

# Effect of delayed intrathecal administration of capsaicin on neuropathic pain induced by chronic constriction injury of the sciatic nerve in rats

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**Purpose:** The current study was designed to examine the antinociceptive effect of intrathecally administered capsaicin, a transient receptor potential vanilloid 1 receptor agonist, in a rat model of neuropathic pain induced by unilateral sciatic nerve chronic constriction injury.

**Methods:** Male adult Sprague Dawley rats were randomly assigned to six groups, and all rats underwent unilateral sciatic nerve chronic constriction injury. Two weeks after injury, five groups received intrathecal administration of either capsaicin in three different dosing regimens or equal volumes of vehicle. The other group received intrathecal capsaicin on the third day after nerve injury. The antinociceptive effect of capsaicin was assessed by measuring the capsaicin-induced change in thermal and mechanical response thresholds.

**Results:** Capsaicin (150–300 µg/100–200 µL), when administered by fast infusion or chronic infusions at 8 µL/hour or 1 µL/hour, attenuated thermal hyperalgesia as indicated by significantly prolonging paw withdrawal latency to noxious thermal stimulation. The antinociceptive effect of capsaicin was more profound in the injured limb compared to that in the uninjured limb. When capsaicin was administered on the third day after nerve injury, it failed to attenuate thermal hyperalgesia. No significant effect on the mechanical response threshold was observed with intrathecally administered capsaicin.

**Conclusion:** Our data suggest that intrathecal capsaicin could significantly attenuate thermal hyperalgesia, depending on the time when the drug is given after nerve injury, and that the antinociceptive efficacy of intrathecal capsaicin positively correlates with the previously reported dynamic profile of spinal transient receptor potential vanilloid 1 activity after nerve injury.

**Keywords:** hyperalgesia, TRPV1, paw withdrawal latency, paw withdrawal threshold

## Introduction

Capsaicin is the pungent ingredient in hot chili peppers that is widely studied as an analgesic agent. When applied to the skin, it activates the transient receptor potential vanilloid 1 (TRPV1) receptors at the peripheral terminals of the primary sensory neurons, producing burning sensations. Repeated and prolonged use of capsaicin leads to sensory desensitization to subsequent stimuli. This property underlies the clinical use of capsaicin as a topical analgesic in a variety of pain disorders.<sup>1–3</sup> Several investigators have examined the analgesic effects of intrathecally administered capsaicin on thermal response thresholds in rats with inconsistent results.<sup>4–6</sup> For example, Yaksh et al<sup>5</sup> demonstrated that the capsaicin increased the thermal response threshold in healthy rats, while Russell et al<sup>4</sup> reported that the capsaicin had no significant effect. A number of variables in these studies complicates the interpretation of the different results. For example, different solvents were used to dissolve capsaicin, and different methods

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were adopted to assess nociceptive responses between the two studies. These two groups further examined the analgesic effect of intrathecally administered capsaicin in two different neuropathic pain models and concluded that the intrathecal capsaicin does not significantly change the thermal response threshold under neuropathic pain conditions.<sup>4,6</sup>

Using the neuropathic pain model induced by the unilateral chronic constriction injury (CCI) of the sciatic nerve, Yamamoto and Yaksh found that the intrathecal capsaicin significantly elevated the thermal response threshold in the uninjured side but failed to do so in the injured side.<sup>6</sup> In this study, the capsaicin effect was evaluated by measuring the capsaicin-elicited change in the thermal response threshold from the preinjury baseline, while the threshold in the untreated hyperalgesic state was not documented.<sup>6</sup> Therefore, it remains unknown if the capsaicin could attenuate the thermal hyperalgesia associated with neuropathy.

Additionally, in the aforementioned studies, the capsaicin was either administered at the time of nerve injury or in the early developing stage of the neuropathic pain, while the effect of capsaicin on chronic neuropathic pain, a developed state of pain, was not investigated. It has been documented that spinal TRPV1 channel expression changes dynamically following peripheral nerve injury with the TRPV1 levels increased 1–2 weeks after the nerve injury.<sup>7</sup> Furthermore, evidence suggests that the efficacy of TRPV1 targeting therapies positively correlates with the TRPV1 activity.<sup>8,9</sup> The potential impact of a nerve injury-induced delayed surge in the spinal TRPV1 activity on the capsaicin's efficacy when administered intrathecally is intriguing and warrants investigation.

