Biochemical and Biophysical Research Communications 444 (2014) 415–419

Contents lists available at ScienceDirect

Biochemical and Biophysical Research Communications

journal homepage: www.elsevier.com/locate/ybbrc

Role of nerve growth factor-tyrosine kinase receptor A signaling in paclitaxel-induced peripheral neuropathy in rats

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ARTICLE INFO

Article history:
Received 14 January 2014
Available online 27 January 2014

Keywords:
Paclitaxel
Nerve growth factor
Tyrosine kinase receptor A
Peripheral neuropathy
Dorsal root ganglia
Spinal dorsal horn

ABSTRACT

The mechanisms underlying paclitaxel-induced peripheral neuropathy remain unknown. Nerve growth factor (NGF) is a representative neurotrophic factor that maintains neuronal function, promotes survival, and mediates neuropathic pain. We investigated expression levels of NGF and its receptors in the dorsal root ganglia (DRG) and spinal dorsal horn (DH) following paclitaxel treatment. Intraperitoneal (I.P.) administration of paclitaxel induced significant mechanical hypersensitivity and cold allodynia in rats, significantly increased the expression of NGF and its receptor tyrosine kinase receptor A (trkA) in the DRG, and increased NGF expression in the DH. In contrast, paclitaxel treatment did not alter the mRNA levels of NGF or its receptors in the DRG, DH, sciatic nerve, or hindpaw skin. Moreover, expression of NEDD4-2, a negative regulator of trkA, was significantly increased in the DRG of paclitaxel-treated rats. Intrathecal (I.T.) administration of the tyrosine kinase receptor inhibitor k252a significantly alleviated mechanical hypersensitivity in paclitaxel-treated rats. Our results suggest that NGF–trkA signaling is involved in mechanical allodynia in paclitaxel-induced neuropathy.

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1. Introduction

Paclitaxel is an antineoplastic drug commonly used to treat solid tumors, but peripheral neuropathy is one of its major adverse effects. The incidence of paclitaxel-induced neuropathy correlates with cumulative dose and dose per cycle [1], and the associated clinical symptoms are hypoesthesia, paresthesia, and distal extremity pain in a “glove and stocking” pattern [2]. Preventing and treating paclitaxel-induced peripheral neuropathy are major concerns in clinical cancer therapy.

The antineoplastic mechanism of paclitaxel is that it stabilizes tubulin and promotes microtubule assembly, but these changes disrupt axonal transport, which is thought to induce peripheral neuropathy [3]. Mitochondrial toxicity in axons [4], increased $\alpha_2\delta$ calcium channel subunit expression in the spinal dorsal horn (DH) [5], and other mechanisms [6] have been proposed for paclitaxel-induced peripheral neuropathy, but the detailed mechanisms have not been fully elucidated.

Nerve growth factor (NGF) is an important neurotrophin for neuronal development and survival [7]. It is also involved in nociception and neuropathic pain [8,9]. Systemic NGF administration has been shown to cause hyperalgesia in adult rats [9]. In neuropathic animal models, NGF levels are increased in the dorsal root ganglia (DRG) [10,11], DH [10,12], and peripheral nerves [12]. NGF binds to tyrosine kinase receptor A (trkA), the high-affinity receptor of NGF, and the resulting complex provokes signals that promote the production of several peptides, thereby facilitating

Abbreviations: BDNF, brain-derived neurotrophic factor; DH, spinal dorsal horn; DRG, dorsal root ganglia; I.P., intraperitoneal; I.T., intrathecal; NEDD4-2, neural precursor cell-expressed developmentally downregulated 4-2; NGF, nerve growth factor; p75NTR, p75 neurotrophin receptor; qPCR, quantitative real-time polymerase chain reaction; SKIN, hindpaw skin; SN, sciatic nerve; SNL, spinal nerve ligation; TrkA, tyrosine kinase receptor A; TrkB, tyrosine kinase receptor B.

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http://dx.doi.org/10.1016/j.bbrc.2014.01.082
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pain transmission [13]. Thus, NGF or NGF–trkA signaling could be a therapeutic target of neuropathic pain [13,14].

