Gabapentin Inhibits Bortezomib-Induced Mechanical Allodynia Through Supraspinal Action in Mice

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Abstract. Bortezomib, an inhibitor of proteasome holoenzyme, is used to treat relapsed and refractory multiple myeloma. Peripheral neuropathy is a treatment-limiting adverse effect of bortezomib and is very difficult to control. In this study, we examined the efficacy of gabapentin in inhibiting bortezomib-induced peripheral neuropathy. Single intravenous injections of bortezomib (0.03 – 0.3 mg/kg) dose-dependently induced mechanical allodynia with a peak effect 12 days after injection. Bortezomib (0.3 mg/kg) also caused mechanical hyperalgesia, but neither affected thermal nociception nor induced cold allodynia. Bortezomib increased the response of the saphenous nerve to weak punctate stimulation but not response to cool stimulation of the skin. When administered 12 days after bortezomib injection, oral and intracisternal gabapentin markedly inhibited mechanical allodynia. Intrathecal, but not intraplantar, gabapentin had a tendency to reduce mechanical allodynia. The antiallodynic activity of orally administered gabapentin was suppressed by noradrenaline, but not serotonin, depletion in the spinal cord. Bortezomib did not affect the expression levels of the calcium channel α₂δ-1 subunit, a high-affinity binding site of gabapentin, in the plantar skin, spinal cord, medulla oblongata, and pons. These results suggest that gabapentin inhibits bortezomib-induced mechanical allodynia, most likely through the activation of the descending noradrenergic system.

Keywords: bortezomib, gabapentin, allodynia, descending noradrenergic system, noradrenaline

Introduction

Bortezomib, an inhibitor of 26S proteasome holoenzyme, is used to treat relapsed multiple myeloma and mantle cell lymphoma (1, 2). Adverse effects of bortezomib include peripheral neuropathy, asthenia, constipation, diarrhea, nausea, and anorexia (3). Peripheral neuropathy occurs in approximately 50% of bortezomib-treated patients (3, 4), and 40% of patients with peripheral neuropathy complain of dysesthesia (unpleasant abnormal sensation) and/or pain (4). Bortezomib-induced dysesthesia and pain tend to have a “stocking and glove” distribution (5). The incidence of bortezomib-induced peripheral neuropathy gradually increases and reaches a plateau after eight cycles of therapy (6). Peripheral neuropathy is the most common adverse event leading to treatment discontinuation (3, 6), although it disappears after treatment cessation or a decrease of the dose administered (6).

Several kinds of rodent models of bortezomib-induced peripheral neuropathy have been developed and the morphological, histological, and neurophysiological changes have been analyzed (7 – 11). However, there is no established standard treatment protocol for bortezomib-induced peripheral neuropathy. Gabapentin, an anticonvulsant, has proven to be effective in the treatment of painful diabetic neuropathy, postherpetic neuralgia, and other neuropathic pain syndromes (12). Recent animal studies showed that gabapentin is effective for the treatment mechanical allodynia (13 – 17), thermal

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Bortezomib was administered orally, intracerebrally, intrathecally, and intraarticularly 12 days after bortezomib administration. For depletion of monoamines in the spinal cord, 6-OHDA (20 μg/mouse) and 5,7-DHT (20 μg/mouse) were injected intrathecally 9 days after bortezomib administration. Desipramine hydrochloride was injected intraperitoneally 30 min before 5,7-DHT injection to block 5,7-DHT uptake into the noradrenergic nerve terminals (19). The volume of intravenous, oral, and intraperitoneal injections was 0.1 ml/10 g body weight. Intracisternal and intrathecal injections were administered in a volume of 5 μl, and intraplantar injection was in a volume of 20 μl.

**Materials and Methods**

**Animals**

Male C57BL/6NCr mice (Japan SLC, Shizuoka), 6 weeks of age at the beginning of the experiments, were used. The mice were housed in a room under controlled temperature (21°C – 23°C), humidity (45% – 65%), and light (lights on from 07:00 to 19:00). Food and water were freely available. Procedures involving animals were approved by the Committee for Animal Experiments at the University of Toyama and were conducted in accordance with the guidelines for investigations of experimental pain in animals published by the International Association for the Study of Pain.

