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Lithium attenuates pain-related behavior in a rat model of neuropathic pain: Possible involvement of opioid system

Hamid R. Banafshe, Azam Mesdaghinia, Meysam Noorani Arani, Mehdi Honarkar Ramezani, Azhdar Heydari, Gholam A. Hamidi *

Physiology Research Center, Department of Physiology & Pharmacology, School of Medicine, Kashan University of Medical Sciences, Kashan, Iran

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ABSTRACT

Lithium is a major drug for bipolar disorder and mania. Recently, many studies have shown the neuroprotective effect of lithium in different models of neurodegenerative diseases. The present study was carried out to examine the effect of lithium in a rat model of neuropathic pain induced by partial sciatic nerve ligation and the possible role of opioid system in this effect. To do so, animals received acute injection of saline, lithium (5, 10 and 15 mg/kg,) and naloxone (1 mg/kg) or the combination of naloxone (1 mg/kg) with lithium (10 mg/kg) intraperitoneally on the testing days. Thermal hyperalgesia, mechanical and cold allodynia were measured on the days 3, 5, 7, 10 and 14 after surgery. Lithium decreased thermal hyperalgesia scores with dose of 5, 10 and 15 mg/kg and cold and mechanical allodynia scores with dose of 10 and 15 mg/kg, significantly. The opioid antagonist naloxone prevented the effect of lithium on thermal hyperalgesia and mechanical allodynia while it did not show any effect on the acetone-induced cold allodynia. Our results suggest that lithium can be considered as a therapeutic potential for the treatment of some aspects of neuropathic pain and that the opioid system may be involved in the lithium-induced attenuation of thermal hyperalgesia and mechanical allodynia.

1. Introduction

Neuropathic pain as a consequence of nerve injury or dysfunction is one of the most difficult challenges in pain treatment. The pathophysiology of neuropathic pain is complex, involving both peripheral and central mechanisms, such as sensitization of afferent nociceptor terminal, alteration of neurotransmitters release and ion channel expression, ectopic activity of neurons, anatomical reorganization and changes in inhibitory pain pathways (Zhuo, 2007; Coderre et al., 1993; Latremoliere and Woolf, 2009). There are several categories of medications that can be used in management of neuropathic pain including anticonvulsant, tricylic antidepressant, local anesthetics and opioids. However, they are limited by incomplete efficacy and dose-limiting adverse effects (Jensen et al., 2009; Hansson and Dickenson, 2005).

Lithium is widely used in treatment of bipolar disorder (Brunello and Tascedda, 2003). Recently, increasing body of evidences report the neuroprotective effects of lithium against cell injuries caused by different noxious stimuli in cultured cells and animal model of neurodegenerative diseases (Chuang et al., 2002; Wada et al., 2005). These stimuli include glutamate excitotoxicity, β amyloid peptide, focal ischemia, potassium deprivation, growth factor withdrawal, irradiation and taupathies caused by tau proteins (Nonaka et al., 1998; Sun et al., 2002; Pérez et al., 2003). Many studies have also shown the interaction between the lithium and the opioid system. For example, lithium can reduce morphine tolerance and dependence (Dehpour et al., 1995; Alborzi et al., 2006), change morphine-induced analgesia (Johnston and Westbrook, 2004; Dehpour et al., 1994) and inhibit modulatory effects of morphine on pentylenetetrazole-induced seizure (Honar et al., 2004). Chronic lithium administration is also demonstrated to increases mu-opioid receptor expression in rats' forebrain (de Gandarias et al., 2000). Lithium also stimulates the release of beta-endorphin, met-enkephalin and dynorphin in brain via an inhibition of autoreceptors (Staunton et al., 1982; Burns et al., 1990; Gillin et al., 1978) and increases dynorphin and prodynorphin mRNA in the basal ganglia of rats (Sivam et al., 1988). The present study was conducted to determine the effect of lithium on a rat model of neuropathic pain and to examine the possible involvement of the opioid system in this effect.