In this study, we attempted to: 1) investigate if the intrathecally administered capsaicin could alleviate thermal hyperalgesia and mechanical allodynia in an animal model of chronic neuropathic pain induced by the CCI of the sciatic nerve; and 2) assess the efficacy of capsaicin administered at 3 days compared to 2 weeks after the nerve injury – the two developing stages of neuropathic pain.

## Materials and methods

Male Sprague Dawley rats (250–300 g; Charles River Laboratories International, Inc., Wilmington, MA, USA) were used in this study and were housed in a temperature-controlled room with a 12/12 hour day/night cycle. Food and water were available ad libitum. All animal handling and treatment procedures were approved by the Institutional Animal Care and Use Committee

of the University of Texas Health Science Center at San Antonio.

## CCI of sciatic nerve

The rat was anesthetized with isoflurane (induced with 3%–4% isoflurane, then maintained with 1.5%–2.5% of isoflurane). The surgical procedure was performed as described by Bennett and Xie.<sup>10</sup> A 2.5 cm incision was made on the lateral thigh; then, the common sciatic nerve was exposed at the level of the middle thigh by blunt dissection through the biceps femoris. Proximal to the sciatica's trifurcation, about 7 mm of nerve was freed of adhering tissue, and four ligatures (4.0 chromic gut) were tied loosely around it with about 1 mm intervals between the ligatures. The fascia was closed using aseptic 3.0 vicryl sutures, and the incision was closed with wound clips.

## Intrathecal cannulation

Two weeks after CCI, the rat was placed under isoflurane anesthesia, and polyethylene 10 tubing was inserted into the spinal canal through the space between L5–L6 following the procedure previously described by Størkson et al.<sup>11</sup> The tubing was advanced cranially for about 25 mm. The intrathecal placement of the tubing was confirmed by the detection of the backflow of the cerebrospinal fluid and a tail-flick or a paw retraction. For rats receiving a fast infusion of capsaicin (group 1), the tubing was removed upon completion of the infusion. For rats receiving chronic infusion of either capsaicin or vehicle (groups 2–6), the proximal end of the tubing was connected to an osmotic pump prefilled with capsaicin or vehicle.

## Placement of miniosmotic pump

Immediately following successful intrathecal tubing placement a 2 cm incision was made on the back between the shoulders, and a small subcutaneous pouch was created by blunt dissection. A miniosmotic pump 15–20 mm in length and 6–8 mm in diameter (ALZET® Osmotic Pumps; Cupertino, CA, USA) and prefilled with either capsaicin or vehicle was placed in the pouch and connected to the intrathecal tubing through a tunnel under the skin. The incision was then closed with wound clips.

## Preparation of capsaicin

Capsaicin (Sigma-Aldrich Co, St Louis, MO, USA) was prepared in saline containing 1.5% alcohol and 1.5% Tween 80. The final concentration of capsaicin was 150 µg/100 µL. This preparation was modified from Wall's preparation<sup>12</sup> and

previously used in our laboratory. The dissolving solution was used as the vehicle.

## Behavioral assessments

### Plantar test (modified Hargreaves method)

The rat was placed in a bottomless Perspex® box over a raised glass platform. Through the glass, the plantar aspect of the hind paws was exposed to a beam of radiant heat generated from a Stoelting apparatus (Stoelting Co, Wood Dale, IL, USA). The paw withdrawal latency (PWL) to thermal stimulation was recorded, with a minimal cut-off value of 0.5 seconds and a maximum cut-off value of 20 seconds. The thermal stimulation was repeated five times at an interval of 5 minutes for each paw, and the mean of five measurements was taken for statistical analysis.

### Von Frey test

The rat was placed in a bottomless Perspex® box over an elevated wire grid, and the plantar aspect of the hind paw was stimulated with a series of Von Frey monofilaments of different forces (2 g, 4 g, 6 g, 8 g, 10 g, and 15 g) with 2 g as the low cut-off force and 15 g as the high cut-off force. The stimulation with each force was repetitively applied five times. The lowest force that evoked a brisk withdrawal response to three of the five repetitive stimulations was taken as the paw withdrawal threshold (PWT).

