Cell Mol Neurobiol (2012) 32:971–977
DOI 10.1007/s10571-011-9782-2

ORIGINAL RESEARCH

Intracerebroventricular 4-Methylcatechol (4-MC) Ameliorates Chronic Pain Associated with Depression-Like Behavior via Induction of Brain-Derived Neurotrophic Factor (BDNF)

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Received: 18 October 2011 / Accepted: 6 December 2011 / Published online: 25 December 2011

Abstract Neuropathic pain concurrent with mood disorder from peripheral nerve injury is a serious clinical problem that significantly affects quality of life. Recent studies have suggested that a lack of brain-derived neurotrophic factor (BDNF) in the limbic system may cause this pain–emotion. BDNF is induced in cultured neurons by 4-methylcatechol (4-MC), but the role of 4-MC-induced BDNF in pain–emotion is poorly understood. Thus, we assessed the possible involvement of BDNF in brain in depression-like behavior during chronic pain following peripheral nerve injury. In addition, we examined whether intracerebroventricular (i.c.v.) 4-MC prevents chronic pain in rats and produces an antidepressant effect. Sprague–Dawley rats implanted intracerebroventricularly with a PE-10 tube were subjected to chronic constriction injury (CCI). Pain was assessed by a reduction in paw withdrawal latency (PWL) to heat stimuli after CCI. We also used a forced swimming testing (FST; time of immobility, in seconds) from day 14 to day 21 after CCI. Modulation of pain and emotional behavior was performed by injection of PD0325901 (a MEK1/2 inhibitor). 4-MC (100 nM) was continuously administered i.c.v. for 3 days during the period from day 14 to day 21 after CCI. To block analgesic and antidepressant effects, anti-BDNF antibody or K252a (a TrkB receptor inhibitor) was injected in combination with 4-MC. Naloxone was also coadministered to confirm the analgesic effect of 4-MC. During the chronic stage after CCI, the rats showed a sustained decrease in PWL (thermal hyperalgesia) associated with extension of the time of immobility (depression-like behavior). PD0325901 significantly reduced the decrease in PWL and the increased time of immobility after CCI. The decreased PWL and increased time of immobility were also reduced by 4-MC and by treatment with an ERK1/2 inhibitor. These effects of 4-MC i.c.v. were reversed by anti-BDNF and K252a. The analgesic effect of 4-MC i.c.v. was also antagonized by naloxone. Based on these results, we suggest that a lack of BDNF and activation of ERK1/2 in the pain–emotion network in the CNS may be involved in depression-like behavior during chronic pain. 4-MC i.c.v. ameliorates chronic pain and depression-like behavior by producing of BDNF and normalization of ERK1/2 activation. Therefore, enhancement of BDNF may be a new treatment strategy for chronic pain associated with depression.

Keywords CCI · Neuropathic pain · Mood disorder · BDNF · 4-Methylcatechol · ERK1/2

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Introduction

Neuropathic pain resulting from peripheral nerve injury or neuronal damage of the central nervous system (CNS) is a significant clinical concern. Chronic pain is also recognized as a mood disorder that affects quality of life (Sun and Alkon 2002). These pain–emotions are related to the functional integrity of the pain pathway and emotional networks associated with the cortex, including the anterior cingulate cortex (ACC), amygdala (AM), hippocampus (HC), and hypothalamus (HT) (Sheline et al. 1996; Bremner et al. 2000). The mechanisms have not been defined, but these neural networks are believed to be involved in pain–emotions.

Recent studies have suggested that chronic pain may mediate excessive neurotransmission related to abnormal intracellular signaling and dysfunction of trans-synaptical inhibitory neurons in the spinal cord and brain-derived descending inhibitory system (Woolf and Salter 2000; Zhuo 2007; Moore et al. 2002). Inhibition of intracellular signaling may be effective for reduction of this pain (Zhuo 2007; Svensson et al. 2003). Activation of extracellular signal-regulated kinase 1/2 (ERK1/2) is thought to have a key role in signaling after central sensitization is evoked physically or pharmacologically (Zhuang et al. 2005; Merighi et al. 2008; Gao and Ji 2009). Thus, excessive neurotransmission reflected by activation of ERK1/2 in the pain pathway and limbic systems may be a pivotal mechanism in chronic pain.

Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin (NT) family of proteins, which comprises nerve growth factor (NGF) and NT-3, NT-4/5, and NT-6 (Hohn et al. 1990). The widespread distribution of BDNF mRNA in the pain pathway and limbic system of the CNS suggests that this protein has an important role in pain–emotion (Phillips et al. 1990). BDNF also affects the survival or differentiation of cultured neurons (Henderson et al. 1993) and regulates glutamate and γ-aminobutyric acid (GABA) neurotransmission (Zafra et al. 1992). Thus, BDNF seems to regulate various activity-dependent events, including neuronal plasticity. BDNF mRNA expression is evoked in association with insults in brain regions (Zhou et al. 1996) and the administration of BDNF intracerebroventricular (i.c.v.) prevents neuronal death (Tsukahara et al. 1995; Beck et al. 1994), suggesting that BDNF has a protective effect on neuronal degeneration. Therefore, BDNF may be useful therapeutically for neurological disorders because of its potent actions on neurons responsible for neurodegenerative disorders. In addition, spinally transplanted cells producing BDNF can attenuate allodynia and hyperalgesia in rat sciatic nerve injury (Cejas et al. 2000). Thus, BDNF may affect chronic pain in association with depression via activation of synaptic neurons and the TrkB receptor. However, the therapeutic applications of BDNF have not been fully investigated.

4-Methylcatechol (4-MC) is a potent stimulator of BDNF synthesis (Furukawa et al. 1989; Kourounakis et al. 1997). 4-MC stimulates regeneration of the sciatic nerve (Kaechi et al. 1995) and protects against or improves diabetes- and acrylamide-induced neuropathies (Hanaoka et al. 1994; Saita et al. 1996). These effects involve nerve regeneration and amelioration of sensory neurons, which suggests that 4-MC may stimulate synthesis of a neurotrophic factor. Thus, 4-MC may contribute to recovery from neuropathic pain by remodeling neurostructures through induction of BDNF, as suggested in cultured neurons. The specific mechanism is not understood, but 4-MC may prevent derangement of neurotransmission by producing BDNF and normalizing cell responses, as reflected by ERK1/2 activity. Thus, in this study we examined the effect of 4-MC i.c.v. on BDNF production in relation to intracellular signaling (including ERK1/2) in the CNS in rats. Our results suggest that 4-MC may be a potential therapeutic agent for treatment of chronic pain associated with mood disorder.

Materials and Methods

All studies were approved by the Ethics Committee for Animal Studies at Yamaguchi University and were carried out according to the Guidelines for Animal Experimentation and the Law (No. 105) and Notification (No. 6) of the Japanese Government.

Animals and Surgical Operations

Sprague–Dawley rats (Kyudo Co., Saga, Japan) weighing 250–350 g were used in the study. The animals were housed in a temperature-controlled room (23 ± 2°C), allowed free access to food and water, and kept on a 12 h light/dark cycle. The neuropathic pain model was made using a specific chronic constriction injury (CCI) of the left sciatic nerve (Bennett and Xie 1988). Under sodium pentobarbital anesthesia (30 mg/kg, i.p.), the common sciatic nerve was exposed and four loose ligatures of 4-0 silk thread were tied around the nerve proximal to the trifurcation at a distance of 1 mm.

Intracerebroventricular Cannulation

Rats were anesthetized with sodium pentobarbital (30 mg/kg, i.p., with supplemental doses if necessary) and placed in a specially designed stereotactic apparatus. A stainless steel cannula was placed with the tip positioned at the coordinates (anterior–posterior -1.0 mm, lateral 1.5 mm; and horizontal 3.5 mm, according to the atlas of Paxinos and Watson (1998). A 3-day recovery period from surgery

was allowed. For i.c.v. injection, the injection cannula was connected via PE-10 tubing to a Hamilton microsyringe. The injection was performed with the rat held by hand (unanesthetized, a painless procedure). The injection was performed at a slow rate (1 μl/min) using a small volume (5 μl).