Conversely, NGF treatment alleviates behavioral and morphological changes in chronic constriction injury (CCI) animals [15]. Arrieta et al. reported that paclitaxel therapy decreased NGF levels in peripheral nerves, and all-trans retinoic acid increased NGF levels and alleviated neuropathy [16]. These effects were considered to result from NGF's ability to maintain neuronal function and survival.

In the present study, we sought to elucidate the roles of NGF and NGF–trkA signaling in paclitaxel-induced peripheral neuropathy by investigating the expression levels of NGF and its receptors in the DRG and DH of paclitaxel-treated rats.

2. Methods

2.1. Animals

Adult male Sprague–Dawley rats (Japan SLC Inc., Shizuoka, Japan) weighing 280–350 g were used. The rats were housed in groups of two per plastic cage on sawdust bedding, with food and water provided ad libitum under a fixed 12-h light–dark cycle (7:00–19:00). This investigation was approved by the Yokohama City University Institutional Animal Care and Use Committee (Approved number: F10-112, Yokohama, Japan).

2.2. Drug administration

Paclitaxel (Paclitaxel®, 100 mg/16.7 ml, Nippon-Kayaku, Tokyo, Japan; 8 mg/kg [1.33 ml/kg]) was diluted to 2.67 ml/kg with saline, and rats received intraperitoneal (I.P.) injections on days 0, 4, 7, and 11. The vehicle consisted of Cremophor EL® and 99.9% ethanol at a 1:1 ratio, and 1.33 ml/kg vehicle was diluted and I.P. injected into control rats as previously described [4,17].

2.3. von Frey test

Hind paw mechanical allodynia and hyperalgesia were tested using 4- and 15-g bending force von Frey filaments (NC12775-99, North Coast Medical Inc., San Jose, CA), which are thought to reflect mechanical allodynia and mechanical hyperalgesia, respectively [17]. Each filament was applied to the mid-planter skin of each hind paw five times until the force slightly bent the tip and was then held for 5 s. Withdrawal responses from both hind paws were counted, and the percentage response was calculated as previously described [4,17]. The test was performed on days 0, 4, 7, 11, 14, and 21 prior to drug administration.

2.4. Western blot analysis

After behavioral testing on day 21, rats were deeply anesthetized with an I.P. injection of sodium pentobarbital and perfused with saline. For protein assays, the spinal DH lumbar enlargements and bilateral DRGs (L4-6) were harvested. The bilateral sciatic nerves and bilateral skin of the hind paws were also harvested for mRNA isolation. Tissues were immediately frozen with liquid nitrogen and stored at −80 °C until protein extraction and RNA isolation.

Proteins were extracted from tissue using a ProteoExtract® Native Membrane Protein Extraction Kit (Calbiochem, San Diego, CA) according to the manufacturer's protocol, and we obtained membrane-enriched (for NGF and brain-derived neurotrophic factor [BDNF] receptors) and cytosolic fractions (for NGF, BDNF, and NEDD4-2). Protein concentrations were measured using a bicinchoninic acid (BCA) Protein Assay Kit (Thermo Fisher Scientific, Waltham, MA).

Sample extracts were dissolved in a loading buffer containing 125 mM Tris–HCl (pH 6.8), 20% glycerol, and 4% sodium dodecyl sulfate (SDS), and 10 μg total protein/sample were separated on a precast SDS–PAGE gel (12.5%; Atto Corp., Tokyo, Japan) and transferred to PVDF membranes. Rabbit anti-NGF-β (1:2500; Millipore, Billerica, MA, USA), rabbit anti-BDNF (1:2500; Abcam, Cambridge, UK), rabbit anti-trkA (1:2000, Millipore), rabbit anti-trkA (phospho Y490) antibody (1:500, Abcam), rabbit anti-trkB (1:1000, Abcam), rabbit anti-p75 NGF receptor (1:2000, Abcam), and rabbit anti NEDD4-2 (1:5000, Abcam) antibodies were used. Mouse anti-β-actin (1:100,000; Sigma–Aldrich, St. Louis, MO) was used as the loading control. Horseradish peroxidase (HRP)-conjugated anti-rabbit IgG (1:20,000; Bio-Rad, Hercules, CA) or HRP-conjugated goat anti-mouse IgG (1:20,000, Bio-Rad) was used as the secondary antibody. The immune complexes were detected by enhanced chemiluminescence (ECL Advance®; GE Healthcare, Buckinghamshire, UK) and visualized with a LAS3000-mini® (Fuji Film, Tokyo, Japan). The bands were densitometrically analyzed using Multi Gauge ver. 3.0 software (Fuji Film). NGF and BDNF bands were normalized to the β-actin band. Data are expressed relative to the control group mean and are shown as mean ± standard error of mean (SEM).

