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*Original Article*

# Changes in TRPV1 Receptor, CGRP, and BDNF Expression in Rat Dorsal Root Ganglion with Resiniferatoxin-Induced Neuropathic Pain: Modulation by Pulsed Radiofrequency Applied to the Sciatic Nerve

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**Pulsed radiofrequency (PRF) is a safe method of treating neuropathic pain by generating intermittent electric fields at the needle tip. Resiniferatoxin (RTX) is an ultrapotent agonist of transient receptor potential vanilloid subtype-1 (TRPV1) receptors. We investigated the mechanism of PRF using a rat model of RTX-induced neuropathic pain. After administering RTX intraperitoneally, PRF was applied to the right sciatic nerve. We observed the changes in TRPV1, calcitonin gene-related peptide (CGRP), and brain-derived neurotrophic factor (BDNF) in the dorsal root ganglia by western blotting. Expressions of TRPV1 and CGRP were significantly lower in the contralateral (RTX-treated, PRF-untreated) tissue than in control rats ($p < 0.0001$ and $p < 0.0001$, respectively) and the ipsilateral tissues ($p < 0.0001$ and $p < 0.0001$, respectively). BDNF levels were significantly higher in the contralateral tissues than in the control rats ($p < 0.0001$) and the ipsilateral tissues ($p < 0.0001$). These results suggest that, while TRPV1 and CGRP are decreased by RTX-induced neuronal damage, increased BDNF levels result in pain development. PRF may promote recovery from neuronal damage with concomitant restoration of TRPV1 and CGRP, and exert its analgesic effect by reversing BDNF increase. Further research is required to understand the role of TRPV1 and CGRP restoration in improving mechanical allodynia.**

**Key words:** pulsed radiofrequency, resiniferatoxin, transient receptor potential vanilloid subtype-1 (TRPV1), calcitonin gene-related peptide (CGRP), brain-derived neurotrophic factor (BDNF)

Neuropathic pain occurs due to damage to the peripheral and/or central nerves and causes symptoms such as spontaneous pain, hyperalgesia, and allodynia [1]. These mechanisms are complex and have not been elucidated in detail. Pulsed radiofrequency (PRF) is a treatment with certified efficacy for treating neuropathic pain [2, 3]. Sluijter *et al.* were the first to use PRF to relieve chronic pain [2]. In this process, the PRF generator generates intermittent electromagnetic waves (here, 20-ms pulses of 50,000 Hz at intervals of 500 ms for 6 min) with a maximum temperature of 42°C at the electrode tip, which is inserted into the tissues close to the target nerve. PRF has been used clinically as a popular pain treatment modality, and its pain relief effect persists for weeks or months. Several randomized controlled trials have reported its efficacy in treating radicular pain [4-6]. Other reports have demonstrated the efficacy of PRF for intransigent pain [7, 8], and the indications for PRF have been expanding.

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Resiniferatoxin (RTX), an ultrapotent transient receptor potential vanilloid subtype-1 (TRPV1) agonist, has been used to study the action of nociceptive C-fiber afferents [9]. The depletion of RTX-sensitive unmyelinated afferents with TRPV1 receptors has been shown to produce long-lasting paradoxical changes in adult rats: diminishing thermal sensitivity but increasing sensitivity to tactile stimulation. Interestingly, these effects mimic the unique clinical features of postherpetic neuralgia. We previously reported the efficacy of PRF in a rat model of neuropathic pain induced by RTX, especially regarding the influence of the duration of mechanical allodynia before the PRF procedures and the PRF exposure time [10, 11].

Pain-related receptors and neuropeptides, such as TRPV1, calcitonin gene-related peptide (CGRP), and brain-derived neurotrophic factor (BDNF), play important roles in the generation and development of neuropathic pain [12-14]. However, the modulation of the expression of these pain-related molecules by PRF in RTX-induced neuropathic pain has not been investigated in depth. Therefore, we hypothesized that PRF irradiation of the sciatic nerve would improve RTX-induced neuropathic pain by altering pain-related molecules. Thus, in this study, we evaluated changes in the expression levels of TRPV1, CGRP, and BDNF in the bilateral dorsal root ganglia (DRG) of rats with RTX-induced neuropathic pain treated unilaterally with PRF.

## Materials and Methods

***Animals.*** This study was approved by the Animal Care Committee of the University of Miyazaki (approval number: 2018-502). Efforts were made to minimize the number of animals used and their suffering. The rats were housed in a temperature- and humidity-controlled environment with a 12-h light-dark cycle and permitted free access to food and water.