Chemicals

4-MC and monoclonal anti-BDNF antibody were purchased from Sigma-Aldrich, Inc. (St Louis, MO, USA). Agents were injected i.c.v. bilaterally through chronically placed cannulas using artificial cerebrospinal fluid (aCSF) as the vehicle. 4-MC (100 nM/5 μl) and anti-BDNF antibody (5.0 μg/5 μl) were administered daily for 3 days before paw withdrawal latency (PWL) tests or forced swimming tests (FST). On the test days, the agents were administered about 1 h before each test. The aCSF solution (pH 7.4) contains (mM) NaCl (124), KCl (3), $MgSO_4$ (1.3), $CaCl_2$ (2.4), $NaHCO_3$ (26), NaH_2PO_4 (1.25), and glucose (10). Control rats received aCSF solution only.

Pain Behavior Test

Thermal hyperalgesia was based on PWL using Hargreaves' plantar test apparatus (UGOBASILE, LMS 7370S, 7371). In brief, the rat was placed on a Plexiglas floor and stabilized for 15 min. Constant infrared thermal stimulation was given alternately to the bottom of the hind limbs and the time to move the lower limb in response (PWL, in seconds) was measured. PWL in both hind paws was measured five times alternately with an interval of at least 5 min and averaged after rejection of the maximum and minimum values. These measurements were made before CCI and on days 3, 7, 10, 14, and 21 after CCI during the day time (10:00–16:00). Hyperalgesia was assessed based on the difference between the latencies of the normal right hind limb and the injured left hind limb.

Forced Swimming Test

The FST was carried out according to the method described by Porsolt et al. (1978). One day prior to the test, a rat was conditioned in a clear plastic tank (45 × 35 × 60 cm) containing 30 cm of water (24 ± 0.5°C) for 5 min as "pretest." They were replaced in the cylinders 24 h later and the total duration of immobility was measured during a 5 min as "test." A rat was judged to be non-swimming when its hind legs were no longer moving and the rat was hunched forward (a floating position). The total duration of immobility (non-swimming) for a 5 min test was recorded as immobility scores. Following each session, the rat was removed from the water tank, dried with a towel, placed in a warm cage for 15 min, and then returned to the home cage. All test sessions were performed during day time (between 10:00 and 16:00).

Experimental Grouping

Rats were randomly divided into seven groups, as defined below. 4-MC (100 nM/5 μl, Sigma, No. M34200, Tokyo, Japan) was administered i.c.v. A PWL test or FST was performed 2 h after administration of 4-MC. The seven groups were as follows: (1) Sham ($n = 10$): anesthesia and skin incision only and observation for 21 days. (2) Untreated (UT: $n = 10$): aCSF (5 μl) injected i.c.v. daily from day 12 after CCI. (3) PD + aCSF ($n = 8$): PD0325901 (MEK1/2 inhibitor, 300 nM) administered i.c.v. daily from day 12 until day 14 after CCI. (4) 4-MC + aCSF ($n = 10$): 4-MC injected i.c.v. daily from day 12 until day 14 and from day 19 until day 21 after CCI. (5) 4-MC + anti-BDNF ($n = 6$): 4-MC injected i.c.v. daily from day 12 until day 14 after CCI and anti-BDNF antibody (AF248, R&D Systems, Minneapolis, MN, USA) coadministered i.c.v. with 4-MC on day 14. (6) 4-MC + Naloxone ($n = 4$): 4-MC injected i.c.v. daily from day 12 until day 14 after CCI and naloxone (5 μg/5 μl) coadministered i.c.v. with 4-MC on day 14. (7) 4-MC + K252a ($n = 5$): 4-MC injected i.c.v. daily from day 12 until day 14 after CCI and K252a (TrkB receptor inhibitor, 25 μg/5 μl; LKT Laboratories, St. Paul, MN, USA) coadministered i.c.v. with 4-MC on day 14.

