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Pregabalin Attenuates Docetaxel-induced Neuropathy in Rats*

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Summary: Chemotherapy-induced neuropathy is a serious clinical problem for patients receiving cancer treatment. The aim of this study was to investigate the potential efficacy of pregabalin in chemotherapy-induced neuropathy in rats. A total of 35 male Sprague-Dawley rats were randomly divided into 5 groups: group 1, naive control; group 2, treated with pregabalin (30 mg/kg *p.o.*, for 8 days); group 3, docetaxel was given by single intravenous infusion at 10 mg/kg; groups 4 and 5, pregabalin at 10 mg/kg and 30 mg/kg respectively was orally administered for 8 days after the docetaxel treatment. On day 8, behavioral test was performed, and substance P and CGRP release in dorsal root ganglion (DRG) and sciatic nerve were analyzed by electron microscope. Our results showed that docetaxel induced mechanical allodynia, mechanical hyperalgesia, heat hypoalgesia, cold allodynia, and sciatic nerve impairment and substance P and CGRP release in DRG. However, oral administration of pregabalin (10 mg/kg and 30 mg/kg) for 8 consecutive days significantly attenuated docetaxel-induced neuropathy by ameliorating heat hypoalgesia, cold allodynia, impairment of sciatic nerve and reducing the release of substance P and CGRP. The findings in the present study reveal that pregabalin may be a potential treatment agent against chemotherapy-induced neuropathy.
Key words: pregabalin; docetaxel; substance P; CGRP; neuropathy

Neuropathic pain is one of the most serious clinical problems affecting patients with diabetes, trauma, herpes infection, and cancer, among others[1]. Cancer-related neuropathic pain has become more common than ever before because of the dramatic rise in the incidence of cancer in recent years. The drugs used for chemotherapy against cancer can cause neuropathic pain, resulting in discomfort, as well as mood and personality disorders, anxiety, depression, fatigue, and sleep disturbance in patients[2]. In serious cases, neuropathy leads to suspension of the chemotherapy regimen, making cancer treatment more difficult. Unfortunately, no effective approach for the prevention or treatment of chemotherapy-induced neuropathy is known.

Docetaxel is one of the most effective semi-synthetic taxane anticancer agents and widely used in the treatment of non-small cell lung cancer, breast cancer, and advanced gastric cancer[3]. Neuropathy caused by docetaxel is less frequent and milder than that induced by paclitaxel. Considering the wide use and cumulative effects of docetaxel, neuropathy caused by the drug deserves significant attention.

Pregabalin, a derivative of γ-aminobutyric acid (GABA), is known as an anticonvulsive agent. It binds selectively with the alpha2-delta protein subunit of voltage-gated calcium channels ($Ca_V\alpha_2\delta$), and is widely used in alleviating various chronic neuropathic pains, such as diabetic peripheral neuropathic pain, postherpetic neuralgia, and fibromyalgia. Recently, pregabalin has been shown to have efficacy in treating somatic pain related to irritable bowel syndrome and chronic pancreatitis[4].

We established a rat model of single docetaxel injection in our previous work and confirmed the neuropathy induced by docetaxel. In the current study, the efficacy of pregabalin against chemotherapy-induced neuropathy in rats was determined. The findings indicate that pregabalin may be a candidate therapeutic agent for the treatment of chemotherapy-induced neuropathy in humans.

1 MATERIALS AND METHODS

1.1 Animals

Young adult male Sprague-Dawley rats, weighing 200 g, were obtained from Experimental Animal Center, Tongji Medical College, Huazhong University of Science and Technology (HUST), Wuhan, China. All experiment protocols complied with the National Institutes of Health Guide for the Care and Use of Laboratory Animals[5]. The Animal Care Committee of HUST approved the experiment. The rats were housed in a cage (temperature: 20°C to 23°C, humidity: 40% to 60%) and fed *ad libitum* in a 12 h light/12 h dark cycle.