## Experimental protocol

As summarized in the Table 1, the rats were randomly assigned to one of six groups, and all rats received CCI in the right sciatic nerve. Two weeks after the CCI, group 1

received a 5-minute fast infusion of 150 µg/100 µL of capsaicin (n=9); group 2 received 300 µg/200 µL of capsaicin delivered at the rate of 8 µL/hour in 24 hours (n=8); group 4 received 200 µL of vehicle at the rate of 8 µL/hour in 24 hours (n=6); group 5 received an infusion of 150 µg/100 µL capsaicin delivered at the rate of 1 µL/hour in 72 hours (n=9); group 6 received 100 µL of vehicle delivered at 1 µL/hour in 72 hours (n=8). Group 3 received 300 µg/200 µL of capsaicin delivered at the rate of 8 µL/hour in 24 hours on the third day after the CCI (n=9). The PWL (seconds) to noxious thermal stimulus and PWT (g) to mechanical stimuli in both hind paws were evaluated according to the following schedule: before the nerve injury as the baseline control; two or three evaluations after the CCI but before the capsaicin or the vehicle administration; three consecutive evaluations after intrathecal capsaicin or vehicle administration, starting on the second day after treatment; one evaluation per day.

## Statistics

For the plantar test, one baseline measurement before the CCI, two to three measurements after CCI but before the capsaicin or vehicle treatment (all but group 3 had three measurements; group 3 had two measurements), and three measurements after the capsaicin or vehicle treatment were taken for statistical analysis. Data generated from the plantar test were expressed as mean ± standard error of the mean and were analyzed by the analysis of covariance (ANCOVA), followed by the Fisher's least significant difference test for pairwise comparisons. For the Von Frey test, similar data points were taken for statistical analysis except that only two instead of three measurements after CCI but before capsaicin or vehicle treatment were taken. The data generated from the Von Frey test were also expressed as mean ± standard error of the mean and analyzed by ANCOVA, followed by Fisher's least significant difference for pairwise comparisons.

The ANCOVA used the baseline as the covariate and included effects for leg (control versus injured), treatment (before and after), group (groups 1–6), both between and within the group variation and the interaction of these factors. A general variance–covariance method was used to account for the correlation of the repeated measures over the animals, as well as between and within the group variation. The residuals of the analysis were checked for normality of distribution and homogeneity of variance to rule out the need for transformations and support the conclusions obtained by the ANCOVA. Statistical significance was taken at  $P \leq 0.05$ . Statistical analysis was completed using

**Table 1** Summary of experimental protocol

	Capsaicin/vehicle given 2 weeks after CCI	Capsaicin given 3 days after CCI
Group 1 (n=9)	150 µg/100 µL of cap in 5 minutes	
Group 2 (n=8)	300 µg/200 µL of cap in 24 hours at 8 µL/hour	
Group 3 (n=9)		300 µg/200 µL of cap in 24 hours at 8 µL/hour
Group 4 (n=6)	200 µL of vehicle in 24 hours at 8 µL/hour	
Group 5 (n=9)	150 µg/100 µL of cap in 72 hours at 1 µL/hour	
Group 6 (n=8)	100 µL of vehicle in 72 hours at 1 µL/hour	

**Abbreviations:** cap, capsaicin; CCI, chronic constriction injury.

SAS version 9.3 for Windows (SAS Institute Inc., Cary, NC, USA).

