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Short communication

Histone deacetylase inhibitors relieve morphine resistance in neuropathic pain after peripheral nerve injury

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ABSTRACT

Neuropathic pain is often insensitive to morphine. Our previous study has demonstrated that neuron-restrictive silencer factor represses mu opioid receptor (MOP) gene expression in the dorsal root ganglion (DRG) via histone hypoacetylation-mediated mechanisms after peripheral nerve injury, thereby causing loss of peripheral morphine analgesia. Here, we showed that histone deacetylase (HDAC) inhibitors, such as trichostatin A and valproic acid, restored peripheral and systemic morphine analgesia in neuropathic pain. Also, these agents blocked nerve injury-induced MOP down-regulation in the DRG. These results suggest that HDAC inhibitors could serve as adjuvant analgesics to morphine for the management of neuropathic pain.

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Neuropathic pain is manifested by combination of positive (hyperalgesia and allodynia) and negative (hypoesthesia and hypoalgesia) symptoms (1). Patients with neuropathic pain are often insensitive to conventional analgesics, including morphine (2). Also, the morphine resistance has been observed in diverse animal models of neuropathic pain caused by peripheral nerve injury (3), post-herpetic neuralgia (4), and bone cancer (5). Under these models, the common event is a down-regulation of mu opioid receptor (MOP) expression in the dorsal root ganglion (DRG) (3–5). Accordingly, previous studies have shown that the intraplantarly administrated morphine fails to produce analgesic effects on neuropathic pain (3), and that injury reduces the pre-synaptic inhibitory action of MOP agonist (6). Therefore, the elucidation of mechanisms underlying MOP down-regulation after injury could be important to overcome the morphine resistance in neuropathic pain.

Neuron-restrictive silencer factor (NRSF, also known as repressor element-1 silencing transcription factor) represses transcription of neuron-restrictive silencer element (NRSE)-containing genes via recruitment of histone deacetylase (HDAC) enzymes through co-repressors, mSin3 and CoREST (7). Our previous study

has demonstrated that NRSF causes injury-induced morphine resistance and hypoesthesia by histone hypoacetylation-mediated silencing of NRSE-containing MOP and sodium channel $Na_v1.8$ genes, respectively (8). We have also reported that HDAC inhibitors, such as trichostatin A (TSA) and valproic acid (VPA), block injury-induced $Na_v1.8$ down-regulation in the DRG and hence improve hypoesthesia (9); yet, the functional involvement of HDAC in morphine resistance remains to be investigated. Thus, we tested here whether HDAC inhibitors could block injury-induced MOP down-regulation, thereby relieving the morphine resistance.

Male C57BL/6J mice weighing 20–25 g were used. They were kept in a room with a temperature of 21 ± 2 °C with free access to a standard laboratory diet and tap water. All experimental procedures were approved by the Nagasaki University Animal Care Committee, and complied with the fundamental guidelines for the proper conduct of animal experiments and related activities in academic research institutions under the jurisdiction of the Ministry of Education, Culture, Sports, Science and Technology, Japan. Partial ligation of the sciatic nerve was performed as described previously (8).

TSA (Wako Pure Chemical Industries, Ltd., Osaka) dissolved in 10% ethanol in physiological saline and VPA sodium salt (Sigma–Aldrich, St. Louis, MO, USA) dissolved in physiological saline were intraperitoneally injected 60 min and 120 min prior to injury, respectively, and once daily post-injury. Analgesic tests were performed 60 min or 120 min after the last treatment of TSA or VPA,

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respectively. Morphine hydrochloride (Takeda Chemical Industries, Osaka) dissolved in physiological saline was injected intraplantarly or subcutaneously. To assess morphine analgesia, the area under the curve was measured by trapezoidal rule with subtraction of the basal value at 0 min from the value for each withdrawal threshold from 10 to 60 min after morphine treatment.

In thermal paw withdrawal tests, the latency to withdrawal from a thermal stimulus (IITC Inc., Woodland Hills, CA, USA) was assessed as a nociception threshold, as described previously (8). A cut-off time of 20 s was set to prevent tissue damage.

We collected L4–6 DRGs just after analgesic tests. The extraction of total RNA from L4–6 DRGs, cDNA synthesis, and real-time PCR using gene-specific primers were performed as described previously (8). Glyceraldehyde-3-phosphate dehydrogenase was used as an internal control for normalization.

Statistical analyses of results were performed using Student's *t*-test or a one-way ANOVA with Tukey–Kramer multiple comparison *post hoc* test. The criterion of significance was set at $P < 0.05$. All results were expressed as means \pm SEM.

Firstly, we confirmed that a single intraperitoneal (i.p.) administration of TSA (1 mg/kg) elevated histone H3 and H4 acetylation in the DRG at least 60 min post-injection (data not shown). To examine whether HDAC inhibitor could relieve the loss of peripheral morphine analgesia after injury, mice were given repeated i.p. injections of TSA (1 mg/kg) for 7 days, starting from 60 min prior to injury. Consistent with previous report (9), neither the basal nociceptive threshold in sham-operated mice nor thermal pain hypersensitivity in nerve-injured mice was affected by TSA (Fig. 1: A, B). Meanwhile, a lack of analgesic action of intraplantarly injected morphine (30 nmol) was remarkably recovered by TSA (Fig. 1: B, C). In contrast, TSA had no effects on peripheral morphine analgesia in sham-operated mice (Fig. 1: A, C).