2. Materials and methods

2.1. Animals and housing conditions

The experiments were performed on male Sprague–Dawley rats (200–250 g) purchased from Razi Institute (Karaj, Iran). They were

* Corresponding author. Tel.: +98 361 5550021; fax: +98 361 5575057.
E-mail address: hamiidi@yahoo.com (G.A. Hamidi).

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housed four per cage, in a room under controlled temperature (23 ± 2 °C), humidity (50%) and lighting (12/12 h light/dark cycle), with food and water available ad libitum. All experiments were approved by the ethical committee of Kashan University of Medical sciences and followed the European Commission Directive (86/609/EEC) for animal experiments.

2.2. Neuropathic pain model: partial sciatic nerve ligation

The rats were anesthetized with sodium pentobarbital (65 mg/kg) intraperitoneally (i.p.) and the sciatic nerve ligation was performed according to the original description of Seltzer (Seltzer et al., 1990). Briefly, an incision was made at the skin overlying the lateral femur then the sciatic nerve was exposed and dissected from surrounding connective tissue near the trocanter, just distal to the branching point of the posterior biceps semitendinosus nerve. A tight ligature was tied around 1/3 to 1/2 of the nerve diameter with 8-0 silk suture. Sham operated rats had the same surgery without any ligature on the sciatic nerve.

2.3. Behavioral tests of neuropathic pain

Hyperalgesia to noxious thermal stimulus and allodynia to cold and mechanical stimuli were determined as behavioral score of neuropathic pain by using the radiant heat plantar, acetone and von Frey test, respectively. These tests were performed during the day portion of the circadian cycle (09:00–16:00 h). After cage exploration and major grooming activities ceased, we made the behavioral tests. The behavioral scores of neuropathic pain were determined 1 day before the surgery as the baseline value and also 30 min after the injections on days 3, 5, 7, 10 and 14 after the surgery.

2.3.1. Thermal hyperalgesia (plantar test)

Thermal hyperalgesia was assessed as previously reported (Hargreaves et al., 1988). Paw withdrawal latency in response to radiant heat was measured by using plantar test apparatus (Ugo Basile, Varese, Italy). Rats were placed within a Plexiglass enclosure (but not restrained) on a transparent glass floor. An infrared beam that constitutes the heat source was moved beneath the mid-plantar surface of the hind paw. Thermal withdrawal latency was defined as the latency (seconds) between the heat stimulus onset and paw withdrawal using a feedback-controlled shut-down unit. A cut-off time of 22 s was used to avoid tissue damage. Each paw was tested three times alternatively at minimum intervals of 5 min between stimulation to avoid sensitization of the hind paw. The mean latency of the withdrawal responses for ipsilateral (operated) and contralateral (non-operated) paws was calculated separately.

2.3.2. Cold allodynia (acetone test)

Cold allodynia was measured using the acetone spray test (evaporation-evoked cooling) described by Choi (Choi et al., 1994). Rats were placed on a wire mesh floor; acetone bubbles formed at the end of a tube connected to a syringe were applied 5 times (at 5 min intervals) to the plantar surface of the hind paw. The frequency of paw withdrawal was expressed as a percentage (the number of paw withdrawals/number of trials × 100).

2.3.3. Mechanical allodynia (von Frey filament stimulation)

Mechanical allodynia was quantified by measuring the hind paw withdrawal response to von Frey filament. We studied the effect of von Frey filament stimulation (with bending forces ranging from 2 to 60 g, Stolting Inc., Wood Dale, IL). Rats were placed on a mesh (0.8 × 0.8 cm cell) floor, covered by an inverted transparent plastic box (18 × 18 × 25 cm) and allowed to adapt for approximately 15 min, or until exploratory behavior ceased. A series of von Frey filament stimuli were delivered in an ascending order of forces to the central region of the plantar surface of the hind paw. The stimulation was applied three times consecutively, pushing down on the hind paw until the rat withdrew its paw or the fiber bowed. Lifting of the paw due to normal locomotor behavior was ignored. The smallest filament size which evoked at least two withdrawal responses during three consecutive applications was considered as withdrawal threshold. Each filament was applied for approximately 1 s and the interstimulus intervals were about 5 s (Chaplan et al., 1994).

