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Short communication

Effect of repeated oral administration of chondroitin sulfate on neuropathic pain induced by partial sciatic nerve ligation in mice

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ABSTRACT

We examined whether chondroitin sulfate (CS), a compound used to treat osteoarthritis and joint pain, is effective against partial sciatic nerve ligation (PSNL)-induced neuropathic pain. Repeated oral administration of CS (300 mg/kg, b.i.d. for 20 days) resulted in inhibition of tactile allodynia observed 21 days after PSNL. On day 21, phosphorylation of spinal p38 mitogen-activated protein kinase (MAPK) was attenuated by CS. CS also inhibited c-Fos upregulation in ipsilateral deep dorsal horn (laminae III–IV) neurons, which receive Aβ-fiber afferent inputs. These findings suggest that CS attenuates PSNL-induced tactile allodynia by inhibiting spinal p38 MAPK phosphorylation and Aβ-fiber activation.

Neuropathic pain is caused by lesions in the peripheral or central nervous system. Several analgesic drugs such as anti-inflammatory drugs and opioids are used to treat neuropathic pain; however, these treatments are often ineffective. Therefore, current therapy for neuropathic pain is limited. Chondroitin sulfate (CS) is a compound categorized as a symptomatic slow-acting drug for the treatment of osteoarthritis (SYSADOA) because of its anti-inflammatory and chondroprotective properties.[1] It is also popular in North America as a dietary supplement intended to alleviate joint pain.[2] In Japan, CS is available as an over-the-counter drug for treating knee-joint pain. The pain relief properties and mechanism of action of CS remain unclear; however, it has been suggested that CS may play a role in pain relief through B_2 bradykinin receptor desensitization.[3] Recently, we reported that repeated oral administration of CS results in attenuation of formalin-induced tactile allodynia through inhibition of p38 mitogen-activated protein kinase (MAPK) phosphorylation and subsequent up-regulation of c-Fos expression in the dorsal lumbar spinal cord.[4] However, the effect of CS on neuropathic pain remains unclear. Thus, in this study, we examined whether CS is effective against partial sciatic nerve ligation (PSNL)-induced neuropathic pain. The findings of this study may help develop effective CS-based drugs that can be used to alleviate neuropathic pain.

Male ddY mice (weighing 22–24 g; Japan SLC, Hamamatsu, Japan) were used in this study. The mice were housed in cages with free access to food and water under controlled conditions (temperature, 22 ± 2 °C; humidity, 55 ± 5% and a 12/12 h light/dark cycle (lights on: 07:00 to 19:00). The mice were used for behavioral experiments (n = 7–8 per group), Western blotting analyses (n = 12 per group), and immunohistochemical experiments (n = 5–7 per group). All experimental protocols were approved by the Ethics Committee of Animal Experiment at Medical and Tohoku Pharmaceutical University. Additionally, all procedures were performed according to the National Institutes of Health Guide for the Care and Use of Laboratory Animals. Efforts were made to use a small number of animals and minimize suffering.

PSNL was performed according to the procedure described by Seltzer et al.[5] Briefly, mice were deeply anesthetized with sodium pentobarbital (50 mg/kg, i.p.). The left sciatic nerve was exposed at the mid-thigh level, after which approximately 1/3 to 1/2 of the nerve diameter was tightly ligated with 9–0 nylon suture. Sham operations were performed in a similar manner but without ligation of the nerve.

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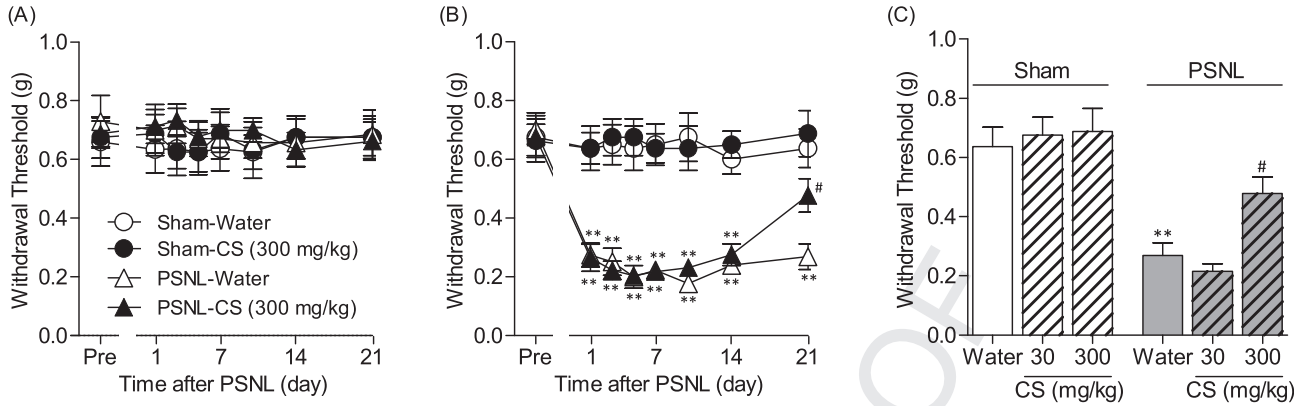