**Materials**

Bortezomib (Toronto Research Chemicals, Ltd., Toronto, Canada) was dissolved in a physiological saline solution containing 0.03% (w/v) mannitol just before use. Gabapentin was synthesized by YS and HT and dissolved in regular tap water for oral administration and in a physiological saline solution for intrathecal, intracisternal, and intraplantar injections. 6-Hydroxydopamine hydrochloride (6-OHDA; Sigma-Aldrich, St. Louis, MO, USA) and 5,7-dihydroxytryptamine creatinine sulfate (5,7-DHT, Sigma-Aldrich) were dissolved in physiological saline solution containing 0.1% ascorbic acid. Desipramine hydrochloride (Sigma-Aldrich) was dissolved in a physiological saline solution.

**Drug administration**

Bortezomib was administered intravenously. The regular clinical dose of bortezomib is 5.2 mg/m² body surface area per cycle (1.3 mg/m² is administered intravenously 4 times for 2 weeks). If body height and weight are 170 cm and 60 kg, respectively, body surface area is 1.69 m², according to Du Bois’s formula for calculating the body surface area. Therefore, the total dose to administer is 8.8 mg per person or 0.15 mg/kg. Thus, in this study, bortezomib was administered at doses of 0.03 to 0.3 mg/kg. Higher doses of bortezomib were not examined because of its limited solubility in the vehicle.

Gabapentin was administered orally, intracerebrally, intrathecally, and intraarticularly 12 days after bortezomib administration. For depletion of monoamines in the spinal cord, 6-OHDA (20 μg/mouse) and 5,7-DHT (20 μg/mouse) were injected intrathecally 9 days after bortezomib administration. Desipramine hydrochloride was injected intraperitoneally 30 min before 5,7-DHT injection to block 5,7-DHT uptake into the noradrenergic nerve terminals (19). The volume of intravenous, oral, and intraperitoneal injections was 0.1 ml/10 g body weight. Intracisternal and intrathecal injections were administered in a volume of 5 μl, and intraplantar injection was in a volume of 20 μl.

**Behavioral experiments**

In the first series of experiments, individual mice underwent either allodynia (mechanical and cold allodynia) tests or hyperalgesia (mechanical and thermal hyperalgesia) tests. For habituation to experimental procedures, the mice underwent scheduled behavioral test(s) for 3 days before bortezomib administration.

Mechanical allodynia was evaluated using a fine von Frey filament of a bending force of 0.69 mN (North Coast Medical Inc., Morgan Hill, CA, USA) (20). The mice were placed individually in an acrylic cage (11 × 18 × 15 cm) with a wire mesh bottom. After an acclimation period of at least 30 min, the von Frey filament was pressed perpendicularly against the central part of the plantar hind paw of freely-moving mice and was held there for 1 – 3 s by slight buckling. Responses to the stimulus were scored as follows: 0, no reaction; 1, lifting of the hind paw; 2, licking and flinching of the hind paw. Stimulations were applied to each hind paw three times at intervals of several seconds, and the allodynia score (the total score of six tests) was expressed as the percentage of a maximum score of 12.

Mechanical hyperalgesia was evaluated by the tail-pressure method, using an Analgesy-Meter apparatus (Ugo Basile, Milan, Italy). The mice were held by the hands, pressure was applied to the base of the tail by a wedge-shaped pusher at a loading rate of 32 g/s with a cut-off of 250 g, and the weight of stimulation eliciting either tail withdrawal or a struggling response was determined as a nociceptive threshold (21).

Thermal nociception was evaluated by the radiant heat method, using a tail-flick apparatus Type 7360 (Ugo Basile). The mice were held by the hands, radiant heat was applied to the plantar hind paws from underneath, and the latency of paw withdrawal was automatically determined (22). The intensity of radiant heat was adjusted to elicit a response around 13 s in normal mice. Stimations were applied twice to each hind paw at intervals of more than 10 min, and the average of 4 tests

hyperalgesia (16), and cold hyperalgesia (18), induced by other chemotherapy agents, including paclitaxel, oxaliplatin, and vincristine. Because bortezomib has been recently developed, it is unclear whether gabapentin is effective for pain and dysesthesia in bortezomib-induced peripheral neuropathy models. In the present study, we therefore examined whether a single administration of bortezomib would cause pain-related behaviors in mice and whether gabapentin could inhibit bortezomib-induced pain-related behaviors.
was considered nociceptive latency.