2.4. Treatment

In the nerve ligated animals (n = 8 per group), different doses of lithium chloride (5, 10 and 15 mg/kg; i.p.), were administered only on the days 3, 5, 7, 10 and 14 after the surgery without any injection on the other days. In the control group (n = 8), rats received equal volume of normal saline instead of lithium chloride. To evaluate the involvement of opioid system on lithium-induced effects, the opioid antagonist naloxone (1 mg/kg, i.p.) was acutely administered 15 min prior to optimum dose of lithium on the days 3, 5, 7, 10 and 14 after the surgery.

2.5. Statistical analysis

All data are presented as Mean ± SEM and differences are considered significant if the P value was less than 0.05. Values for behavioral response were analyzed using analysis of variance (ANOVA) with repeated measures followed by Tukey's honest squares difference (HSD) test. Drug treatment was considered as the between-subjects and day as within-subjects.

3. Results

3.1. The effect of lithium on behavioral tests of neuropathic pain

The majority of the animals appeared healthy and well-groomed. The rats did not show any sign of autotomy after the sciatic nerve ligation and common adverse effects of lithium such as tremor, ataxia and convulsion. The gesture of ipsilateral paw was slightly altered; but this did not interfere with the normal activity of the rats. Lithium had no effect on behavioral responses evoked from the sham-operated animals and did not show any analgesic effect (data not shown).

3.1.1. Thermal hyperalgesia

Partial sciatic nerve ligation decreased paw withdrawal latency to the thermal stimulus in ipsilateral ($P<0.001$) (Fig. 1a1) and contralateral paw ($P<0.05$) significantly (Fig. 1a2), but sham operation did not produce any significant change in withdrawal latency. Lithium chloride (5, 10 and 15 mg/kg) blocked thermal hyperalgesia in ipsilateral paw dose-dependently (Fig. 1a1) and also increased withdrawal latency of contralateral paw but this change was only significant with the dose of 15 mg/kg on 14th day (Fig. 1a2).

3.1.2. Cold allodynia

The results of the behavioral tests for cold allodynia have been shown in Fig. 1b. The ipsilateral paw of nerve ligated animals became much more sensitive to acetone application ($P<0.001$) but the contralateral paw remained unresponsive throughout the experiments for all the groups. Sham operation did not produce any modification of the nociceptive response. Lithium chloride (10 and 15 mg/kg) significantly reduced the withdrawal frequency in comparison with control group ($P<0.001$) (Fig. 1b).

3.1.3. Mechanical allodynia

Fig. 1c shows the effects of lithium chloride on mechanical allodynia. Partial sciatic nerve ligation led to a significant decrease of withdrawal threshold of ipsilateral paw in comparison with sham-