## Results

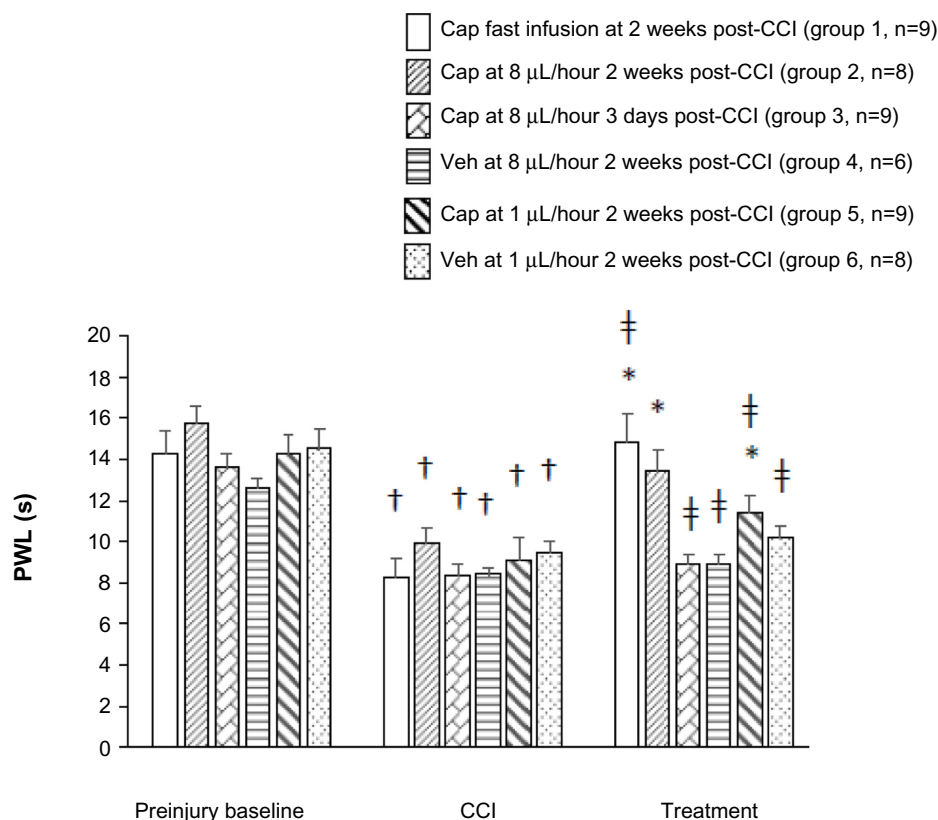
### PWL to noxious thermal stimuli

The results are presented as the following three subsequent time points: preinjury baseline; CCI (the average of two or three measurements); and treatment (the average of three measurements). The preinjury baseline defines the period before the CCI. The CCI defines the period after right sciatic nerve injury but before treatment. Treatment defines the period after either the capsaicin or vehicle administration.

Before nerve injury, there was no significant difference in the baseline PWL to noxious thermal stimulation between two hind paws in any groups; there was no significant difference in the baseline PWL across the groups either. The nerve injury elicited a significant reduction in PWL from

preinjury baseline in the injured side (CCI versus preinjury baseline;  $P<0.0001$ ; Figure 1) and a significant difference in PWL between the two hind paws ( $P<0.0001$ ). In group 1 ( $n=9$ ), the fast infusion of the capsaicin significantly prolonged PWL from CCI (treatment versus CCI;  $P<0.0001$ ) and preinjury baseline (treatment versus preinjury baseline;  $P<0.0001$ ) in the injured side (Figure 1). This dosing regimen also significantly elevated PWL from the preinjury baseline (treatment versus preinjury baseline;  $P=0.004$ ) in the uninjured side (Figure 2) and eliminated the injury-induced difference in PWL between the two hind paws ( $P=0.1615$ ).