2.5. Quantitative real-time polymerase chain reaction (qPCR)

Total RNA was obtained from the DH, bilateral DRGs (L4-6), bilateral sciatic nerve, and the bilateral hindpaw skin using Sepasol RNA Super G (Nacalai Tesque, Kyoto, Japan) and reverse transcribed with ReverTra Ace® PCR RT Master Mix with genomic DNA Remover (Toyobo Co., Ltd., Osaka, Japan) according to the manufacturer's protocol.

The sequences of the primers used for NGF, TrkA, and β-actin were as follows: NGF primers, forward, 5′-ACCTCTTCGGACACTCTGG-3′, and backward, 5′-CGTGGCTGTGGTCTTATCTC-3′; trkA primers, forward, 5′-CCATGCTACAGCACCAACAC-3′, and backward, 5′-AAGGACCAGGAGCCACATC-3′; and β-actin primers, forward, 5′-TGACGTTGACATCCGTAAAGAC-3′, and backward, 5′-AGAGCCACCAATCCACACA-3′. qPCR was performed using a Bio-Rad iCycler® qPCR system and SYBR® Ex Premix taq™ (Takara Bio Inc., Shiga, Japan). The cycling conditions for all primer pairs were as follows: 5 s at 95 °C and 30 s at 60 °C, according to manufacturer's protocol. The ratios of NGF and trkA mRNA expression to the β-actin level in each sample were considered as the mRNA levels and are expressed relative to the mRNA levels of the control group [18]. Data are shown as mean ± SEM.

2.6. k252a administration

The rats were anesthetized with 2% isoflurane, and a small L5 laminectomy was performed to expose the dura. A PE-10 catheter (Clay Adams, Parsippany, NJ) was placed in intrathecal (I.T.) space of the lumbar spinal cord as previously described [11]. At least 6 days after catheter insertion, k252a (2 μg/20 μl, Sigma–Aldrich) or vehicle (saline containing 25% DMSO) was administered via the catheter 15 min prior to each paclitaxel injection on days 0, 4, 7, and 11. The von Frey tests were performed before each drug administration on days 0, 4, 7, and 11, and again on days 14 and 21.

2.7. Statistical analyses

Behavioral assays were analyzed with Bonferroni-adjusted Mann–Whitney *U*-tests to determine inter-group differences. Western blotting and qPCR results were analyzed with Student's *t*-tests. Data are shown as mean ± SEM.

3. Results

3.1. Paclitaxel induced mechanical hypersensitivity

Paclitaxel administration (8 mg/kg I.P., cumulative dose 32 mg/kg) evoked significantly more responses to 15-g stimuli on days 7, 14, and 21. In the 4-g von Frey test, paclitaxel-treated rats showed significantly more responses on day 21 (Fig. 1A and B).

3.2. Protein expression changes of NGF, BDNF, and their receptors

NGF, BDNF, trkA, phosphorylated trkA (p-trkA), and p75NTR expressions in DRG or DH were measured using protein extracted from tissues collected on day 21 (Fig. 2A). BDNF is known to be synthesized in the DRG and bind to tyrosine kinase receptor B (trkB) in the DH, where it acts as a neuromodulator [19,20]. Therefore, we only examined trkB protein levels in the DH. We observed significantly increased protein levels for NGF (+35.9%, $p < 0.01$), BDNF (+13.9%, $p < 0.05$), trkA (+223%, $p < 0.05$), and p-trkA (+195%, $p < 0.001$) in the DRG in the paclitaxel-treated group compared to the control group ($n = 6$/group, Fig. 2A). Only p75NTR protein levels were not significantly increased (+6.86%, NS).

