induces L-LTP directly in central nervous system.

We showed that blockage of TrkB signaling with TrkB blocker (K252a) or BDNF scavenger (TrkB-Fc) did not affect LTP produced by HFS but abolished L-LTP induced by LFS. The results were similar to a previous study that pretreatment of hippocampus slice with BDNF antibody has no effect on LTP produced by 4 trains of 100 Hz tetani but inhibits L-LTP induced by theta burst stimulation or by pairing postsynaptic depolarization with 1 Hz stimulation (Kang et al., 1997). It appears that BDNF may be differentially involved in the LTP produced by different patterns of electrical stimulation.

In an *in vitro* study Lever et al. (2001) show that short high-frequency burst stimulation but not HFS or LFS (1 Hz) induces significant increase in BDNF release. In the experiment dorsal root was stimulated and the concentration of BDNF was measured in superfusates. However, the concentration of BDNF in superfusates may not represent that within spinal dorsal horn, as poor tissue penetrability and/or loss of detectable BDNF-LI through surface adhesion (Anderson

et al., 1995; Leibrock et al., 1989). Although we don't know how much BDNF is needed for spinal LTP, our electrophysiological data showed that TrkB signaling was involved in the L-LTP but not E-LTP induced by LFS.

Differential role of NMDA receptors in BDNF-LTP in hippocampus and spinal dorsal horn

In hippocampus, BDNF-LTP at CA3-CA1 synapses does not require activation of NMDA receptors (Messaoudi et al., 2002). In contrast, we showed that BDNF-LTP in spinal dorsal horn was NMDA receptor-dependent. According to the data available, we attempted to explain the difference as following. In hippocampus, BDNF is released from both presynaptic and postsynaptic elements (Gartner et al., 2006). It has been suggested that BDNF from presynaptic sites may be necessary for E-LTP, while L-LTP may require sustained supply of BDNF through activity-dependent transcription and translation in the postsynaptic neurons (Lu et al., 2008). In spinal dorsal horn, however, primary afferent C-fiber terminals containing SP and glutamate may be the only source of BDNF (Luo et al., 2001; Michael et al., 1997) and TrkB receptors is located in postsynaptic neurons (Zhou et al., 1993). Furthermore, it has been demonstrated that activation of NMDA receptors is crucial for BDNF release in spinal dorsal horn (Lever et al., 2003). In CA1 region of hippocampus, NMDA receptor is exclusively expressed on postsynaptic structures, while in the spinal dorsal horn many NMDA receptors are located in the presynaptic C-fiber terminals, immediately adjacent to the vesicle release site at the active zone (Liu et al., 1994). In cultured hippocampal neurons BDNF induces BDNF release via autocrine loop (Canossa et al., 1997). So, it is likely that in spinal dorsal horn blockage of NMDA receptors may inhibit BDNF release from afferent terminals, and thereby prevent BDNF-LTP, if BDNF also increases BDNF release in afferent terminals in spinal dorsal horn, which remained to be determined.

The roles of MAPK family members and NF-κB in hippocampal LTP and in spinal LTP

Several lines of evidence have shown that in hippocampus activation of ERK signaling pathway is needed for either L-LTP induced by HFS (Thomas and Huganir, 2004) or BDNF-LTP (Rosenblum et al., 2002). Previous works have demonstrated that ERK is activated in superficial spinal dorsal horn within a minute following noxious stimulation and that inhibition of ERK attenuates the second phase of formalin-induced pain (Ji et al., 1999) and behavioral signs of neuropathic pain in CCI model (Song et al., 2005) and in spinal nerve ligation model (Zhuang et al., 2005). We have shown previously that in spinal dorsal horn ERK and cAMP response element binding protein (CREB) are activated after LTP induction by HFS in spinal dorsal horn and that spinal application of PD98059 prevents LTP induction (Xin et al., 2006). In the present work, we found that inhibition of ERK prevented spinal BDNF-LTP. Therefore, activated ERK may exert similar effect on plastic change of synaptic transmission in hippocampus and in spinal dorsal horn.

However, the roles of p38 MAPK and JNK in the plasticity of synaptic transmission in hippocampus and in spinal dorsal horn may be different. In spinal dorsal horn we found that inhibition of either p38 MAPK or JNK does not affect LTP induction by HFS in intact rats but prevents LTP induced by spinal application of tumor necrosis factor-alpha (TNF-α) in the rats with nerve injury (Liu et al., 2007). The present results further showed that BDNF-LTP was prevented by p38 MAPK inhibitor. The results are consistent with the previous results showing that activation of both p38 MAPK and JNK in spinal dorsal horn is required for initiation and maintenance of neuropathic pain (Ji and Suter, 2007; Zhuang et al., 2006). In hippocampus inhibition of JNK and p38 MAPK also does not affect LTP induction by HFS but prevents the inhibition of LTP produced by amyloid β-peptide, which has been strongly implicated as a causal factor in Alzheimer's disease (Wang et al., 2004). Furthermore, it has been shown that activation of p38 MAPK plays a pivotal role in the inhibitory effects of lipopolysaccharide and interleukin-1 beta and TNF-α on hippocampal LTP (Butler et al., 2004; Kelly et al., 2003). Taken together, p38 MAPK and JNK may not be involved in synaptic plasticity in physiological conditions. In pathological conditions, however, they may facilitate LTP induction in spinal dorsal horn but inhibit LTP in hippocampus. So, in pathological conditions inhibition of p38 MAPK and JNK may improve memory in hippocampus but depress neuropathic pain.

NF-κB, one of the key transcription factors, which is initially recognized as a regulator of immune system, has been found to play an important role in long-lasting synaptic plasticity in recent years (Mattson, 2005). Freudenthal et al. (2004) have demonstrated that LTP induction by HFS activates nuclear NF-κB in the intact mouse hippocampus. Pretreatment of hippocampal slices with kappaB decoy DNA prevents induction of long-term depression (LTD) and significantly reduces the magnitude of LTP (Albensi and Mattson, 2000). The data indicate that activation of NF-κB may be involved in both LTP and LTD. Our previous data have shown that spinal application of NF-κB inhibitor does not affect baseline of synaptic transmission but prevents spinal LTP induced by TNF-α in rats with nerve injury (Liu et al., 2007). In the present study, we further showed that pretreatment with PDTC completely blocked BDNF-LTP in intact rats. Thus, NF-κB may play an important role in long-lasting increase in pain synaptic transmission in spinal dorsal horn, which is consistent with the recent studies demonstrating that inhibition of NF-κB attenuates pathological pain produced by inflammation, nerve injury and proinflammatory cytokines (Tegeder et al., 2004; Wei et al., 2007).

Acknowledgments

This work was supported by grants from the National Natural Science Foundation of China (Nos. 30200076, 30370474, 30570599) and by a grant from the Department of Science and Technology in Guangdong province of China (2005A30801002).

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