Statistical Analysis

Data are expressed as means ± standard error of the mean (SEM). Statistical analysis was performed using two-way ANOVA followed by a Tukey PSLD test for multiple comparisons of PWL and FST results among groups. A paired Student t test was performed to evaluate the modulatory effects of inhibitors on the analgesic effect of 4-MC during the chronic stage. $P < 0.05$ was considered to be statistically significant.

Results

Analgesic Effect of Intracerebroventricular Administration of 4-MC

The effects of 4-MC on chronic pain and depression-like behavior were evaluated in the CCI model in rats (Fig. 1). Rats given aCSF i.c.v. without CCI (Sham group) showed no changes in PWL over the 3-week experimental period. Untreated rats with CCI (untreated group) showed a significant decrease in PWL on days 7, 10, 14, and 21 after CCI. The decreases in PWL on days 14 and 21 were significantly reduced in the 4-MC group compared with the

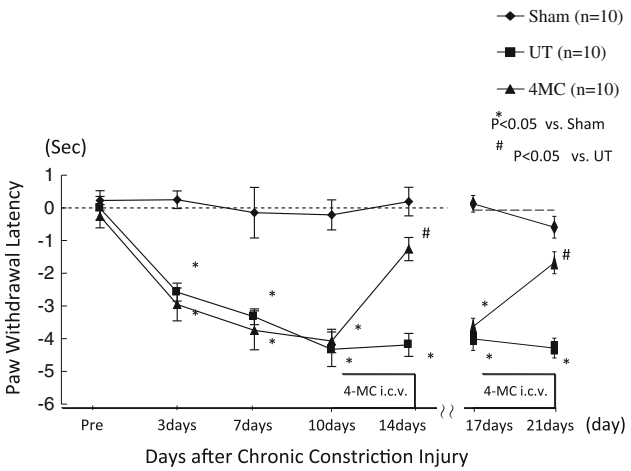


Fig. 1 Effect of intracerebroventricular administration of 4-methylcatechol (4-MC) on paw withdrawal latency (PWL) after CCI. 4-MC (100 nM/5 µl, i.c.v.) reduced the decrease of PWL in response to thermal stimulation of an injured hind paw. Values are shown as the mean ± SEM. Sham-operated ($n = 10$), untreated (UT) ($n = 10$), 4-MC ($n = 10$). $^{*}P < 0.05$ versus Sham-operated, $^{\#}P < 0.05$ versus untreated

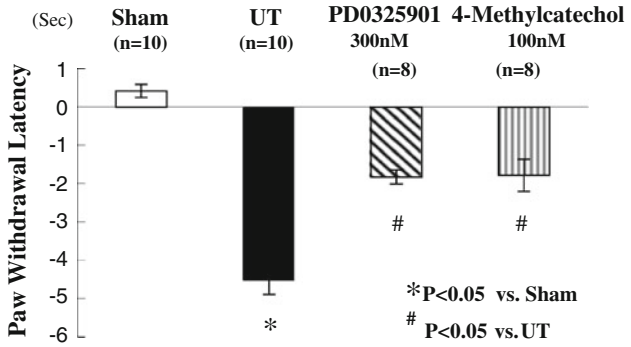


Fig. 2 Effect of intracerebroventricular administration of PD0325901 (MEK inhibitor) on paw withdrawal latency (PWL) after CCI. PD0325 901 reduced the decrease of PWL, similarly to 4-MC. Values are shown as the mean ± SEM. Sham-operated ($n = 10$), untreated (UT) ($n = 10$), PD ($n = 8$), 4-MC ($n = 8$). $^{*}P < 0.05$ versus Sham-operated, $^{\#}P < 0.05$ versus untreated

untreated group (Fig. 1). Administration of an MEK1/2 inhibitor, PD0325901, i.c.v. reduced the decrease in PWL on day 14 after CCI, similarly to the effect of 4-MC (Fig. 2).