For the evaluation of cold allodynia, the plantar hind paw was stimulated with acetone (23). The mice were placed individually in an acrylic cage (11 × 18 × 15 cm) with a wire mesh bottom. After an acclimation period of at least 30 min, a droplet of acetone was applied to the plantar skin of freely-moving mice. Response scoring was performed similarly to that of mechanical allodynia, although responses were observed between 3 and 20 s after application. Because paw lifting is generally observed immediately (within a few seconds) after acetone stimulation in healthy mice, this behavior was ignored. Stimulations were applied twice to each hind paw at intervals of more than 20 s, and the cold allodynia score (the total score of four tests) was expressed as the percentage of a maximum score of 8.

Electrophysiological recording

The saphenous nerve activity was recorded on day 12 after bortezomib injection. Mice were anesthetized with sodium pentobarbital (80 mg/kg, intraperitoneal; Sigma-Aldrich). The animals were turned on their back, and the skin and muscles were excised to expose the saphenous nerve. Extracellular recording of nerve activity was performed using bipolar electrodes made of silver wire (Unique Medical Co., Ltd., Tokyo) and an AC bioelectric amplifier (AB651; Nihon Kohden, Tokyo) with a band-pass filter (high-cut filter, 3 kHz; low-cut filter, 150 Hz). Thirty minutes after the beginning of the recording, spontaneous firing was measured for 10 min, followed by firing induced by punctate stimulations with the von Frey filament (0.69 mN strength, for 10 s) and acetone application (10 μl/site). Compound action potentials were analyzed with spike height histogram software (PowerLab/8s; AD Instruments Pty, Castle Hill, Australia).

Measurement of monoamine contents

Monoamine contents were determined as previously reported (19). On day 12 after bortezomib injection, the spinal cord was excised after the behavioral examination and homogenized in 0.2 M perchloric acid containing 100 mM ethylenediaminetetraacetic acid disodium and 100 ng 3,4-dihydroxybenzylamine hydrobromide (Sigma-Aldrich) as an internal standard. Homogenates were centrifuged at 20,000 × g for 10 min at 4°C. The supernatant was filtered through a 0.45-μm membrane filter, and the pH was adjusted to 3.0 with sodium acetate. Monoamines were determined using a high-performance liquid chromatography with an Eicom SC-500DS column (3.0 mm inner diameter × 150 mm; Eicom, Kyoto) and an electrochemical detector (HTEC-500, Eicom), which was set at a potential +750 mV against an Ag/AgCl reference electrode. The mobile phase consisted of 0.1 M acetate–citrate buffer (pH 3.5), 190 mg/l sodium 1-octanesulfonate, 5 mg/l ethylenediaminetetraacetic acid disodium, and 17% methanol. The flow rate was maintained at 0.5 ml/min.

Western blotting

Twelve days after bortezomib injection, the mice were euthanized by transcardiac perfusion of phosphate-buffered saline (PBS) under pentobarbital anesthesia (80 mg/kg, intraperitoneal). The pons, medulla oblongata, spinal cord (L4 and L5 levels), and plantar skin were excised, and proteins were extracted from the tissue samples with a lysis buffer (20 mM Tris HCl pH 7.5, 137 mM NaCl, 1% NP-40, 10% glycerol, 1 mM phenylmethyl sulfonyl fluoride, 10 μg/ml aprotinin, and 1 μg/ml leupeptin). The extracted proteins (20 μg) were separated by electrophoresis using a 10% sodium dodecyl sulfate–polyacrylamide gel and transferred to polyvinylidene difluoride membranes. After blocking with a 5% skim milk solution for 1 h, the membranes were incubated with rabbit anti-α2δ-1 subunit antibody (Alomone Labs, Jerusalem, Israel) or rabbit anti-glycer-aldehyde 3-phosphate dehydrogenase antibody (Imgenex Co., San Diego, CA, USA) overnight at 4°C. After several washes, the membranes were incubated with horseradish peroxidase–conjugated anti-rabbit immunoglobulin G antibody (GE Healthcare, Buckinghamshire, UK) for 90 min at room temperature and then treated with chemiluminescence reagents (GE Healthcare). Chemiluminescent signals were detected using using a normal radiography and analyzed with an NIH Image software. The data were normalized to the level of glyceraldehyde 3-phosphate dehydrogenase.