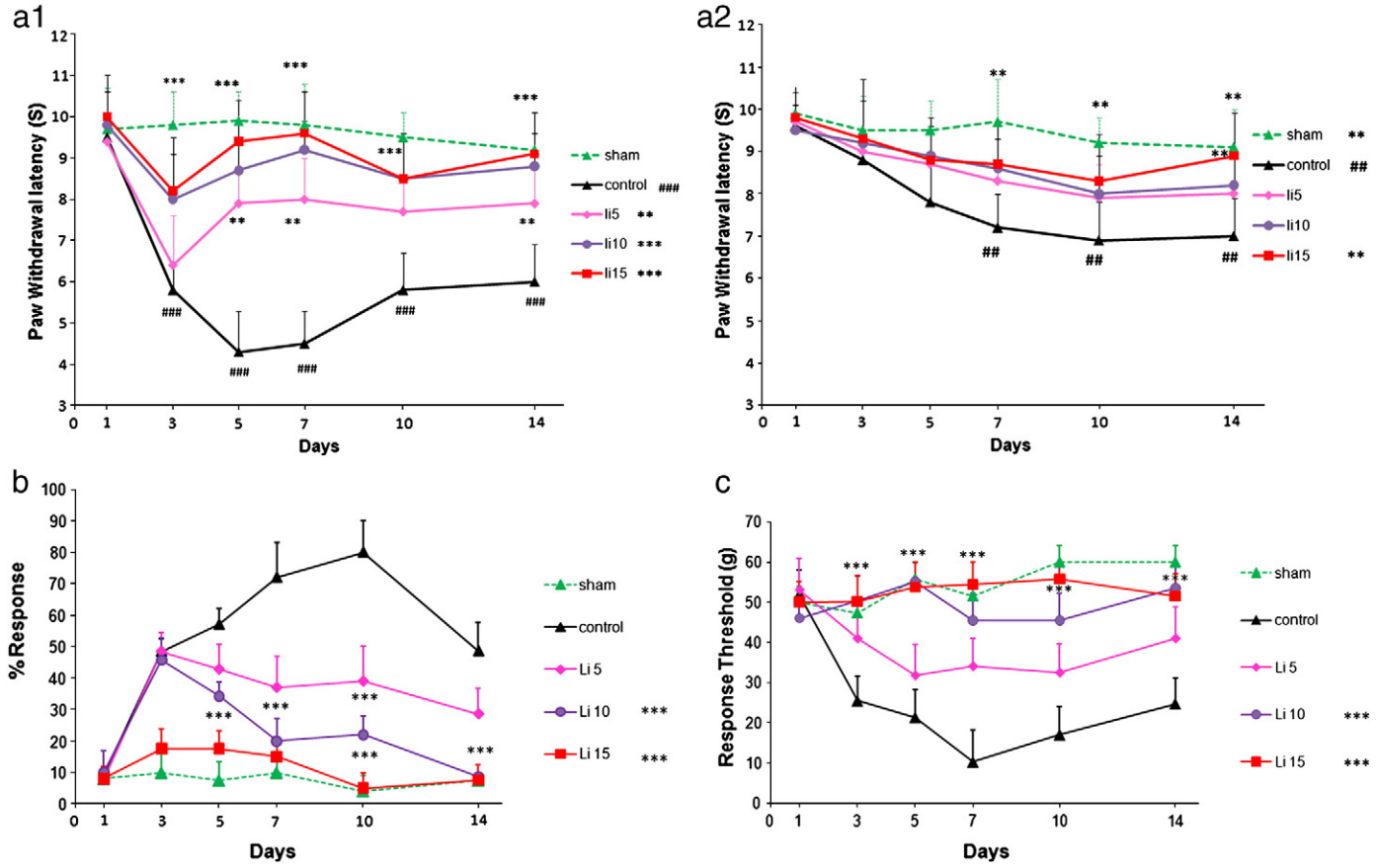

Fig. 1. Effect of lithium on development of neuropathic pain in sciatic nerve ligated rats. The behvioral manifestations of neuropathic pain were evaluated by using plantar test (a); paw withdrawal latency (S) of ipsilateral (a1) and contralateral paw (a2), acetone test (b); the percentage of foot withdrawals to repeated cold stimuli and von Frey model (c); mechanical withdrawal threshold (g). The behavioral responses were determined 3, 5, 7, 10 and 14 days after sciatic nerve surgery. The results are expressed as Mean ± SEM. ** $P<0.01$, *** $P<0.001$ versus control group, ## $P<0.05$, ### $P<0.001$ versus sham group.

operated group ($P<0.001$). The withdrawal thresholds of contralateral paw ranged from 52.2 to 60 g and 48.1 to 60 g in the nerve ligated and sham-operated animals respectively. These scores were not different significantly ($P>0.05$). Lithium chloride with dose of 10 and 15 mg/kg, significantly increased withdrawal threshold of ipsilateral paw ($P<0.001$).