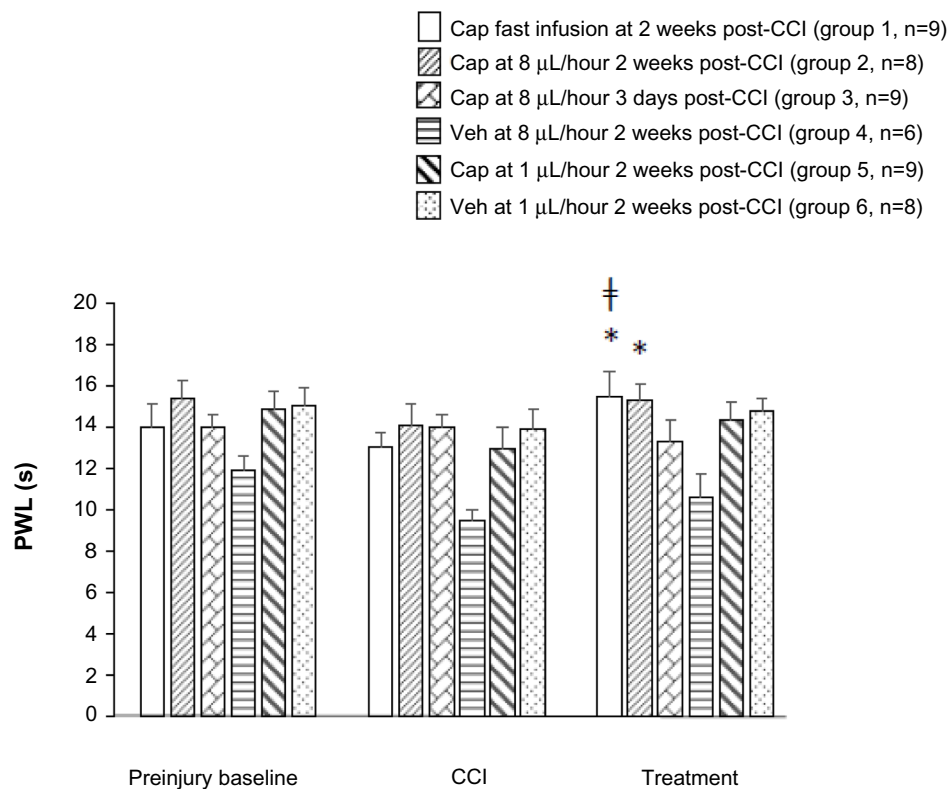
In group 2 ( $n=8$ ), the chronic infusion of 300  $\mu\text{g}/200\ \mu\text{L}$  capsaicin at 8  $\mu\text{L}/\text{hour}$  significantly increased the PWL from the CCI ( $P<0.0001$ ) but not preinjury baseline ( $P=0.1771$ ) in the injured side (Figure 1) and significantly increased PWL from CCI ( $P=0.0411$ ) in the uninjured side (Figure 2). However, PWL in the injured side was still significantly



**Figure 1** Intrathecal capsaicin increased PWL to noxious thermal stimulation in paw ipsilateral to nerve injury.

**Notes:** PWL of the hind paw to noxious thermal stimulation at three time points: 1) preinjury baseline; 2) CCI (average of two or three measurements); and 3) the treatment (average of three measurements). \*Indicates significant difference ( $P<0.05$ ) between CCI and treatment; †indicates significant difference ( $P<0.05$ ) between treatment and preinjury baseline; ‡indicates significant difference ( $P<0.05$ ) between CCI and preinjury baseline. CCI significantly shortened the PWL in all six groups. Two weeks after CCI, fast infusion of capsaicin significantly elevated PWL and abolished thermal hyperalgesia (group 1); chronic infusions of capsaicin at 8  $\mu\text{L}/\text{hour}$  (group 2) significantly elevated PWL and restored it to preinjury baseline; chronic infusions of capsaicin at 1  $\mu\text{L}/\text{hour}$  (group 5) significantly elevated PWL but failed to restore it to preinjury baseline; infusions of vehicle at 8  $\mu\text{L}/\text{hour}$  (group 4) and 1  $\mu\text{L}/\text{hour}$  (group 6) did not significantly affect PWL. Capsaicin administered at the third day after the CCI did not significantly affect PWL (group 3).

**Abbreviations:** cap, capsaicin; veh, vehicle; PWL, paw withdrawal latency; CCI, chronic constriction injury.



**Figure 2** Intrathecal capsaicin increased PWL to noxious thermal stimulation in paw contralateral to nerve injury.

**Notes:** PWLs at three time points were presented as: preinjury baseline; CCI (average of two or three measurements); and treatment (average of three measurements). \*Indicates significant difference ( $P < 0.05$ ) between CCI and treatment; †indicates significant difference ( $P < 0.05$ ) between treatment and preinjury baseline. Unilateral CCI of sciatic nerve did not alter PWL of contralateral hind paw from preinjury baseline. Two weeks after CCI, fast infusion of capsaicin (group 1) significantly elevated PWL from CCI and preinjury baseline. Chronic infusion of capsaicin at 8 µL/hour (group 2) significantly elevated PWL from CCI.