Adult male Sprague-Dawley rats weighing 250-400 g were divided into groups described below. RTX (LC Laboratories, Woburn, MA, USA) was dissolved in a mixture of 10% Tween-80 and 10% ethanol in normal saline. The experimental rats (n = 5) received a single intraperitoneal injection of 200 μg/kg RTX under 2-3% sevoflurane anesthesia at the beginning of the experiment. PRF was applied to the right sciatic nerve 1 week after RTX treatment. The PRF conditions are described below (see PRF condition). Behavioral experiments and western blot analyses were conducted separately for the PRF tissues (ipsilateral side) and the non-PRF tissues (contralateral side) in the RTX-treated rats. The rats (n = 5) in the control group received neither RTX treatment nor PRF.

***Behavior analysis.*** All rats were evaluated for sensitivity to mechanical stimulation using von Frey (VF) filaments (Stoelting, Wood Dale, IL, USA) by an experienced observer who was blinded to the treatment. The VF test was performed before and at 1, 2, 3, 4, and 5 weeks after RTX treatment. The paw withdrawal threshold with VF filaments was determined by placing each rat on a mesh floor in a suspended chamber. After an acclimation period of 30 min, a series of calibrated VF filaments were applied perpendicular to the plantar surface of the right and left hind paws with sufficient force to bend the filament for 5 sec. Brisk withdrawal or paw flinching was considered a positive response. In the absence of a response, the filament was applied with greater force. If a response was elicited, the filament was applied with lower force. The tactile stimulus producing a 50% likelihood of withdrawal response was calculated using the up-down method [15].

***PRF conditions.*** Rats were anesthetized with medetomidine (0.375 mg/kg; ZENOAQ, Koriyama, Japan), buprenorphine (2.5 mg/kg; Meiji Seika, Tokyo, Japan), and midazolam (2 mg/kg; SANDOZ, Tokyo, Japan). They were then positioned prone on the operating table, and the lumbar skin was prepared with an antiseptic solution. An indifferent electrode connected to a radiofrequency generator was taped to the abdominal skin. The right-side of all RTX-treated rats was selected to receive PRF treatment to the sciatic nerve. A 54-mm, 22-gauge guiding needle with a 4-mm active tip (Ac-4; Hakko, Tokyo, Japan) was introduced percutaneously at an anatomically defined region known as the sciatic notch. This location (between the greater trochanter and ischial tuberosity) has been used in neurobehavioral experiments. After the puncture, the stylet of the needle was replaced with a radiofrequency probe, tissue impedance was measured, and the presence of muscle contractions was evaluated starting with 3-Hz electrical stimulation to a maximum of 1.0 V. If muscle contractions were observed with an output lower than 0.5 V, the electrode was retracted by 1 mm. If muscle contractions were observed with an output higher than 1.0 V or no contractions were observed, the electrode was advanced by 1 mm. The procedure

was repeated until muscle contractions were observed with a proper output between 0.5 and 1.0 V: this criterion was taken to indicate that the electrode was near the sciatic nerve but not penetrating it. PRF was applied after proper electrode placement. A radiofrequency generator with standard clinical specifications (model JK3; RDG Medical, Surrey, UK) was used. The PRF current was applied in 20-msec pulses every 500 msec (20 msec of 500-kHz RF pulses, delivered at a rate of 2 Hz) for 360 sec. The maximum temperature was automatically maintained at 42°C. The PRF exposure time and timing after RTX treatment were selected according to previous research identifying the most effective PRF condition for mechanical allodynia [10].