3.2. The effects of naloxone on lithium-induced effects

Naloxone (1 mg/kg, i.p.) on itself had no effect on behavioral tests of neuropathic pain in nerve ligated and sham-operated rats. Fig. 2a shows the effects of naloxone on thermal anti-hyperalgesic effect of lithium (10 mg/kg). Naloxone significantly prevented anti-hyperalgesic effect of lithium in radiant heat plantar test ($P<0.001$) (Fig. 2a1). As shown in Fig. 2c, naloxone blocked the anti-allodynic effects of lithium in the von Frey filament test but could not change the effect of lithium in the acetone test significantly ($P>0.05$) (Fig. 2b).

4. Discussion

Our study demonstrated that an acute i.p. injection of lithium attenuates thermal hyperalgesia and mechanical and cold allodynia in a rat sciatic nerve ligation model of neuropathic pain and potent opioid antagonist naloxone prevents these effects of lithium on hyperalgesia and mechanical allodynia but could not change the effect of lithium on cold allodynia. Our results are in agreement with previous data reported that intrathecal injection of lithium reduces neuropathic pain responses in chronic constrictive injury (CCI) model in rats (Shimizu et al., 2000). No considerable adverse effects of lithium such as tremor, ataxia or convulsion were observed in the lithium-treated rats. It seems the absence of adverse effects is expectable because of the low dose of lithium in our experiments. Lithium has no significant effect on responses evoked from sham-operated animals. This result is consistent with previous studies that suggested that the effect of lithium is anti-hyperalgesic rather than analgesic (Zhang et al., 1994; Shimizu et al., 2000). Lithium decreases exploratory activity, rearing, aggression, and locomotor activity in a dose range of 32 mg/kg to 127 mg/kg in rats (Tenk et al., 2005). The effect of lithium on spontaneous behavior is limited to certain behaviors and certain doses. Changes that occur at therapeutic doses are not caused by general motor impairment. Indeed, it has been shown that therapeutic doses of lithium, which effectively alter drug-induced locomotion, do not change baseline locomotion in tests with a sufficient time course (O'Donnell and Gould, 2007).

Lithium is a small monovalent cation with similar ionic radius to magnesium and inhibits some enzymes through competition for this essential cofactor. Lithium with therapeutic concentration inhibits inositol monophosphate phosphatase (IMPase), inositol polyphosphate 1-phosphatase (IPPase), phosphoglucomutase (PGM) and glycogen synthase kinase-3 (GSK-3) (Wada, 2009; Quiroz et al., 2004). The best-defined targets of lithium are IMPase and IPPase involved in the normal recycling of membrane phosphoinositides. This recycling is necessary to continue phosphoinositol-mediated signaling in central nervous system where inositol is not freely available. Lithium's inhibitory effect on IMPase and IPPase led to the inositol depletion hypothesis. This hypothesis suggests that lithium exerts its effect by relative decrease of inositol and thus phosphoinositide 4,5-bisphosphate (PIP2) available for signaling cascades that depend