Modulation of the Analgesic Effects of 4-MC

The decrease in PWL observed in the untreated group was significantly reduced on day 14 in 4-MC-treated rats. The 4-MC-induced reduction in the decrease in PWL was significantly reversed by anti-BDNF and K252a (Fig. 3a). The analgesic effect of 4-MC was also reversed by naloxone, a μ_1 receptor antagonist (Fig. 3b).

Antidepressant Effect of 4-MC and Modulation of This Effect

The effect of 4-MC on the time of immobility during chronic pain and the potential involvement of BDNF activity in the brain were examined in FSTs (Fig. 4). In untreated rats, a profound increase in time of immobility was observed, with no movements beyond keeping the head above the water surface. This extended time of immobility indicates depressive behavior. Significant antidepressant effects were observed with 4-MC and with a MEK1/2 inhibitor (Fig. 4). The antidepressant action of 4-MC was abolished by coadministration of anti-BDNF antibody or K252a.

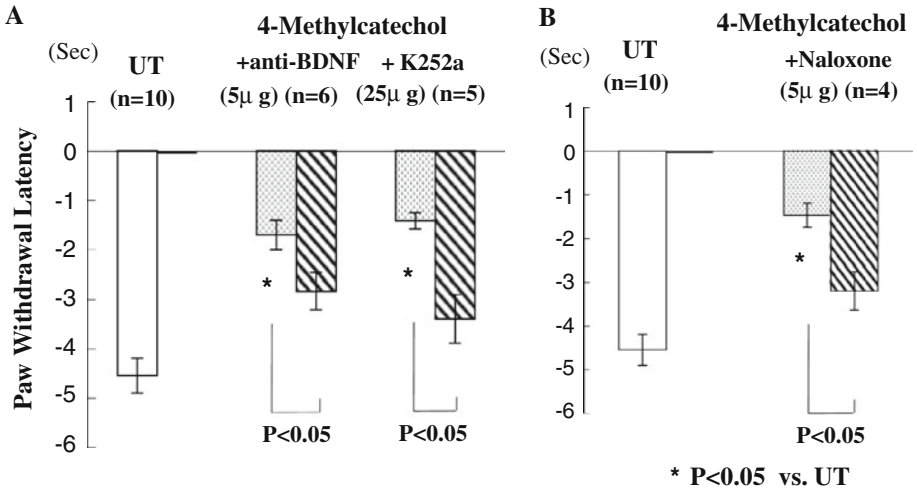
We also evaluated the correlation of depression-like behavior with the intensity of hyperalgesia produced by CCI in rats in different groups (Fig. 5). A significant linear relationship between these variables was obtained over all trials, including in rats that received 4-MC.

Discussion

This study clearly demonstrates that i.c.v. administration of 4-MC, a stimulator of BDNF synthesis, produces an analgesic effect concurrent with reduction of depression-like behavior after peripheral nerve injury in rats. Both effects were antagonized by coadministration of an anti-BDNF antibody and a TrkB receptor inhibitor, suggesting the possible involvement of BDNF in these effects. The CCI rat model used in this study involves mild peripheral nerve injury that is pathologically and physiologically applicable to clinical situations of slow development of chronic pain that is often associated with mood disorder. Many studies have proposed dis-inhibition mechanisms underlying chronic pain based on damage of regulatory inter-neurons containing GABA at spinal cord due to insufficient level of BDNF to maintain morphlogic condition (Cejas et al. 2000; Ishikawa et al. 2001).

BDNF is distributed widely in the sensory and limbic systems and is essential for maintenance of the related functions of pain, memory, and depression/anxiety. BDNF plays an important role in development, neurostructural and synaptic plasticity, including axonal sprouting, and enhancement of neurotransmission (Kafitz et al. 1999), and protects against ischemic cell damage in the rat HC (Beck et al. 1994). In particular, ACC-specific deletion of BDNF in adult mice has been reported to produce hyperalgesia and/or depression (Heldt et al. 2007). Thus, there is a relationship between the lack of BDNF and chronic pain associated with depression-like behavior.