As shown in Fig. 2B, DH NGF protein levels were increased (+24.6%, $p < 0.05$) in the paclitaxel-treated group compared to control ($n = 6$/group). Changes in BDNF (−4.09%), trkA (−17.3%), p75NTR (−8.67%), and trkB (−15.0%) protein levels were not statistically significant. p-trkA protein levels in the DH of paclitaxel-treated rats were under the detection threshold (Fig. 2E).

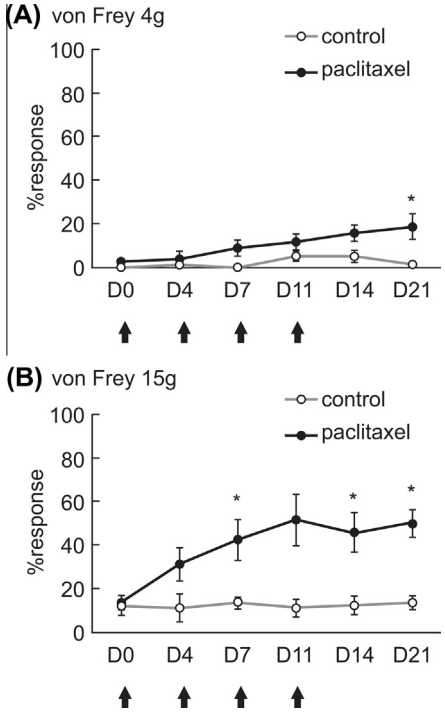

Fig. 1. Paclitaxel-induced mechanical allodynia and hyperalgesia. Rats received I.P. injections of paclitaxel (8 mg/kg) on days 0, 4, 7, and 11. Response ratios to von Frey 4 g (A), and 15 g (B) are shown. On day 21, the paclitaxel-treated group ($n = 7$–8) showed significantly more frequent responses to mechanical stimuli compared to the control group ($n = 8$). The arrows indicate paclitaxel or vehicle injection. Results are expressed as the mean ± SEM. *Statistically significant analyzed with Bonferroni-adjusted Mann–Whitney *U*-tests.

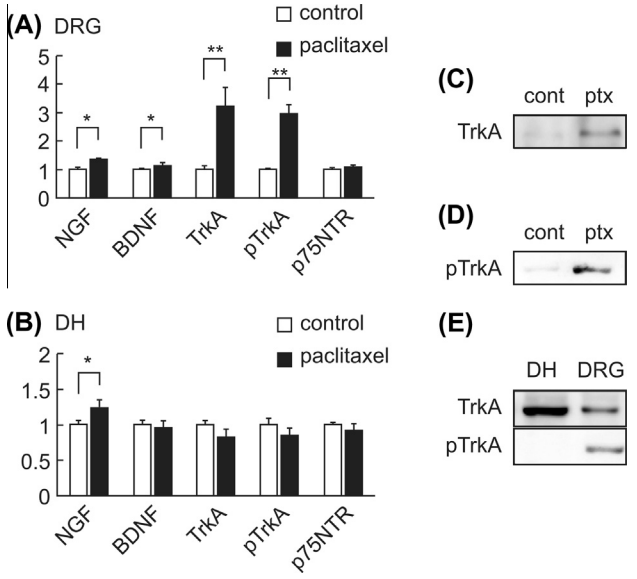

Fig. 2. Protein levels of NGF, BDNF, and their receptors in the DRG and lumbar DH. Protein levels of NGF, BDNF, trkA, and p-trkA were significantly increased in the bilateral L4–L6 DRG of the paclitaxel-treated group compared to the control group on day 21 (A). Paclitaxel treatment led to 3-fold increases in trkA (C) and p-trkA (D) levels in the DRG compared to control. In the lumbar DH, NGF protein levels were significantly increased in paclitaxel-treated rats compared to control rats on day 21 (B). p-trkA protein levels in the DH of paclitaxel-treated rats were under the detection threshold (E). Data are expressed relative to the mean of the control group and are shown as mean ± SEM. $n = 6$/group, $^{*}p < 0.05$ and $^{**}p < 0.01$ (Student's *t*-test).