**Abbreviations:** cap, capsaicin; veh, vehicle; PWL, paw withdrawal latency; CCI, chronic constriction injury.

shorter than that in the uninjured side ( $P = 0.0326$ ) after capsaicin treatment.

In group 3 ( $n = 9$ ), capsaicin did not elicit a significant change in PWL from CCI (treatment versus CCI;  $P = 0.4247$ ), and PWL following capsaicin treatment was significantly shorter than the preinjury baseline (treatment versus preinjury baseline;  $P < 0.0001$ ) in the injured side (Figure 1). In group 4, an infusion of the vehicle did not elicit a significant change in PWL from CCI (treatment versus CCI;  $P = 0.4922$ ) in the injured side (Figure 1).

In group 5 ( $n = 9$ ), the chronic infusion of 150 µg/100 µL capsaicin at 1 µL/hour significantly increased PWL from the CCI in the injured side (treatment versus CCI;  $P = 0.0014$ ) and almost achieved a significant increase in PWL from CCI ( $P = 0.0539$ ) in the uninjured side (Figure 2). In group 6 ( $n = 8$ ), the intrathecal vehicle administration at 1 µL/hour elicited no significant change in PWL in both the injured side ( $P = 0.2470$ ; Figure 1) and the uninjured side ( $P = 0.3055$ ; Figure 2). Intrathecal capsaicin elicited a more profound increase in PWL in the injured side compared to the uninjured side (Figure 3) in both group 1 ( $P = 0.0001$ ) and group 2 ( $P = 0.003$ ).

This effect was not observed in any other groups. The previously mentioned data are summarized in Table 2.

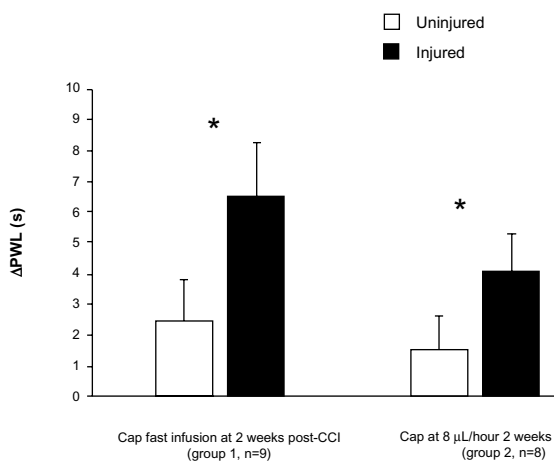
## PWT to mechanical stimuli

The data from all groups except group 3 were used for analysis. The data from group 3 were not used, because the mechanical allodynia had not reliably developed at the time of the capsaicin infusion. There was no significant difference in PWT to mechanical stimuli between the two hind paws before CCI. After the CCI, the PWT in the injured hind paw was significantly decreased compared to that in the contralateral uninjured hind paw and the same side before CCI in all five groups. No treatments significantly improved PWT to mechanical stimuli (Figure 4).

## Discussion

The purpose of the current study was to investigate the analgesic potential of intrathecally administered capsaicin on neuropathic pain and to determine if this treatment would have different efficacies when administered at two different time windows after peripheral nerve injury. Our study





**Figure 3** Intrathecal capsaicin produced a more profound increase in the thermal response threshold in the injured side as compared to the uninjured side.

**Notes:** Capsaicin elicited an increase in the thermal response threshold on both the uninjured side (open bar) and the injured side (solid bar) in group 1 and group 2. Fast infusion (group 1) and chronic infusion of capsaicin at 8  $\mu\text{L}/\text{hour}$  (group 2) elicited a more profound elevation in PWL on the injured side as compared to the uninjured side. \*Represents significant difference at  $P \leq 0.05$  comparing two paws.

**Abbreviations:** cap, capsaicin; veh, vehicle; PWL, paw withdrawal latency; CCI, chronic constriction injury.

demonstrates that intrathecal capsaicin attenuates CCI-induced thermal hyperalgesia when administered 2 weeks following nerve injury; however, it is ineffective if given on the third day after nerve injury.