1.2 Experimental Protocol

Rats (n=35) were randomly and evenly divided into 5 groups: group 1, naive control; group 2, the rats were treated with pregabalin (30 mg/kg *p.o.*, for 8 days); group 3, docetaxel was given by single intravenous

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infusion at 10 mg/kg; groups 4 and 5, pregabalin at 10 mg/kg and 30 mg/kg respectively was orally administered for 8 days after the docetaxel treatment. The day the rats were administered docetaxel or pregabalin was defined as day 1. On day 1, pregabalin was administered 2 h after the docetaxel injection, and continued for 8 consecutive days (from day 1 to 8) in groups 4 and 5. On day 8, all rats were assessed by a behavioral test; some were subsequently sacrificed for substance P and CGRP examination and neuropathological analysis.

1.3 Agents

Docetaxel (Aventis Pharma, France) was dissolved in neutral saline and prepared immediately before administration at a concentration of 2 mg/mL. For groups 3, 4 and 5, each rat received docetaxel solution at 10 mg/kg by tail vein injection. Pregabalin (Pfizer, Germany) was dissolved in distilled water with the final concentration of 10 mg/mL and 30 mg/mL according to the drug dose used, and then the solutions were administered orally to groups 4 and 5 (1 mL/kg), respectively[6]. Meanwhile, group 2 received pregabalin of 30 mg/mL alone. Based on Meeh's formula, a 10 mg/kg dose of pregabalin in rats corresponds to a 100 mg/day dose in humans[7].

1.4 General Toxicity

General toxicity of pregabalin and docetaxel to the rats was monitored daily. Body weights of the rats were measured, and clinical parameters, such as general appearance, health status, and motor activity, were monitored every other day between day 1 and 8.

1.5 Behavioral Test: Mechanical Threshold

Mechanical threshold was evaluated as described previously using von Frey filaments[8]. The rats were placed in a separate chamber with a metal mesh floor. After allowing the rats to habituate to the chamber for 10 min, the von Frey filament was used to stimulate the mid-plantar aspect of each hind paw five times, with each application held for 5 s. Withdrawal responses to the filaments from both hind paws were counted and expressed as the overall percentage response. According to previous researches, the withdrawal responses to von Frey filament with bending forces of 4 g were defined as allodynia-like behavior while the responses to 15 g were defined as hyperalgesia-like behavior.

1.6 Behavioral Test: Thermal Nociceptive Threshold

The nociceptive threshold was evaluated by hot plate as Hargreaves described[9]. The rats were placed in individual Plexiglas platforms under a clean acrylic box. After 30 min of habituation in the equipment, radiant heat was focused on the mid-plantar aspect of the hind paw using a Plantar Test Apparatus (Ugo Basile, Comerio, Italy). The heat was turned off automatically upon paw withdrawal or after 20 s to prevent skin damage. Paw withdrawal latencies were recorded automatically. Each trial was repeated 3 times, and the means were recorded.

1.7 Behavioral Test: Cold Allodynia (Acetone Drop Test)

To assess the cold sensitivity of the hind paw, the withdrawal response of the rats to acetone stimulation was recorded as described by Choi *et al.*[10] with a minor modification. Rats were placed on a metal mesh floor in a plastic cage. After allowing the rats to habituate to the cage for 30 min, a drop of acetone was applied to the mid-plantar region of each hind paw using a syringe. The response to acetone was described as a hind paw withdrawal, and the duration time was from the time of paw withdrawal until the paw was allowed to rest, timed with a stopwatch for at least 1 s and recorded. A cut-off time of 20 s was set for each trial and the mean of 3 trials was calculated for each rat.

1.8 Immunohistochemistry

Five rats from each group were sacrificed on day 8 in order to obtain dorsal root ganglion (DRG) for immunohistochemical analysis according to the manufacturer's protocol. Substance P (SC9758, goat polyclonal IgG antibody, Santa Cruz Biotechnology), CGRP (SC8856, Santa Cruz Biotechnology) and secondary antibody (KPL, USA) were used.