***Western blot.*** The L4-L6 DRG of rats from each group were dissected five weeks after RTX treatment. The samples were homogenized in ice-cold lysis buffer consisting of 10 mM Tris-HCl (pH 7.4) with 1 mM ethylenediaminetetraacetic acid, 1 mM iodoacetamide, 1 mM phenylmethylsulfonyl fluoride, and three protease inhibitors: 2 μM leupeptin, 1.5 μM aprotinin, and 0.15 μM pepstatin. The homogenates were centrifuged at 12,000 rpm for 10 min at 4°C, and the supernatants were used for the assay. The concentrations of the protein were determined using Bradford's method-based protein assay kit (Aproscience, Naruto, Japan), with bovine serum albumin (BSA) as a protein standard. The stored supernatants were solubilized in a 2× sodium dodecyl sulfate (SDS) electrophoresis sample buffer and heated at 98°C for 5 min. Equal amounts of protein (8.0 μg per lane) were separated by 12% sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) and transferred to polyvinylidene difluoride (PVDF) membranes (Immobilon-P, Merck Millipore, Burlington, MA, USA). The membrane was subsequently incubated with 2% BSA in Tween-Tris-buffered saline (10 mM Tris-HCl [pH 7.4], 150 mM NaCl, and 0.1% Tween-20) as a blocking solution. The membranes were incubated overnight at 4°C in Can Get Signal® solution 1 (TOYOBO, Osaka, Japan) with primary antibodies. Rabbit anti-TRPV1 monoclonal IgG (1 : 1000, NBP1-97417, Novus Biologicals, Centennial, CO, USA), rabbit anti-CGRP monoclonal IgG (1 : 1000, ab139264, Abcam, Cambridge, MA, USA), rabbit anti-BDNF monoclonal IgG (1 : 1000, ab108319, Abcam), and mouse anti-β-actin monoclonal IgG (1 : 5000, A5441, Sigma-Aldrich, St Louis, MO, USA) were used as the primary antibodies. After repeated rinsing, immunoreactive bands developed with Can Get Signal® solution-2 with horseradish peroxidase-conjugated anti-rabbit antibody (1 : 5000, GE Healthcare Japan Corporation, Tokyo, Japan) or anti-mouse antibody (1 : 3000, Santa Cruz, Dallas, TX, USA) were visualized using ECL Prime reagents (GE Healthcare, Buckinghamshire, UK) and captured in a LAS-4000 Lumino image analyzer (Fuji Film, Tokyo, Japan). The commercially available molecular weight markers Precision Plus Protein Kaleidoscope Standards (Bio-Rad Laboratories Inc., Hercules, CA, USA), consisting of proteins with molecular weights of 10-250 kDa, were used as the molecular weight references. The band size was confirmed via visual inspection of the molecular weight markers. The densities of the protein blots were quantified using ImageJ [16], and the protein levels were normalized to β-actin levels.

***Statistical analysis.*** Behavioral tests were conducted using five rats from each group. Repeated measures of behavioral data were analyzed using two-way analysis of variance (ANOVA), followed by the post-hoc Tukey test. Western blot data were analyzed using one-way ANOVA variance followed by Tukey's test. Data are expressed as the means ± standard errors (SEMs) for the VF test or mean ± standard deviation (SD) for western blotting. Statistical significance was set at $p < 0.05$. Statistical analyses were performed using the JMP Pro 16 (JMP Statistical Discovery LLC, Cary, NC, USA) software for Macintosh.

## Results

***Behavioral test.*** In the contralateral and ipsilateral groups, the paw withdrawal threshold was significantly lower 1 week after RTX injection compared with that in the control group (Fig. 1). This decrease continued to be observed 5 weeks after RTX injection in the contralateral group. In the ipsilateral (PRF-treated) group, the paw withdrawal threshold was significantly higher than that in the contralateral group starting 1 week after PRF and continuing 4 weeks after PRF irradiation. These results are similar to those of our previous studies [10, 11].

***Western blot analysis of TRPV1, CGRP, and BDNF in the DRG.*** Five weeks after RTX injection (4 weeks after PRF irradiation in the ipsilateral group), the expressions of TRPV1 and CGRP in the contralateral DRG samples were significantly lower than that in the

control ($p<0.0001$ and $p<0.0001$, respectively) and ipsilateral tissues ($p<0.0001$ and $p<0.0001$, respectively) (Fig. 2A and 2B). In addition, the BDNF levels in the contralateral DRG were significantly higher than those in the control ($p<0.0001$) and ipsilateral ($p<0.0001$) DRG (Fig. 2C).

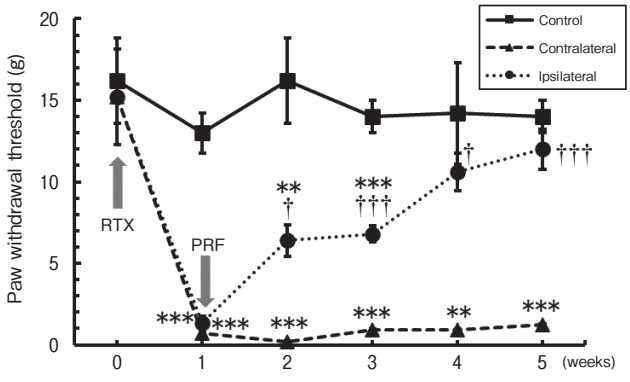


Fig. 1 Effects of RTX and PRF on the paw withdrawal threshold. One week after RTX administration, the paw withdrawal threshold was significantly lowered in the RTX-treated rats compared with those in the control group. One week after PRF irradiation, the paw withdrawal threshold in the ipsilateral DRG tissues was significantly restored compared with that in the contralateral tissues. Data are expressed as means ± SEDs, n = 5 in each group. In the contralateral group, the error bars are hidden under the symbols. $^{**}p<0.01$, and $^{***}p<0.001$, vs. control group. $^{\dagger}p<0.05$, $^{\dagger\dagger\dagger}p<0.001$, vs. contralateral group.