Data processing

Data were represented as the mean ± standard error of the mean (S.E.M.). Statistical significance was analyzed by one-way analysis of variance (ANOVA) or two-way repeated measures ANOVA followed by the post-hoc Tukey’s honestly significant difference test, except for electrophysiological data that was analyzed with Student’s t-test. A P-value < 0.05 was considered statistically significant.

Results

Mechanical hypersensitivities, thermal hyperalgesia, and cold allodynia after bortezomib administration

Single intravenous injections of bortezomib (0.03 – 0.3 mg/kg) dose-dependently induced mechanical allodynia (Fig. 1A). A single injection of bortezomib (0.3 mg/kg) also induced mechanical hyperalgesia (Fig. 1B). These effects started to appear 3 days after bortezomib admin-
istration, peaked on day 12, and almost disappeared by day 24 (Fig. 1: A and B). On the other hand, bortezomib (0.3 mg/kg) neither induced cold allodynia nor affected nociceptive responses to heat stimulation (Fig. 1: C and D).

Effects of bortezomib on saphenous nerve activity
The spontaneous and evoked activities of the saphenous nerve were compared between bortezomib- and vehicle-administered mice on day 12 after administration. Bortezomib had a tendency to increase the spontaneous activity of the saphenous nerve (Fig. 2). The responses to punctate stimulation with a fine von Frey filament (0.69 mN strength) were significantly increased after bortezomib administration, whereas the responses to acetone stimulation were not significantly increased (Fig. 2).

Effects of gabapentin on bortezomib-induced mechanical allodynia
The effects of gabapentin on bortezomib-induced mechanical allodynia were examined on day 12 after bortezomib (0.3 mg/kg) administration. Oral administration of gabapentin (30 and 100 mg/kg) produced a significant dose-dependent inhibition of mechanical allodynia. The effects peaked 1 h after gabapentin administration and almost disappeared after 6 h (Fig. 3A). Intracisternal injections of gabapentin (30 and 100 μg/site) also produced a significant, dose-dependent inhibition of mechanical allodynia. The effects peaked 30 min after injection and almost disappeared after 2 h (Fig. 3B). Intraplantar injections of gabapentin (30 and 100 μg/site) had a tendency to reduce mechanical allodynia but this apparent difference was not statistically significant (Fig. 3C). Intraplantar injections of gabapentin (30 and 100 μg/site) did not affect mechanical allodynia for 3 h after administration (Fig. 3D).

Effects of intrathecal neurotoxins on the antiallodynic action of gabapentin
Three days after intrathecal injection of the catecholaminergic neurotoxin 6-OHDA (Fig. 4A), the noradrenaline content in the spinal cord was markedly and significantly reduced in these mice compared to that in the vehicle-treated mice (VH2-treated groups), although dopamine and 5-hydroxytryptamine contents were unaffected (Fig. 4B). Treatment with 6-OHDA did not affect mechanical allodynia on day 12 after bortezomib (0.3 mg/kg) administration; allodynia scores before gabapentin administration were 1.11 ± 0.09 and 1.25 ± 0.06 (n = 6 each) in the gabapentin + VH2 and gabapentin + 6-OHDA groups, respectively. In mice treated with 6-OHDA, gabapentin (100 mg/kg) inhibited mechanical allodynia, but the effects were significantly reduced compared to the gabapentin + VH2 group (Fig. 4C).

Three days after intrathecal injection of the serotonergic neurotoxin 5,7-DHT (Fig. 4D), the 5-hydroxytryptamine content in the spinal cord was markedly and significantly reduced in these mice compared to that in vehicle-treated mice (VH3-treated groups), although noradrenaline and dopamine contents were unaffected (Fig. 4E). Treatment with 5,7-DHT did not affect mechanical allodynia on day 12 after bortezomib administration; allodynia scores before gabapentin administration were 1.19 ± 0.05 and 1.28 ± 0.04 (n = 6 each) in
gabapentin + VH3 and gabapentin + 5,7-DHT groups, respectively. Pretreatment with 5,7-DHT did not affect the antiallodynic action of gabapentin (100 mg/kg) (Fig. 4F).