In contrast to earlier studies that measured capsaicin-elicited changes in the thermal response threshold from preinjury baseline,<sup>5,6</sup> we documented capsaicin-elicited changes from both the CCI-induced hyperalgesic state and the preinjury baseline. We started with a 5-minute

**Table 2** Pairwise comparisons of averaged PWLs to thermal stimulation in the paw ipsilateral to CCI at three different time points – preinjury baseline, CCI, and treatment

	Preinjury baseline versus CCI(s)	Preinjury baseline versus treatment(s)	CCI versus treatment(s)
Group 1 (n=9)	14.28 versus 8.40 ( $P < 0.0001$ ) <sup>†</sup>	14.28 versus 15.81 ( $P < 0.004$ ) <sup>‡</sup>	8.4 versus 15.81 ( $P < 0.0001$ ) <sup>*</sup>
Group 2 (n=8)	15.75 versus 9.78 ( $P < 0.0001$ ) <sup>†</sup>	15.75 versus 13.40 ( $P = 0.1771$ )	9.78 versus 13.40 ( $P < 0.0001$ ) <sup>*</sup>
Group 3 (n=9)	13.58 versus 8.19 ( $P < 0.0001$ ) <sup>†</sup>	13.58 versus 8.84 ( $P < 0.0001$ ) <sup>‡</sup>	8.19 versus 8.84 ( $P = 0.4247$ )
Group 4 (n=6)	12.58 versus 8.15 ( $P < 0.0001$ ) <sup>†</sup>	12.58 versus 8.14 ( $P < 0.0001$ ) <sup>‡</sup>	8.14 versus 8.81 ( $P = 0.4922$ )
Group 5 (n=9)	14.30 versus 8.49 ( $P < 0.0001$ ) <sup>†</sup>	14.30 versus 11.17 ( $P < 0.0001$ ) <sup>‡</sup>	8.49 versus 11.17 ( $P = 0.0014$ ) <sup>*</sup>
Group 6 (n=8)	14.50 versus 9.19 ( $P < 0.0001$ ) <sup>†</sup>	14.50 versus 10.17 ( $P < 0.0001$ ) <sup>‡</sup>	9.19 versus 10.17 ( $P = 0.2470$ )

**Notes:** <sup>†</sup>Indicates significant difference ( $P < 0.05$ ) comparing CCI and preinjury baseline; <sup>‡</sup>indicates significant difference ( $P < 0.05$ ) comparing treatment and preinjury baseline; <sup>\*</sup>indicates significant difference ( $P < 0.05$ ) comparing CCI and treatment.

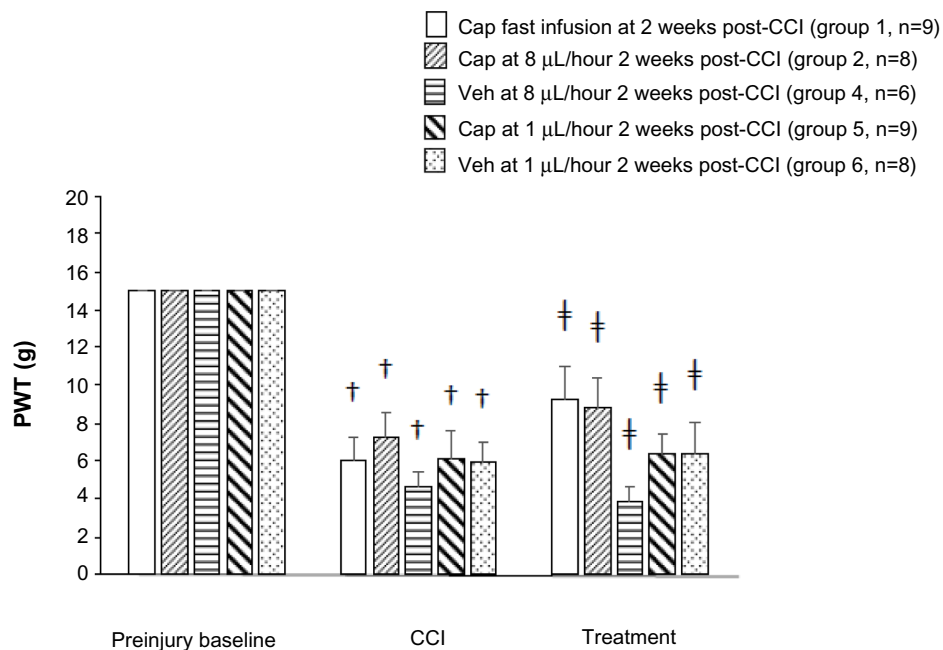
**Abbreviations:** PWL, paw withdrawal latency; CCI, chronic constriction injury.