3.3. Enhanced protein production and attenuated degradation did not increase trkA and p-trkA levels

We performed qPCR to examine mRNA expression levels in the DH, DRG, sciatic nerve (SN), and hindpaw skin (SKIN). No significant changes in NGF and trkA mRNA levels in the DH were found between the two groups, although NGF mRNA expression tended to be increased in the paclitaxel-treated group (+24.3%, $p = 0.07$, Fig. 3A). The two groups showed no significant differences in NGF and trkA mRNA levels in the DRG (Fig. 3B), SN, or SKIN (Fig. 3C and D).

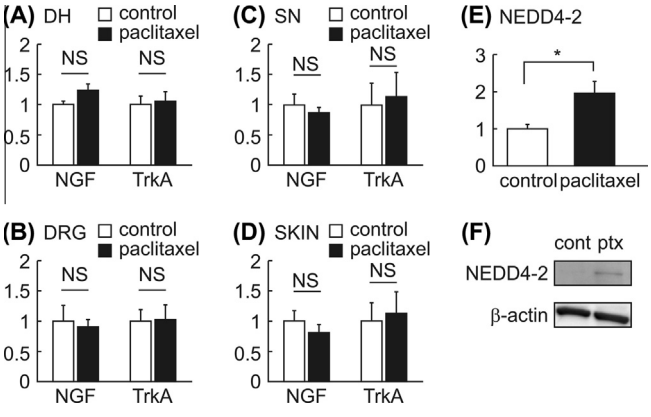

Fig. 3. NGF and trkA mRNA expression levels. No significant differences in NGF and trkA mRNAs levels were found in the lumbar DH (A), DRG (B), sciatic nerve (SN) (C), or SKIN (D) between the two groups. Data are expressed as relative to the mean of the control group and are shown as mean ± SEM. $n = 6$/group. NEDD4-2 protein levels increased in paclitaxel-treated rats. In DRGs, NEDD4-2 protein levels were significantly increased in the paclitaxel-treated group compared to control rats on day 21 (E). Representative Western blots are shown in (F). Data are expressed relative to the mean of the control group and are shown as mean ± SEM. $n = 6$/group, $^{*}p < 0.05$ (Student's *t*-test).

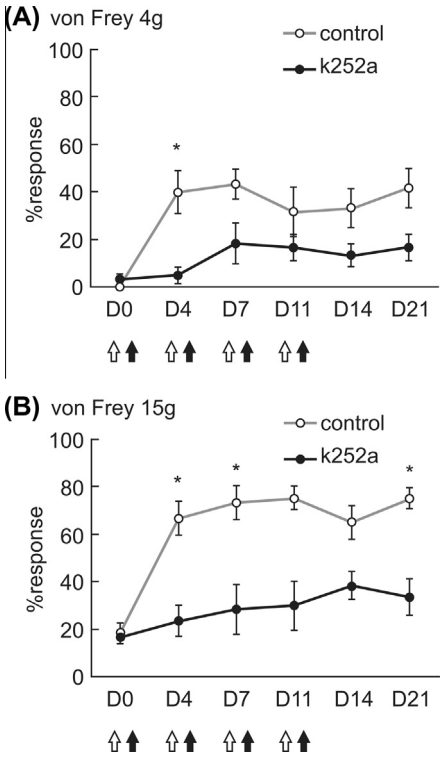

Fig. 4. Alleviation of paclitaxel-induced mechanical hyperalgesia by k252a treatment. Rats received I.T. injections of k252a (2 μg/20 μl in 25% DMSO) or vehicle (25% DMSO, 20 μl) 15 min prior to each paclitaxel injection. Mechanical hyperalgesia (von Frey 15 g) was significantly antagonized by k252a treatment on days 4, 7, and 21 (B). In the 4-g von Frey test (A), k252a treatment significantly reduced stimuli-induced responses on day 4. The open arrows indicate k252a or vehicle injection, and the closed arrows indicate paclitaxel injection. Results are expressed as the mean ± SEM. $n = 6$/group, *Statistically significant analyzed with Bonferroni-adjusted Mann–Whitney *U*-tests.