1.9 Substance P and CGRP in DRG Determined by RT-PCR

Five rats from each group were sacrificed under 3% chloral hydrate anesthesia, and substance P and CGRP in DRG were evaluated on day 8. After total RNA extraction from DRG using TRIzol® reagent (Invitrogen, USA) according to the manufacturer's instruction[11], the cDNA was synthesized by reverse transcriptase. The primer sequences for substance P, CGRP and β-actin were as follows (Invitrogen, USA): substance P forward, 5'-CAGAGGAAATCGGTGCCAAC-3'; substance P reverse, 5'-CTGCTGAGGCTTGGGTCTTC-3'; CGRP forward, 5'-CTTTCCTGGTTGTCAGCATCTT-3'; CGRP reverse, 5'-AAGTTGTCCTTCACCACACCTC-3'; β-actin forward, 5'-CGTTGACATCCGTAAAGACCTC-3'; β-actin reverse, 5'-TAGGAGCCA- GGGCAGTAATCT-3'. Samples were heated to 95°C for 1 min, 95°C for 15 s, 58°C for 20 s, and 72°C for 20 s for 40 cycles. The final elongation was at 72°C for 5 min. The threshold cycle (Ct) of duplications were used to measure the relative mRNA expression and normalized to the ratio of β-actin.

1.10 Neuropathological Analysis

The neuropathological analysis of the sciatic nerve was conducted as described previously[12]. Two rats from each group were sacrificed under 3% chloral hydrate anesthesia on day 8. After the left sciatic nerves were harvested, the samples were fixed by immersion in 2% glutaraldehyde in 0.12 mol/L PBS and post-fixed in 2% osmium tetroxide. Then, the specimens were dehydrated in graded ethanol and embedded in epoxy resin. Finally, ultrathin sections were prepared and stained with uranyl acetate and lead citrate, and examined with a transmission electron microscope (FEI Tecnai G12, Netherlands).

1.11 Statistical Analysis

All behavioral data are presented as mean ± standard error of means (SEM). The data were analyzed by one-way ANOVA, followed by Bonferroni's test. All data were analyzed using SPSS 13.0 and $P<0.05$ was considered statistically significant.

2 RESULTS

2.1 General Toxicity

None of the rats died in the present experiment. No difference was found in the weight of the rats between group 1 and group 2. Motility and food intake of the rats in group 3 was decreased, resulting in a significant weight loss as compared with group 1.

2.2 Mechanical Allodynia

The frequency of paw withdrawal response to non-noxious mechanical stimuli (4 g) was significantly

increased in group 3 as compared with group 1 [group 1: (8.6±3.4)% *vs*. group 3: (32.9±4.2)%, $P<0.001$], which is a phenomenon described as mechanical allodynia (fig. 1A). However, pregabalin administration was ineffective in attenuating docetaxel-induced mechanical allodynia. Furthermore, the administration of pregabalin alone (pregabalin per se) did not evoke mechanical allodynia.

2.3 MechanicalHyperalgesia

The rats in group 3 developed mechanical hyperalgesia by significant increase of the paw withdrawal frequency after nociceptive mechanical stimuli (15 g) as compared with the rats in group 1 [group 1: (14.3±3.7)% *vs*. group 3: (47.1±5.5)%, $P<0.001$] (fig. 1B). However, pregabalin administration was ineffective in the attenuation of docetaxel-induced mechanical hyperalgesia. Furthermore, the administration of pregabalin alone (pregabalin per se) did not induce mechanical hyperalgesia.

2.4 Thermal Sensitivity

The paw withdrawal latency to a nociceptive heat stimulus was significantly increased in group 3 as compared with group 1 (group 1: 10.7±0.8 s *vs*. group 3: 17.4±1.3 s, $P<0.001$), which is defined as heat hypoalgesia (fig. 1C). The administration of pregabalin (10 mg/kg and 30 mg/kg, *p.o*.) caused significant attenuation of heat hypoalgesia with a reduction of 30.5% and 25.3%, respectively ($P<0.01$ and $P<0.05$), and no difference was observed between the groups receiving 10 mg/kg and 30 mg/kg of pregabalin. Additionally, the rats receiving pregabalin alone did not develop heat hypoalgesia.

2.5 Cold Allodynia

The duration time of the acetone drop was significantly increased in group 3 as compared with group 1 (group 1: 0.6±0.3 s *vs*. group 3: 2.9±0.6 s, $P<0.01$), which showed as cold allodynia (fig. 1D). The administration of pregabalin (30 mg/kg) evoked significant alleviation of cold allodynia with a reduction of 65.5% ($P<0.05$), while the pregabalin (10 mg/kg) showed no significant effect in cold allodynia. Moreover, pregabalin injection alone did not induce cold allodynia.