BDNF is a large protein that cannot penetrate the blood–brain barrier, and therefore it is difficult to deliver BDNF from the periphery to the CNS. Moreover, BDNF is rapidly



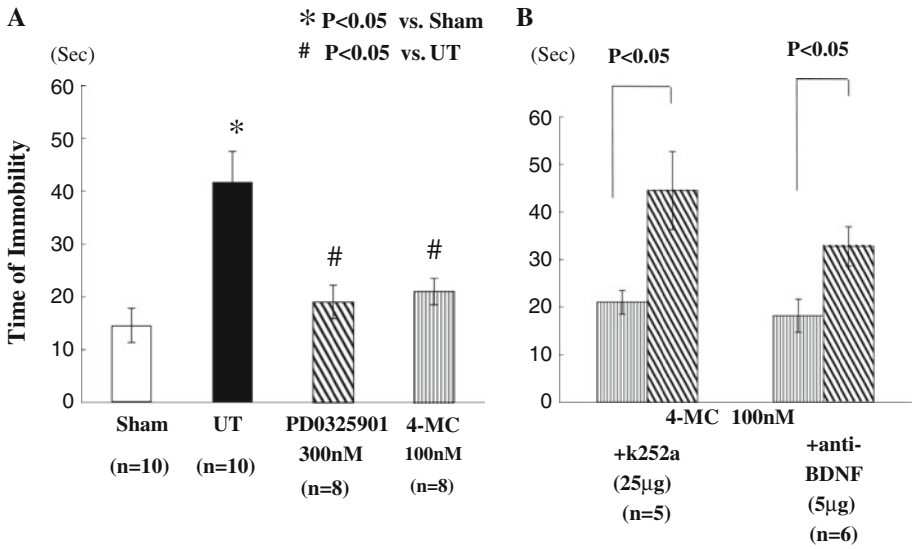


Fig. 3 Modulation of the analgesic effect of 4-MC on paw withdrawal latency (PWL) after CCI. The reduction of decreased PWL by 4-MC was significantly reversed by an anti-BDNF antibody and K252a, suggesting that 4-MC has a BDNF-like action in pain control (**a**). The analgesic effect of 4-MC was also reversed by naloxone (μ_1 receptor antagonist), which suggests that 4-MC has an activating effect on the descending inhibitory system (**b**). $^{*}P < 0.05$ versus untreated (UT)

Fig. 4 Antidepressive effect of 4-MC and modulation of this effect. 4-MC reduced the extended time of immobility in a similar manner to that of a MEK inhibitor, indicating an association with the action of BDNF (**a**). The antidepressive effect of 4-MC was reversed by coadministration of K252a (TrkB receptor antagonist) or an anti-BDNF antibody with 4-MC (**b**), suggesting that the antidepressive effect is mediated by decreased BDNF function in association with neurotransmission during chronic pain. Values are shown as the mean ± SEM. $^{*}P < 0.05$ versus Sham, $^{\#}P < 0.05$ versus untreated (UT)

incorporated into the liver (Pardridge et al. 1994), resulting in a short half-life in the blood. Therefore, a direct administration of BDNF i.c.v. may be most appropriate therapeutically, although this approach involves serious technical and ethical problems. Transfection of cells with the BDNF gene delivered by viral vectors and transplantation of cells producing the BDNF gene may be promising approaches, but the clinical safety of these applications has not been fully established (Levivier et al. 1995). Thus, we thought that indirect stimulation of synthesis of neurotrophic factors may be a potential approach to induction of neurotrophic actions for therapeutic purposes.