## Discussion

The behavioral experiments of this study showed that both contralateral and ipsilateral paw withdrawal thresholds 1 week after RTX administration were significantly lower than those of the control; the contralateral paw withdrawal threshold continued to be low throughout the experimental period. The ipsilateral paw withdrawal threshold 1 week after PRF irradiation was significantly higher than the contralateral paw withdrawal threshold. These results are similar to those of our previous reports [10, 11], and confirm the establishment of a neuropathic pain model induced by RTX. Western blot analysis showed that 5 weeks after RTX administration (4 weeks after PRF irradiation), the expression levels of TRPV1 and CGRP in the contralateral DRG continued to be significantly decreased compared with those in the control DRG while those in the ipsilateral DRG showed significant recovery compared with those in the contralateral DRG. In addition, the BDNF level in the contralateral DRG was significantly increased compared with that in the control DRG, and

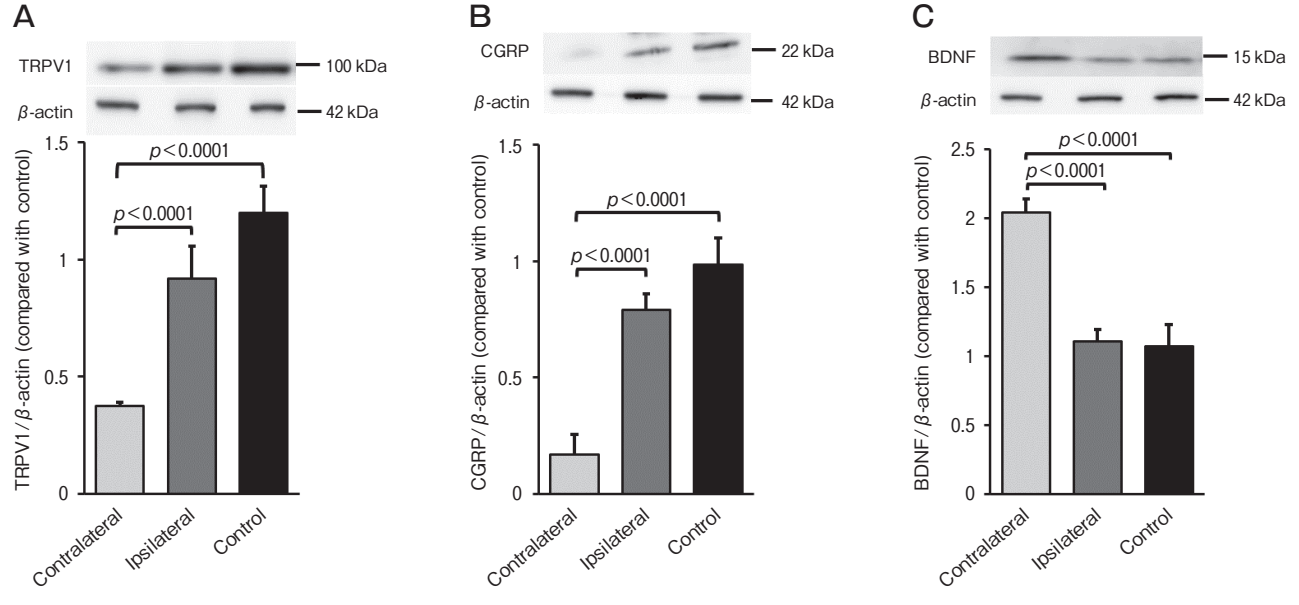


Fig. 2 Western blot analysis of (A) TRPV1, (B) CGRP, and (C) BDNF in the L4-L6 DRG. Representative western blots and quantitative densitometric analyses of each expression ratio for western blot showing that the protein levels of TRPV1 and CGRP were downregulated by RTX, whereas that of BDNF was upregulated. This BDNF upregulation was reversed by PRF treatment. The samples were harvested 5 weeks after RTX treatment (4 weeks after PRF in ipsilateral group). Data are expressed as means ± SDs, n = 5 samples (one animal per sample) in each group.

the BDNF level in the ipsilateral DRG was significantly decreased compared with that in the contralateral DRG.