Effects of bortezomib on the expression of the calcium channel $\alpha_\delta$-1 subunit in the skin, spinal cord, medulla oblongata, and pons

The calcium channel $\alpha_\delta$-1 subunit was substantially expressed in the plantar skin, spinal cord, medulla oblongata, and pons. Single intravenous injection of bortezomib (0.3 mg/kg) did not affect the expression level of the $\alpha_\delta$-1 subunit in these regions examined 12 days after bortezomib administration (Fig. 5).

Discussion

Patients treated with bortezomib report pain after light touch, and burning pain worsens during walking and manual activities such as knitting or typing (5). Thus, bortezomib induces mechanical allodynia and/or mechanical hyperalgesia in humans. In the present study, a single intravenous injection of bortezomib induced mechanical allodynia and mechanical hyperalgesia in mice. These results are consistent with those observed by other groups, which reported the mechanical hyperalgesic effects of bortezomib in rats (9 – 11). We also observed on the day when mechanical allodynia peaked that bortezomib (0.3 mg/kg) significantly increased the activity of the saphenous nerve after punctate stimulation with a fine von Frey filament. These results suggest that bortezomib-induced mechanical allodynia is mediated by the increased reactivity of primary afferents to tactile stimulation.

In patients with myeloma, bortezomib increases heat pain threshold, suggesting thermal hypoalgesia (5). Similarly, bortezomib (a cumulative dose of 12 mg/kg) has been shown to induce thermal hypoalgesia in mice (7). However, in the present study, bortezomib (0.3 mg/kg) did not affect heat nociceptive responses in mice, which is consistent with another study in rats using a cumulative dose of 4.8 mg/kg bortezomib (10). Thus, it is suggested that thermal hypoalgesia might occur when using higher doses of bortezomib and that C-fiber function is not inhibited under our experimental conditions.

Bortezomib (0.3 mg/kg) did not induce cold allodynia in the acetone test and did not affect the reactivity of primary afferents to acetone stimulation. Regarding cold sensitivity, repeated administration of bortezomib (0.2 mg/kg per day, a total of 1 mg/kg) was reported to cause long-lasting cold allodynia in rats (11). However, repeated administration of bortezomib (0.8 mg/kg per day, a total of 6.4 mg/kg) was reported not to affect the temperature of cold response threshold (9.4°C – 10.5°C) in mice (24). The reason for the discrepancies is unclear except for species differences. In patients with myeloma, bortezomib does not affect the temperature of cool detection threshold (approximately 28°C), but it increases pain threshold to skin cooling from 3°C (healthy subjects) to approximately 10°C (5). Thus, we do not exclude the possibility that bortezomib causes cold hyperalgesia, for example, an increase in pain-like behavioral responses to ice-cold stimulation in mice.

Treatment with 6-OHDA or 5,7-DHT that selectively
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decreased the contents of noradrenaline or serotonin, respectively, in the spinal cord did not affect bortezomib-induced allodynia. Therefore, it is suggested that bortezomib-induced allodynia is not due to changes in the function of the descending noradrenergic or serotonergic system.

Bortezomib-induced mechanical allodynia was markedly inhibited after systemic administration of gabapentin. Gabapentin has been shown to inhibit mechanical allodynia induced by other chemotherapeutic agents such as paclitaxel (13, 16) and oxaliplatin (13, 18). In the present study, bortezomib-induced mechanical allodynia was markedly inhibited by intracisternal injections of gabapentin, whereas gabapentin intrathecal injections were less effective, and intraplantar injections had no effect on the allodynia. These results suggest that gabapentin inhibits bortezomib-induced allodynia mainly through its supraspinal action and that its actions on primary sensory neurons and spinal neurons are minimal in bortezomib-treated mice. In contrast to bortezomib-induced mechanical allodynia, intrathecal injections of gabapentin have been shown to markedly inhibit paclitaxel-induced mechanical allodynia (13). Thus, the mechanisms of the antiallodynic action of gabapentin seem to be different, depending on the type of chemotherapeutic agents.