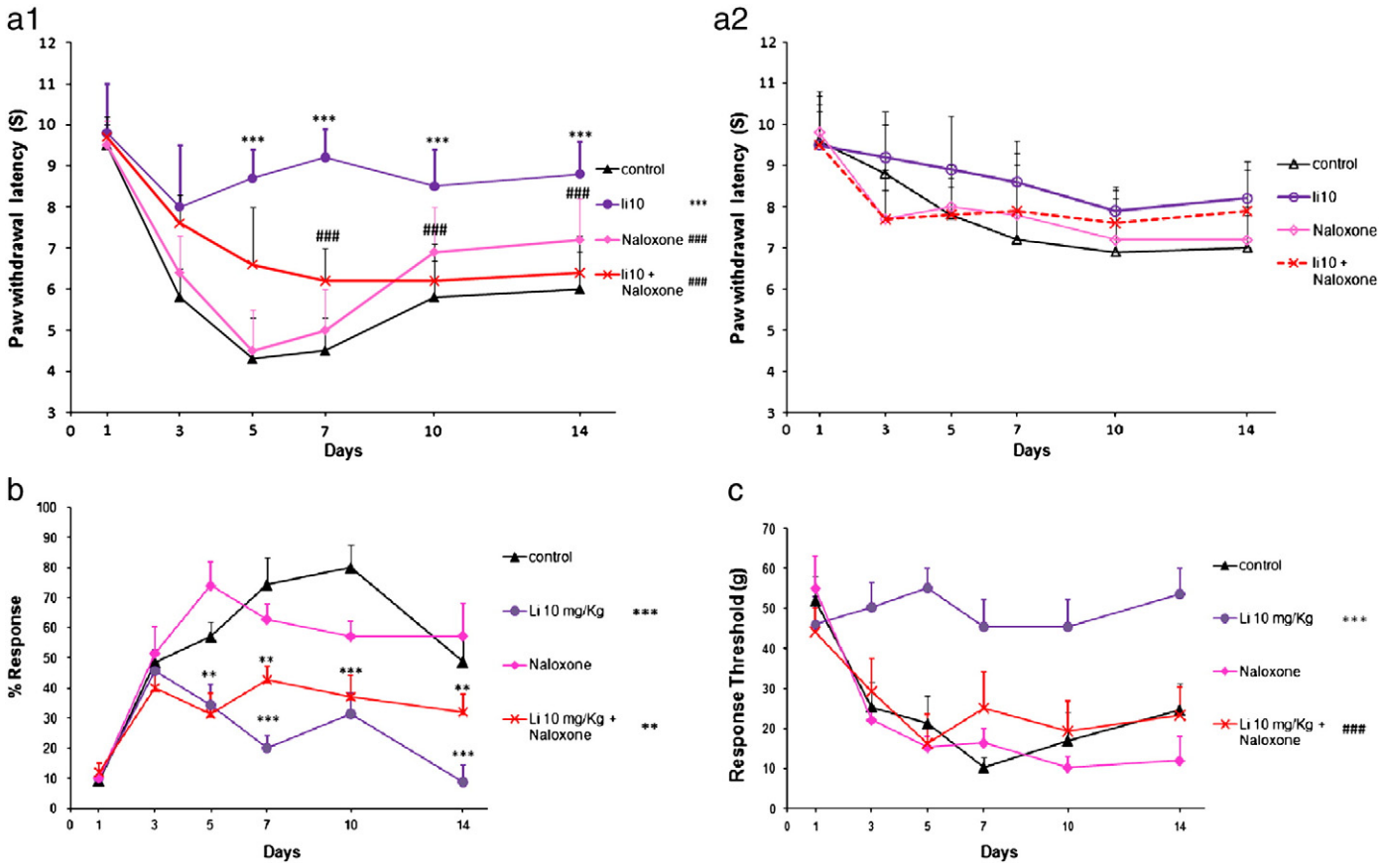

Fig. 2. Effects of i.p. injection of saline (control), lithium (10 mg/kg), naloxone (1 mg/kg) and lithium (10 mg/kg) + naloxone (1 mg/kg) on heat hyperalgesia in ipsilateral (a1) and contralateral paw (a2), cold allodynia (b) and mechanical allodynia (c).The results are expressed as Mean ± SEM. ** P<0.01, *** P<0.001 versus control group, ### P<0.001 versus lithium (10 mg/kg).

on phospoinositides like neurtrophin, tyrosine kinase receptors and some G protein-mediated signaling pathways (Berridge et al., 1989; Liou et al., 2007). A number of studies using animal models have indicated that the intracellular phosphatidylinositol (PI) second messenger system has a critical role in development of neuropathic pain (Mao et al., 1992, 1995; Coderre et al., 1993). It has been also reported that intrathecal injection of myo-inositol canceled the effect of lithium in the reduction of hyperalgesia and cold allodynia in a rat model of peripheral neuropathy without any effect on mechanical allodynia (Shimizu et al., 2000).