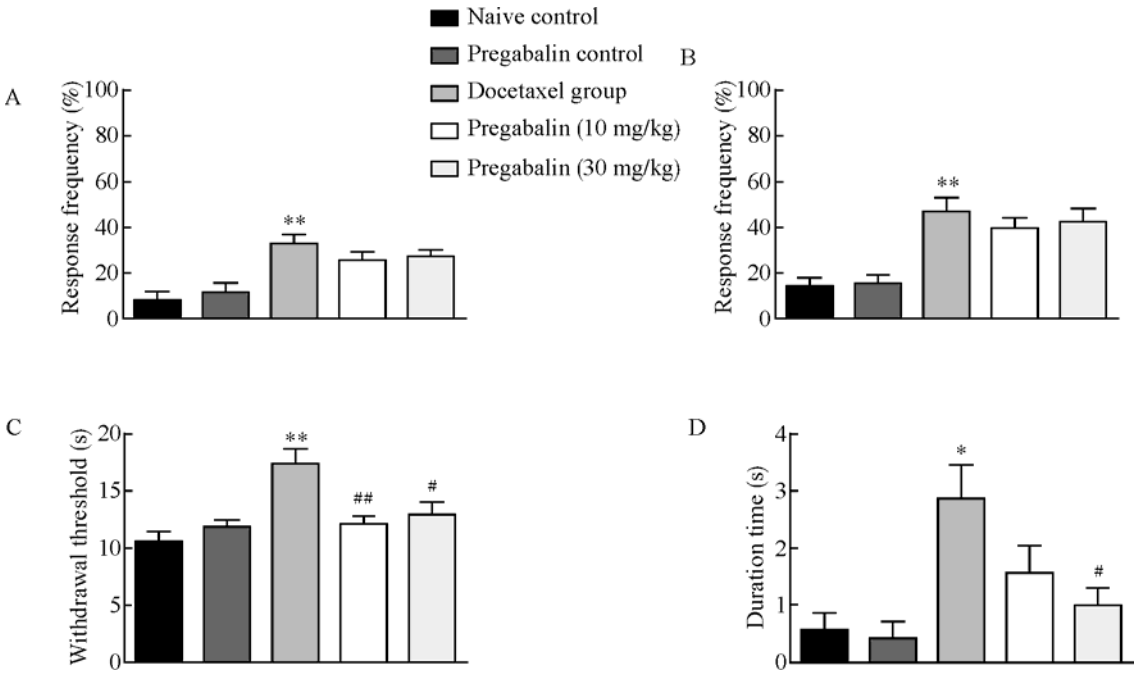

Fig. 1 A: Mechanical allodynia, B: Mechanical hyperalgesia, C: Heat hypoalgesia, D: Cold allodynia in the five groups (n=7 for each group)

$^{*}P<0.01$, and $^{**}P<0.001$ *vs*. naive control (group 1); $^{\#}P<0.05$ and $^{\#\#}P<0.01$ *vs*. docetaxel group (group 3)

2.6 Protein expression of Substance P and CGRP in DRG

As shown in table 1, docetaxel significantly increased the substance P and CGRP release in DRG, while pregabalin reduced the release of substance P and CGRP induced by docetaxel (both $P<0.001$). Moreover, pregabalin alone did not change the substance P and CGRP release.

2.7 mRNA expression of Substance P and CGRP in DRG

The release of substance P and CGRP was significantly increased in group 3 as compared with group 1, while pregabalin alone did not decrease substance P and CGRP (fig. 2). However, in groups 4 and 5, pregabalin (30 mg/kg) can reduce the release of substance P and CGRP induced by docetaxel with a reduction of 72.0% and 57.3%, respectively ($P<0.001$).