TRPV1 is a ligand-gated cation channel and polymodal nocitransducer that is expressed in regions of the peripheral and central nervous systems involved in the regulation of pain transmission [12]. CGRP, synthesized in the DRG, is a neurotransmitter that plays an important role in establishing peripheral sensitization and enhancing pain. CGRP expression is upregulated during inflammation and neuropathic pain [13]. CGRP has been implicated in the maintenance of neuropathic pain, and CGRP receptor antagonists reduce neuropathic pain [17]. However, several studies have established that both TRPV1 and CGRP in the DRG decrease after RTX administration [18-20]. RTX induces small-fiber degeneration and diminishes thermal pain sensitivity in a manner similar to that observed in postherpetic neuralgia [9]. Our results are consistent with those of these previous reports. The decrease in TRPV1 and CGRP is due to RTX binding to TRPV1 and causing $Ca^{2+}$ influx into the cells, resulting in the death of TRPV1-expressing small-fiber afferent neurons [21], in which CGRP receptors are also expressed [22]. Bayir *et al*. reported the effect of PRF on nerve healing after sciatic nerve anastomosis in rats [23]. Thirty days after treatment, the number of axons in the PRF group was increased compared with that in the controls, suggesting that PRF may promote nerve healing in the early stages of nerve injury. Therefore, the restoration of TRPV1 and CGRP expression in our study may also be due to PRF promoting healing of the RTX-induced nerve injury. Our study is the first to confirm that PRF irradiation of the sciatic nerve restores the expression of TRPV1 and CGRP in the DRG in the RTX-induced neuropathic pain model. Restoration of TRPV1 and CGRP expression levels is speculated to be associated with nerve regeneration, and further studies are needed to understand the role of TRPV1 and CGRP restoration in improving mechanical allodynia.

BDNF is also a neurotransmitter involved in pain sensitization [14]. It was previously reported that BDNF expression in the DRG was elevated for at least 2 weeks after RTX administration [24]. In this study, the mRNA and protein levels of BDNF in the DRG were elevated 14 days after RTX administration, consistent with our previous results. In addition, BDNF is upregulated in several neuropathic pain models [24-27]. Our study is the first to confirm that PRF irradiation of the sciatic nerve reverses BDNF upregulation in the DRG in the RTX-induced neuropathic pain model. Similar to our results, in a study on SNI rats, PRF applied to the L4-L5 DRG inhibited mechanical allodynia and reversed BDNF upregulation in the spinal cord [28]. In a study on chronic constriction injury (CCI) mice, BDNF levels increased in a prominent and time-dependent manner in the injured DRG, and the injection of BDNF siRNA into the DRG improved mechanical, thermal, and cold hypersensitivity [26]. Inhibition of TrkB.T1, a BDNF receptor, reduced RTX-induced mechanical allodynia [24]. Therefore, it is likely that one of the main mechanisms responsible for PRF's effect is the inhibition of BDNF upregulation in neuropathic pain. Similar to our previous report that PRF suppressed the upregulation of $Na_V1.7$ [11], which is a voltage-dependent $Na^+$ channel, the present results indicate that PRF exerts its analgesic effects by suppressing BDNF upregulation in a rat model of RTX-induced neuropathy. The relationship between $Na^+$ channels and BDNF in the generation and development of pain remains unclear. Rose *et al*. reported that BDNF acts as a modulator of ion channels; however, it can also directly and rapidly gate an $Na^+$ channel [29]. Furthermore, the upregulation of $Na_V1.7$ enhances the excitability of the peripheral nerves, which increases the release of BDNF and contributes to central sensitization [30]. Further studies are required to elucidate the mechanisms by which PRF reduces BDNF upregulation and the association between $Na_V1.7$ and BDNF in the development of RTX-induced neuropathy.

In conclusion, the expression of TRPV1 and CGRP decreased, and that of BDNF increased in a rat model of RTX-induced neuropathic pain. PRF effectively alleviated RTX-induced pain. It was suggested that, while TRPV1 and CGRP are decreased by RTX-induced neuronal damage, increased BDNF levels result in pain development. PRF may promote recovery from neuronal damage with concomitant restoration of TRPV1 and CGRP, and exert its analgesic effect by reversing BDNF increase. Further research is required to understand the role of TRPV1 and CGRP restoration in improving mechanical allodynia.

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