Lithium also inhibits glycogen synthase kinase-3 (GSK-3). GSK-3 is a normally active kinase that is a part of many intracellular signaling pathways such as neurotrophic signaling, the insulin phosphatidylinositol 3 kinase (PI3K) and the Wnt pathways (Ryves and Harwood, 2001). Activation of these pathways inhibits GSK-3 and this inhibitory effect has been linked to neuroprotection and activation of cell survival signaling pathways (Noble et al., 2005; Wada, 2009). Lithium causes up-regulation of a brain-derived neurotrophic factor (BDNF) and antiapoptotic Bcl2, down-regulation of apoptotic p53, caspase and Bax, induction of neuronal regeneration and activation of cAMP response element binding protein (CREB) (Hashimoto et al., 2002; Chuang, 2004). Several studies have shown the significant increase in apoptosis and pro-apoptotic Bax, apoptotic protease-activating factor-1 (apaf-1), caspase-7 and p53 in neuropathic pain (de Novellis et al., 2004; Gradl et al., 2004; Scholz et al., 2005). According to these studies lithium may attenuate neuropathic pain through up-regulation of cell survival molecules and down- regulation of proapoptotic activity.

Multiple lines of studies have demonstrated interaction between lithium and opioid system (Honar et al., 2004; Dehpour et al., 1995; Zarrindast et al., 2008). Lithium stimulates release of beta-endorphin, met-enkephalin and dynorphin in brain (Staunton et al., 1982; Burns et al., 1990) and increases the prodynorphin mRNA abundance and enkephalin content in striatum (Sivam et al., 1988). Chronic lithium administration also increases mu-opioid receptor expression (de Gandarias et al., 2000). On the other hand, peripheral nerve injury results in down-regulation of mu-opioid receptor (MOR) in dorsal horn of spinal cord (Porreca et al., 1998; Goff et al., 1998). This loss of spinal MOR is associated with behavioral manifestation of neuropathic pain and the reduction of opioid analgesic effect (Rashid et al., 2004; Back et al., 2006). Thus, the enhancement of opioid system activity can be considered as one of the possible mechanisms of lithium in attenuation of neuropathic pain. Our results also showed naloxone prevents the effect of lithium in reduction of heat hyperalgesia and mechanical allodynia scores while it did not change its effect on cold allodynia. This difference is probably due to different nociceptors and neuronal pathways involved in different sensory modalities. Non-noxious tactile stimulus is transmitted chiefly through low-threshold, large diameter, myelinated Aβ fibers, while cold stimulus is transmitted to the spinal cord through high-threshold, thin unmyelinated primary C-fiber nociceptors (Yeomans and Proudfit, 1996). In particular, that painful reaction to innocuous thermal stimuli seems not to be due to a simple decrease in nociceptor thresholds. The increasing body of evidences demonstrated the involvement of distinctive warm and cold receptors in thermal allodynia (Gautron et al., 1990; Xing et al., 2007). Recent studies on transient receptor potential melastatin 8 (TRPM8) knockout mice indicate the involvement of cold and menthol-sensitive receptor TRPM8 in cold allodynia while it does not have any involvement in mediation of heat or mechanical pain (Dhaka et al., 2007; Chung and Caterina, 2007).

In addition, it is important to note the evidences for the involvement of the sympathetic nervous system in neuropathic pain-related behavior. Surgical lumbar sympathectomy had no effect on the mechanical allodynia and mechanical hyperalgesia induced by spared nerve injury model (SNI). However, the sympathectomy significantly attenuated the cold allodynia induced by SNI (Zhao et al., 2007). Other studies also demonstrate allodynia is under endogenous noradrenergic rather than opioidergic control in rat models of neuropathic pain (Yaksh et al., 1995; Kontinen et al., 1998; Xu et al., 1999).

In conclusion, our study showed that lithium reduces behavioral scores of neuropathic pain and the opioid system may be involved in the attenuation of heat hyperalgesia and mechanical allodynia induced by lithium. Other mechanisms also may be involved in this effect of lithium, particularly in attenuation of cold allodynia. Further investigations are required to clarify the other possible mechanisms of lithium in attenuation of neuropathic pain.

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