To elucidate the mechanism of increased trkA in the DRG following paclitaxel treatment, we performed Western blotting for NEDD4-2 (neural precursor cell-expressed, developmentally downregulated 4-2), which negatively regulates TrkA in the DRG. On day 21, NEDD4-2 was significantly increased (+97.4%, $p < 0.05$) in paclitaxel-treated rat DRG compared to control rats (Fig. 3E).

3.4. Effects of k252a on paclitaxel-treated rats

Because trkA and p-trkA DRG levels were markedly increased in paclitaxel-treated rats, we hypothesized that NGF–trkA signaling in the DRG could be associated with paclitaxel-induced hypersensitivity. k252a was administered I.T. simultaneously with paclitaxel, and mechanical hypersensitivity was assessed. No significant differences were observed between the two groups at baseline. k252a significantly reduced responses to 15-g von Frey filament forces on days 4, 7, and 21 (Fig. 4B). The antiallodynic effect of k252a on paclitaxel-treated rats was weak, but it significantly reduced the response to the 4-g von Frey filament on day 4 (Fig. 4A).

4. Discussion

We found that NGF protein levels were increased in the DRG and DH following paclitaxel treatment. trkA and p-trkA protein levels were also increased by 3-fold. However, mRNA levels of NGF and trkA were not increased in the DH, DRG, SN, or SKIN. We did find that paclitaxel administration led to a 2-fold increase of NEDD4-2, which negatively regulates trkA expression. Similarly, k252a alleviated paclitaxel-induced hyperalgesia.

NGF protein levels were increased in both the DH and DRG. NGF facilitates neuronal development and maintenance [7] and mediates neuropathic pain [8]. NGF levels increased in an L5 spinal nerve ligation (SNL) animal model, and anti-NGF antibody therapy prevented SNL-induced thermal hyperalgesia [11] and CCI [21]. Our results are in accordance with the CCI results reported by Vivoli et al. [10]. In contrast, a previous report suggested that decreased NGF levels in the SN might be involved in paclitaxel-induced peripheral neuropathy, and all-trans retinoic acid was shown to alleviate neuropathy and recover NGF levels [16]. Moreover, NGF treatment alleviated paclitaxel-induced thermal hyperalgesia and recovered substance P levels [22]. Those studies suggested that reduction of NGF levels in the SN due to inhibited retrograde axonal transport from peripheral tissues might lead to nerve degeneration [16,23]. However, we focused on the DRG and DH and found that NGF was increased in both regions in a model of paclitaxel-induced peripheral neuropathy.

We demonstrated 3-fold increases in trkA and p-trkA protein levels in L4-6 DRG after paclitaxel treatment. During nociceptive pain conduction, NGF binds to trkA expressed in the primary afferents of small fibers, and the NGF–trkA complex is retrogradely transported to the DRG, where it promotes the production of neuromodulators or ion channels that facilitate pain conduction to secondary neurons, resulting in sensitization [7,13,24]. Previous studies have shown that trkA mRNA and protein levels increase in the DRG of neuropathic or osteoarthritic animals [25,26], suggesting that increased trkA in the DRG could be related with pain development. We found that trkA and p-trkA increases were greater than that of NGF in the DRG of the paclitaxel-treated group. On the other hand, trkB expression tended to be reduced in the DH of paclitaxel-treated rats. Based on the existing evidence, we hypothesized that increased trkA and p-trkA levels in the DRG may mainly be attributed to paclitaxel-induced allodynia and hyperalgesia; therefore, we investigated the mechanisms underlying increased trkA and p-trkA in the DRG.

mRNA levels of trkA were not increased by paclitaxel. These results indicate that trkA protein synthesis is not increased and does not likely explain elevated trkA and p-trkA in the DRG.