In this study, we demonstrated that 4-MC reduces hyperalgesia and produces an antidepressant effect. Furukawa et al. (1989) suggested that catecholamines including 4-MC, an alkylcatechol, induce neurotrophic factors in rodent astrocytes. In fact, 4-MC can improve derangements in various neuropathies (Hanaoka et al. 1994; Saita et al. 1996). Thus, 4-MC may contribute to recovery from neuropathic pain by induction of BDNF, as suggested in cultured neurons, but the mechanism underlying improvement of neuropathic pain is not understood. However, 4-MC at doses of 10–100 nM, similar to the dose used in this study, accelerates synthesis of BDNF in the CNS (Nitta et al. 1999), and 4-MC i.c.v. affects memory function and mood disorder, with these effects antagonized by coadministration of an anti-BDNF antibody (Sun and Alkon 2008). Thus, 4-MC may improve chronic pain associated with depression via induction of BDNF.

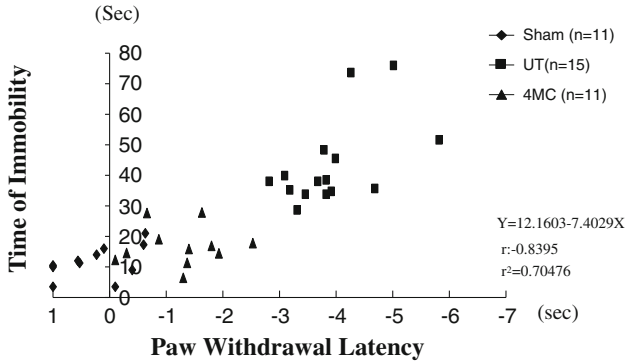


Fig. 5 Correlation between time of immobility and latency of pain response. A significant linear relationship between these variables was obtained over multiple trials and this relationship seemed to be maintained in rats that received 4-MC

Our results showed that CCI-induced thermal hyperalgesia associated with depression was attenuated by 4-MC and that this effect was reversed by an anti-BNDF antibody, a TrkB receptor inhibitor, and a MEK1/2 inhibitor. These results are in good agreement with the finding that BDNF injection prevents hypersensitivity following noxious stimuli (Cejas et al. 2000). In fact, we recently found that 4-MC normalized pERK1/2 activation in the pain–emotion system, which suggests that 4-MC induces BDNF and prevents abnormal activation of ERK1/2 (Ishikawa 2011). These findings are supported by the evidence that 4-MC stimulates BDNF synthesis in cultured infant rat brains (Furukawa et al. 1989) and can induce BDNF mRNA in vivo rat brain (Fukumitsu et al. 1999). Collectively, these results clearly demonstrate that 4-MC has beneficial effects on neuropathic pain.

Taken together, the results of this and previous studies suggest that the analgesic and antidepressant effects of 4-MC are mediated through active remodeling of neural structures and signaling cascades (Sun and Alkon 2005). In addition, BDNF has a feedback interaction with PKC that has a critical role in emotional function (Alkon et al. 2005). Therefore, the activity of BDNF can be evoked by PKC and both BDNF and PKC can activate ERK1/2 in the CREB pathway (Tao et al. 1998). These results show that BDNF plays an important role in pain–emotion systems, including ACC and associated structural processes, and balanced mood, and is essential in antidepressant action (Schmidt and Duman 2007). Therefore, the therapeutic value of 4-MC for neuropathic pain in humans warrants further investigation.

Conclusion

In summary, we suggest that a lack of BDNF and ERK1/2 activation may be involved in induction of chronic pain. The administration of 4-MC i.c.v. attenuates chronic pain associated with depression-like behavior and these pain–emotional effects of 4-MC can be reversed by an anti-BDNF antibody and a TrkB receptor antagonist. Therefore, 4-MC may exert analgesic and antidepressive effects on chronic pain via induction of BDNF in the brain.

Acknowledgments This study was supported in part by Scientific Research Grant No. 15390475 to TI from the Ministry of Education, Culture, Sports, Science and Technology of Japan. We are grateful to Prof. S. Furukawa (Gifu Pharmacological College) for advice on 4-methylcatechol.

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