Table 1 Protein expression of SP and CGRP in DRG (n=5)

Group	Substance P	CGRP
1	0.1189±0.0106	0.1855±0.0108
2	0.1274±0.0104	0.2214±0.0122
3	0.3790±0.0222*	0.4199±0.0302*
4	0.2848±0.0148$^{\#}$	0.2953±0.0539$^{\#}$
5	0.2363±0.0215$^{\#}$	0.2642±0.0183$^{\#}$

$^{*}P<0.001$ *vs*. group 1; $^{\#}P<0.001$ *vs*. group 3

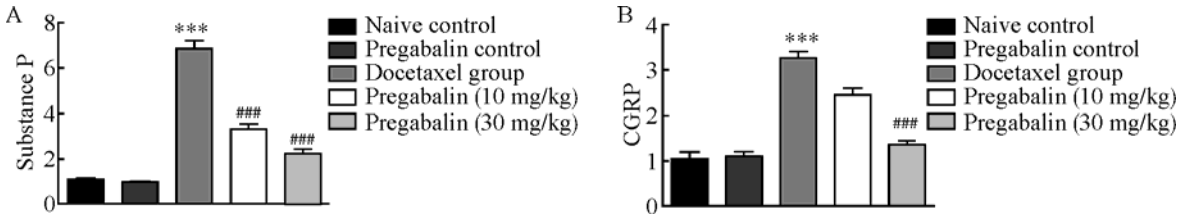

Fig. 2 Pregabalin reduced the substance P and CGRP release in DRG induced by docetaxel (n=5)
***P<0.001 *vs.* Naive control (group 1), ###P<0.001 *vs.* Docetaxel group (group 3)

2.8 Neuropathological Analysis

As compared with the rats in group 1, the rats receiving docetaxel showed evidence of myelinated and unmyelinated fiber damage (fig. 3). Under electron microscope, demyelination and atrophy was observed in the sciatic nerve fibers, especially in large myelinated fibers and unmyelinated fibers. In contrast, the impairment in groups 4 and 5 seemed mild and occasional, and there seemed no significant difference between the two groups.

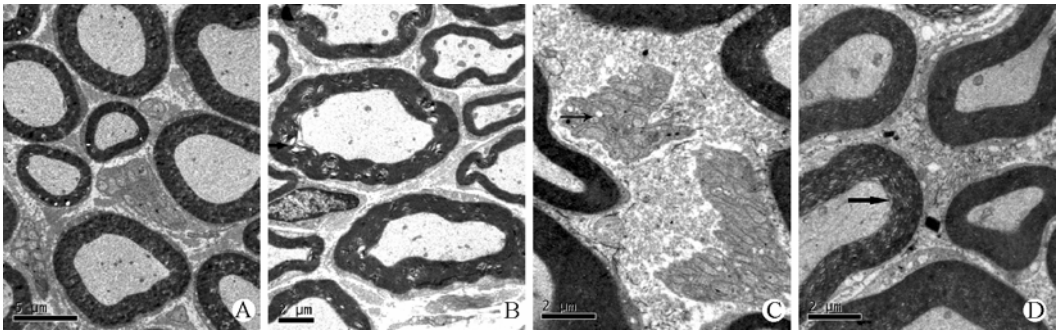

Fig. 3 Neuropathological analysis of sciatic nerves by electron microscope
(A) Naive control, group 1; (B), (C) Docetaxel treated group, group 2; (D) Pregabalin 30 mg/kg treated group, group 5 (*n*=2). More severe impairment of nerve fiber is observed in group 2 as compared to group 5. The black arrows in (B) and (D) show demyelination in myelinated fiber. The black arrow in (C) shows vacuolation in unmyelinated fiber.

3 DISCUSSION

Chemotherapy-induced neuropathy is a serious side effect that oncologists must consider when treating cancer patients. To help alleviate the problem, many drugs such as anticonvulsants, antidepressants, and opioids have been tested *in vivo* and *in vitro* but no drug against chemotherapy-induced neuropathy has yet been found effective[1,13].

Pregabalin is an anticonvulsant used widely to treat various chronic neuropathies in clinical practice. Pregabalin is the only agent supported by the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation in 2011[14]. And now it is used widely in treating various chronic neuropathic pains. Considering that pregabalin attenuated the neuropathic pain by inhibiting excitatory neurotransmitters such as substance P and CGRP release, while chemotherapy agent also increased the excitatory neurotransmitters release, we can hypothesize that pregabalin may be a good candidate drug for the treatment of chemotherapy-induced neuropathy.