Fig. 1. Effect of CS on PSNL-induced tactile allodynia in mice. Thresholds for (A) contralateral and (B) ipsilateral paw withdrawal to von Frey filaments monitored for 21 days after PSNL. CS (300 mg/kg) or water was orally administered twice daily starting 24 h after PSNL. Threshold was measured before the first dose of CS or water was administered. Values are presented as means ± S.E.M. (n = 7–8 mice) (A) Two-way repeated ANOVA: group ($F_{3,27} = 0.23$, $p > 0.05$), time ($F_{7,189} = 0.17$, $p > 0.05$), group × time ($F_{21,189} = 0.18$, $p > 0.05$) (B) Two-way repeated ANOVA: group ($F_{3,27} = 58.13$, $p < 0.01$), time ($F_{7,189} = 10.14$, $p < 0.01$), group × time ($F_{21,189} = 3.26$, $p < 0.01$). One-way ANOVA: pre, $F_{3,27} = 0.06$, $p > 0.05$; 1 day, $F_{3,27} = 14.22$, $p < 0.01$; 3 days, $F_{3,27} = 20.69$, $p < 0.01$; 5 days, $F_{3,27} = 22.27$, $p < 0.01$; 7 days, $F_{3,27} = 24.98$, $p < 0.01$; 10 days, $F_{3,27} = 18.37$, $p < 0.01$; 14 days, $F_{3,27} = 24.55$, $p < 0.01$; 21 days, $F_{3,27} = 8.40$, $p < 0.01$ (C) Threshold for ipsilateral paw withdrawal to von Frey filaments monitored on day 21 after PSNL. CS (30 and 300 mg/kg) or water was orally administered twice daily starting 24 h after PSNL. Values are presented as means ± S.E.M. (7–8 mice). Two-way ANOVA: dose ($F_{2,41} = 3.53$, $p < 0.05$), group ($F_{1,41} = 52.54$, $p < 0.01$), dose × group ($F_{2,41} = 2.39$, $p > 0.05$). One-way ANOVA: $F_{5,41} = 12.75$, $p < 0.01$. ** indicates $p < 0.01$ when compared to the sham-water group, whereas # indicates $p < 0.05$ when compared to the PSNL-water group.

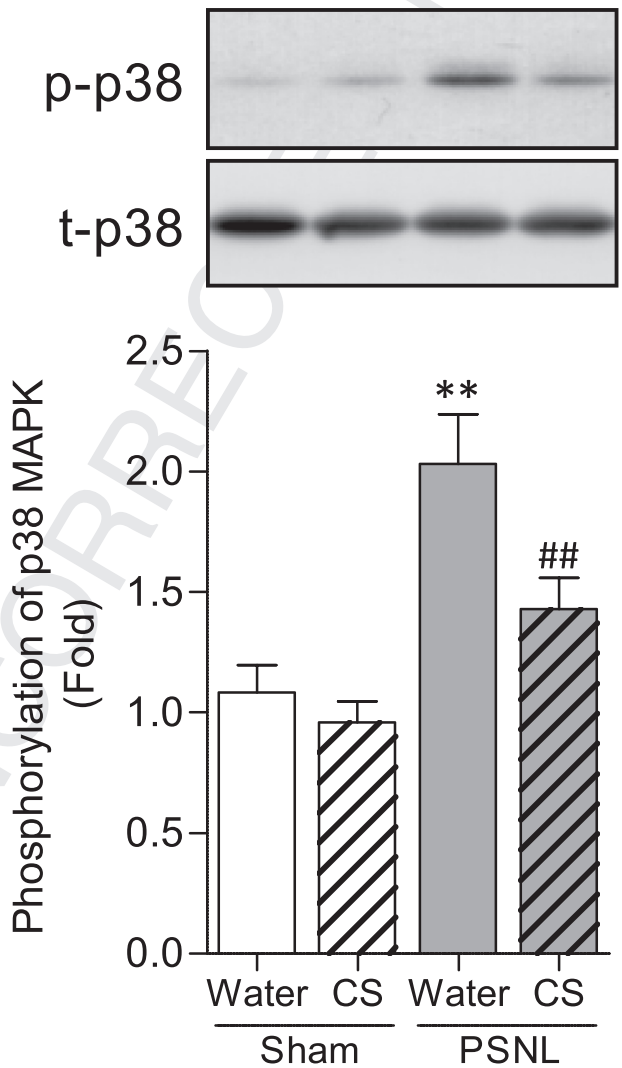

Fig. 2. Effects of CS on PSNL-induced changes in phospho-p38 MAPK levels in the ipsilateral lumbar dorsal spinal cord. CS (300 mg/kg) or water was orally administered twice daily starting 24 h after PSNL. Spinal cord samples were collected on day 21. Upper panel: Representative western blot images showing phospho- and total-p38 MAPK. Lower panel: Relative quantification of phospho-p38 MAPK to total-p38 MAPK set as 1.0 in the sham-water group. Values are presented as means ± S.E.M. (n = 12 mice per group). Two-way ANOVA: group ($F_{1,44} = 25.72$, $p < 0.01$), treatment ($F_{1,44} = 6.81$, $p < 0.05$), group × treatment ($F_{1,44} = 2.91$, $p > 0.05$). One-way ANOVA: $F_{3,44} = 11.81$, $p < 0.01$. ** indicates $p < 0.01$ when compared to the sham-water group, whereas ## indicates $p < 0.01$ when compared to the PSNL-water group.

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