Degradation also regulates trkA protein expression. The ubiquitin ligase NEDD4-2 is a negative regulator of sodium channels and downregulates trkA [27,28]. NEDD4-2 protein levels were 2-fold higher in the DRG of paclitaxel-treated rats compared to controls. We hypothesize that upregulation of NEDD4-2 in the DRG of paclitaxel-treated rats is a compensatory response to the increase of trkA or other proteins regulated by NEDD4-2.

Anterograde axonal transport dysfunction is one explanation for the trkA increase in the DRG. Paclitaxel stabilizes β-tubulin, promotes microtubule assembly, and also affects neuronal microtubules [3]. However, Flatters and Bennett demonstrated that microtubules were not affected by paclitaxel treatment [4]. Nakata and Yorifuji also reported that paclitaxel treatment did not alter microtubule morphology in SN, but it did functionally inhibit both anterograde and retrograde axonal transport [29]. However, we did not investigate anterograde axonal transport dysfunction, and whether it was a cause of paclitaxel-induced trkA increase in the DRG remains to be elucidated.

To evaluate whether NGF–trkA signaling is involved in paclitaxel-induced peripheral neuropathy, we assessed the effect of the tyrosine kinase receptor inhibitor k252a. Previous studies have shown that I.T. administration of substances, including small interfering RNA [30], protein [31], and k252a [32], could act in both spinal cord and the DRG. There were no significant increases in trkB levels in the DH, but we did note a 3-fold increase of trkA in the DRG following paclitaxel treatment. Furthermore, p-trkA was

under detection threshold in the DH of paclitaxel-treated rats. These results suggest that k252a mainly inhibited trkA in the DRG. Intrathecal k252a partially but significantly alleviated paclitaxel-induced mechanical hyperalgesia and allodynia at some time points. Thus, NGF–trkA signaling may be involved in paclitaxel-induced peripheral neuropathy. We suppose that NGF–trkA signaling has a role in paclitaxel-induced peripheral neuropathy, but it is not the only cause. Previous studies have shown that mitochondrial toxicity in axons [4], increased $\alpha_2\delta$ calcium channel subunit expression in the DH [5], tetrodotoxin-sensitive sodium channels [33], and other mechanisms [6] are also involved in paclitaxel-induced peripheral neuropathy.

We did not directly investigate anterograde axonal transport dysfunction due to technical difficulties. NEDD4-2 negatively regulates voltage-gated sodium channels [34] and is involved in pain development and transmission [35], so it is possible that these factors play a role in paclitaxel-induced peripheral neuropathy. Indeed, Nieto et al. reported that paclitaxel-induced neuropathy was inhibited by tetrodotoxin [33]. I.T. administration of k252a antagonized paclitaxel-induced mechanical hyperalgesia and tended to alleviate mechanical allodynia, but the optimal dose and administration of k252a remain to be defined.

5. Conclusion

In conclusion, we observed increased NGF and trkA levels in the DRG of rats with paclitaxel-induced peripheral neuropathy, and k252a partially attenuated pain behaviors. The mechanism of trkA increase in the DRG following paclitaxel treatment does not appear to involve increased protein synthesis or inhibited protein degradation. Our findings suggest that NGF–trkA signaling may play a role in paclitaxel-induced peripheral neuropathy.

Competing interests

The authors declare no competing interests.

Acknowledgments

We would like to thank Yuki Yuba, M.S. for technical assistance. Paclitaxel® was provided by Nippon-Kayaku Co., Ltd. This work was supported by Grants-in-Aid for Young Scientists (B) (Project No. 21791462) and Grants-in-Aid for Scientific Research (C) (Project No. 24592352) from the Ministry of Education, Science, Sports, and Culture of Japan to Y. Kamiya.

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