The N-type voltage-dependent calcium channel in the primary sensory neuron has been claimed to be involved in the antinociceptive effect of intrathecal gabapentin (25). The $\alpha_2\delta-1$ subunit of the voltage-dependent calcium channel has been shown to be a key gabapentin binding site mediating its antiallodynic action (26). Paclitaxel increases the expression of the $\alpha_2\delta-1$ subunit in the spinal dorsal horn and dorsal root ganglia (13, 16), and oxaliplatin increases the expression of the $\alpha_2\delta-1$ subunit in the dorsal root ganglia (13). The $\alpha_2\delta-1$ subunit is mainly present in small-sized dorsal root ganglion neurons, and paclitaxel increases the number of medium/large-sized dorsal root ganglion neurons expressing the $\alpha_2\delta-1$ subunit (16). Paclitaxel decreases thresholds for activation of $A\delta$- and $A\beta$-fibers (mainly the axons of medium/large-sized dorsal root ganglion neurons) (16). These findings taken together suggest that the up-regulation of the $\alpha_2\delta-1$ subunit in the A-fiber sensory neurons is associated with the antiallodynic effect of gabapentin mediated by its action on primary sensory neurons. However, in the present study, western blot analyses showed that bortezomib did not affect the expression level of the $\alpha_2\delta-1$ subunit in the spinal cord and plantar skin. Thus, it is suggested that bortezomib does not up-regulate the $\alpha_2\delta-1$ subunit in the A-fiber sensory neurons, which may be a reason for the minimal or no antiallodynic effects after intrathecal and intraplantar gabapentin injections in bortezomib-treated mice.

The antiallodynic effects observed after systemic administration of gabapentin were partially but significantly reduced by noradrenaline depletion but not by serotonin depletion in the spinal cord. The reduction of antiallodynic activity of systemic administration of gabapentin was not due to changes in allodynia after noradrenaline depletion because intrathecal treatment with 6-OHDA did not affect bortezomib-induced allodynia. Thus, it is suggested that the descending noradrenergic system is involved in the antiallodynic action
of gabapentin in bortezomib-treated mice. This idea is consistent with the result that an intracisternal injection of gabapentin inhibited bortezomib-induced allodynia. In a mouse model of surgery-induced peripheral neuropathy, the antiallodynic effects of gabapentin after systemic and intracerebroventricular injections were reduced by intracisternal pretreatment with 6-OHDA (27). In the locus coeruleus, a nucleus of origin of the descending noradrenergic system (28), \( \gamma \)-aminobutyric acid (GABA) released from GABAergic neurons was shown to regulate the activity of descending noradrenergic neurons (29, 30). Moreover, the calcium channel \( \alpha_2\delta-1 \) subunit is highly expressed in the locus coeruleus (31), and it has been shown that gabapentin can activate descending noradrenergic neurons through a disinhibition of GABAergic neurons in the locus coeruleus (32). Taken together, these findings suggest that the antiallodynic effects of gabapentin in bortezomib-treated mice result from the activation of descending noradrenergic neurons via the disinhibition of GABAergic neurons in the locus coeruleus. However, bortezomib did not affect the expression level of the calcium channel \( \alpha_2\delta-1 \) subunit in the pons that includes the locus coeruleus. Thus, increasing the expression of the \( \alpha_2\delta-1 \) subunit does not seem necessary for the descending noradrenergic system–mediated antiallodynic action of gabapentin.
Moreover, it has been shown that gabapentin can inhibit the release of excitatory amino acids in the spinal dorsal horn and regulate glutamatergic synaptic transmission in conditions where the \( \alpha_{2}\delta-1 \) subunit expression level is normal (33, 34). Thus, it is possible that presynaptic mechanisms are also responsible for the antiallodynic effects of gabapentin.

In summary, bortezomib induced mechanical allodynia and hyperalgesia, but not thermal hypoalgesia/hyperalgesia and cold allodynia in mice. Gabapentin attenuated bortezomib-induced mechanical allodynia most likely through supraspinal activation of the descending noradrenergic system. Gabapentin may be effective for the management of mechanical allodynia and hyperalgesia in patients treated with bortezomib.

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Conflicts of Interest

The authors declare no conflicts of interest.

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