Next, we assessed whether HDAC inhibitors could restore the systemic morphine analgesia after injury. Mice were treated with subcutaneous (s.c.) injections of morphine at a dose of 1 mg/kg that fails to produce analgesia in nerve-injured mice (3). The loss of systemic morphine analgesia at day 3 post-injury was recovered by TSA (Fig. 2: A–C). In addition to TSA, we used VPA, another HDAC inhibitor, at a dose of 200 mg/kg that exerts no anti-hyperalgesic action (10) but blocks injury-induced Na_v1.8 down-regulation in the DRG (9). Repeated i.p. treatments with VPA also restored the systemic morphine analgesia in nerve-injured mice (Fig. 2D). Moreover, VPA significantly improved the sensitivity to peripherally injected morphine, but not thermal hyperalgesia, after injury (data not shown). In contrast, both HDAC inhibitors had no effects

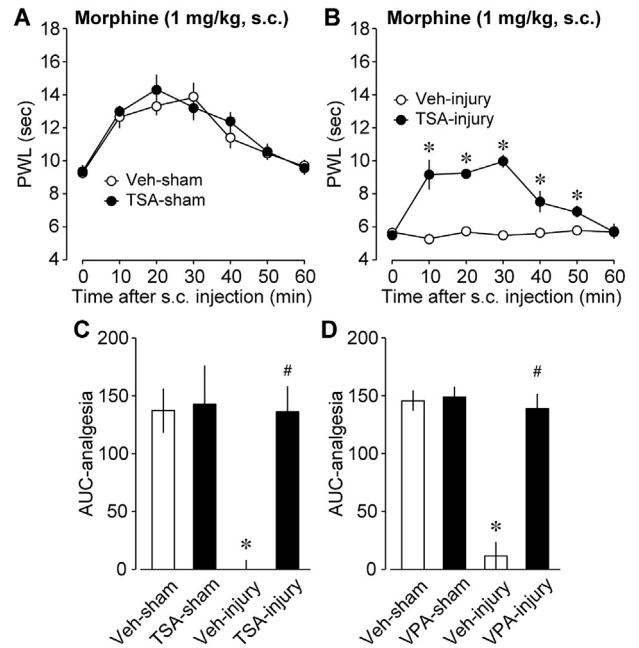


Fig. 2. Prevention of injury-induced loss of systemic morphine analgesia by HDAC inhibitors. TSA (1 mg/kg, i.p.) or VPA (200 mg/kg, i.p.) was administered 60 min or 120 min prior to injury, respectively, and once daily for 3 days after nerve injury. Thermal pain threshold was assessed at day 3 post-injury, using a thermal paw withdrawal test. A and B) Time-courses of thermal paw-withdrawal latencies (PWL, in seconds) after morphine (1 mg/kg, s.c.) injection in sham-operated mice (A) and nerve-injured mice (B). * $P < 0.05$, vs. vehicle (Veh)-treated group. C and D) Comparison of morphine analgesia after TSA (C) and VPA (D) treatments by area under the curve (AUC). * $P < 0.05$, vs. Veh-treated and sham-operated group and # $P < 0.05$, vs. Veh-treated and nerve-injured group. Data are expressed as the means \pm SEM from at least five mice.

on the systemic morphine analgesia in sham-operated mice (Fig. 2: A, C, D).

To test whether HDAC inhibitors could block injury-induced MOP down-regulation, we isolated L4–6 DRGs at day 3 post-injury, and mRNA expression levels were quantified by real-time PCR. Injury-induced reduction of MOP mRNA expression was significantly recovered by treatments with TSA and VPA (Fig. 3: A, B). In contrast, these agents had no effects on MOP expression in sham-operated mice, in agreement with the behavioural data (Fig. 2).

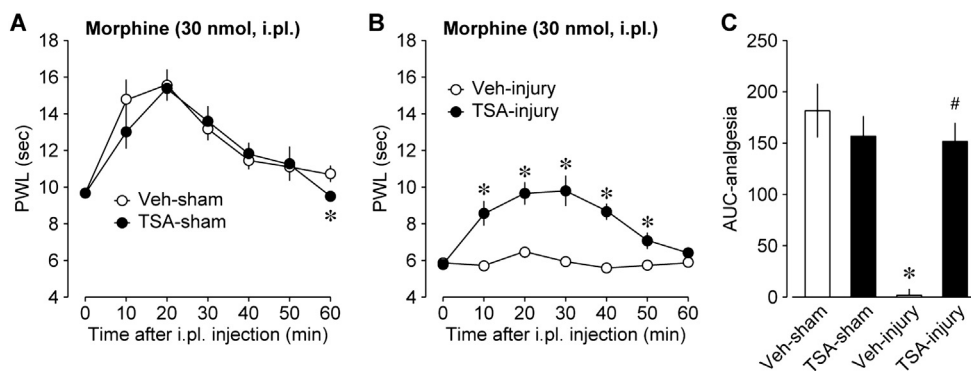


Fig. 1. Blockade of injury-induced loss of peripheral morphine analgesia by TSA. TSA (1 mg/kg, i.p.) was administered 60 min prior to injury and once daily for 7 days after nerve injury. Thermal pain threshold was assessed at day 7 post-injury, using a thermal paw withdrawal test. A and B) Time-courses of thermal paw-withdrawal latencies (PWL, in seconds) after intraplantar injection of morphine (30 nmol) in sham-operated mice (A) and nerve-injured mice (B). * $P < 0.05$, vs. vehicle (Veh)-treated group. C) Comparison of morphine analgesia by area under the curve (AUC). * $P < 0.05$, vs. Veh-treated and sham-operated group and # $P < 0.05$, vs. Veh-treated and nerve-injured group. Data are expressed as the means \pm SEM from at least ten mice.

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