Our previous work demonstrated that a single injection of docetaxel can evoke significant neuropathy and the peak was on day 8. The present study demonstrated that a single injection of docetaxel into rats can lead to a significant neuropathic pain characterized by mechanical allodynia, mechanical hyperalgesia, heat hypoalgesia, cold allodynia, increased release of substance P and CGRP in DRG, and neuropathological changes in the sciatic nerve. The characteristics of docetaxel-induced neuropathy are similar to those induced by other chemotherapy agents, such as paclitaxel, oxaliplatin, and vincristine[15-17]. In chemotherapy-induced neuropathy, the chemotherapy agents can cause neuronal hyperexcitation followed by an influx of calcium, leading to large and extended release of excitatory neurotransmitters, such as glutamate, substance P, and norepinephrine, which present as mechanical allodynia, cold allodynia, and so on[18]. In the current study, docetaxel was demonstrated to increase the release of substance P, which corresponded to the study by Tatsushima *et al.*[19] who found that paclitaxel evokes the release of excitatory neurotransmitters such as substance P, and Ling *et al.*[18] who demonstrated that substance P was increased after a single injection of oxaliplatin. Furthermore, the characteristics of chemotherapy-induced neuropathy in the rat model in the present study are similar to those in human patients, further validating the use of the rat model in chemotherapy-induced neuropathy research.

The analgesic effects of pregabalin were evaluated both behaviorally and neuropathologically in the docetaxel-induced neuropathy model. In the current study, the oral administration of pregabalin was well tolerated, and led to significant attenuation of docetaxel-induced neuropathy in addition to reverting heat hypoalgesia and cold allodynia. Moreover, pregabalin reduced the release of substance P and CGRP in DRG of docetaxel-induced neuropathy model, whereas pregabalin alone cannot change substance P and CGRP release in the normal rats. The exact mechanism by which pregabalin attenuates docetaxel-induced neuropathy is not clear. The blockage of $Ca_V\alpha_2\delta$ of N-type calcium channels and decrease in

the release of excitatory neurotransmitters in diabetic neuropathy and inflammation-induced neuropathy by pregabalin as an analog of GABA is supported by evidence. Substance P and CGRP are important transmitters in pain pathway and involved in neuropathy. They have been reported to be upregulated in the spinal cord of the neuropathic rat model, and its application evoked mechanical allodynia in the rat model. In contrast, the spinal injection of agents can produce analgesia by modifying the release of substance P and CGRP. Based on these findings, pregabalin may be hypothesized to develop analgesic effects in docetaxel-induced neuropathy by binding to $Ca_V\alpha_2\delta$. This decreases the influx of calcium ions, which results in a reduced release of excitatory neurotransmitters, such as substance P, which was increased by docetaxel. In physiological conditions, substance P was not released[20]. Future experiments are expected to elucidate the precise mechanism of action of pregabalin.

The sciatic nerve is a major peripheral nerve that is often damaged in neuropathy, especially in chemotherapy-induced neuropathy. Generally, chemotherapy-induced neuropathy is considered as a factor that lead to defects in the axonal transport, peripheral nerve, and DRG[21]. In clinical settings, patients with damage to the peripheral nerve present with reduced touch sensation, peripheral neuropathy, and, rarely, a defective sensation of vibration. In the rat model in the present study, mechanical allodynia, heat hypoalgesia, and cold allodynia were observed. Electron microscopic analysis demonstrated that docetaxel caused serious impairment of myelinated and unmyelinated fibers in the sciatic nerve, including Type Aδ and Type C fibers[22], which increased substance P and CGRP release in the cerebrospinal fluid after stimulation and are associated with mechanical allodynia, and cold allodynia. The oral administration of pregabalin seemed to partially relieve these impairments of the peripheral nerve.

In conclusion, docetaxel was found to induce neuropathies, such as behavioral changes, substance P and CGRP release and sciatic nerve damage, in the rat model. However, pregabalin can attenuate heat hypoalgesia and cold allodynia, reduce the release of substance P and CGRP, along with nerve impairment, and may be an effective option for the treatment of docetaxel-induced neuropathy in humans.

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