fast infusion of capsaicin at a dose that was two to three times as high as those used in the previous studies.<sup>4,6</sup> This dosing regimen, when administered 2 weeks after the nerve injury, abolished the CCI-induced thermal hyperalgesia and significantly elevated thermal response threshold from the preinjury baseline (Figure 1). However, it caused significant side effects – such as apnea, hematuria, weight loss, or even death – in some instances. Subsequently, we examined if the analgesic effect of capsaicin could be achieved by chronic infusion. Two weeks after the CCI, the chronic infusions of capsaicin at 8  $\mu\text{L}/\text{hour}$  (300  $\mu\text{g}/200 \mu\text{L}$  in 24 hours) and 1  $\mu\text{L}/\text{hour}$  (150  $\mu\text{g}/100$  in 72 hours) significantly elevated the thermal response thresholds in the CCI-induced hyperalgesic state. However, only infusion at 8  $\mu\text{L}/\text{hour}$  restored thermal response thresholds to the preinjury baseline (Figure 1).

No aforementioned side effects were observed with the chronic infusions of capsaicin. In the uninjured leg, only the fast infusion of capsaicin significantly elevated thermal response thresholds from the baseline while the chronic infusions at 8  $\mu\text{L}/\text{hour}$  and 1  $\mu\text{L}/\text{hour}$  did not elicit significant changes from the baseline (Figure 2). The observed analgesic effect was unlikely to be caused by the solvent used in the study, since the chronic infusions of vehicle at 8  $\mu\text{L}/\text{hour}$  (200  $\mu\text{L}$ ) and 1  $\mu\text{L}/\text{hour}$  (100  $\mu\text{L}$ ) did not elicit significant changes in the thermal response threshold in both hind paws (Figures 1 and 2).

Next, we investigated if the capsaicin administered at a different time window following the nerve injury would have a different impact on therapeutic efficacy. It has been documented that the TRPV1 expression in the hemispinal cord ipsilateral to the injured nerve stays normal in the first few days after the nerve injury, but it becomes increased 1 week later and remains elevated 2 weeks after the injury.<sup>7</sup> The increased TRPV1 expression is accompanied by the spinal TRPV1 sensitization as indicated by the increased capsaicin-induced release of the calcitonin gene-related peptide in the spinal cord of the rats with the CCI compared to sham.<sup>7</sup>

The depletion of the neuropeptides, such as the calcitonin gene-related peptide and the substance P at nerve terminals, is commonly regarded as the mechanism of capsaicin-induced analgesia.<sup>13</sup> Thus, it is conceivable that the capsaicin's analgesic efficacy would be enhanced in states in which TRPV1 is upregulated. Our results support this notion, as the capsaicin exhibited higher analgesic efficacy when administered after nerve injury, at time windows during which the TRPV1 activity would be expected to increase.



**Figure 4** Intrathecal capsaicin did not alter PWT to mechanical stimulation in the injured side.

**Notes:** PWT of the hind paw ipsilateral to the injury to mechanical stimulation. PWTs at three time points were presented as: preinjury baseline, CCI (the average of two measurements), and treatment (the average of three measurements). ‡Indicates significant difference ( $P < 0.05$ ) between treatment and preinjury baseline; †represents significant difference at  $P \leq 0.05$  when comparing CCI with preinjury baseline. CCI significantly decreased PWT from preinjury baseline in all five groups (group 3 is not presented). Neither capsaicin nor vehicle administration restored PWT to preinjury baseline.

**Abbreviations:** PWT, paw withdrawal threshold; cap, capsaicin; veh, vehicle; CCI, chronic constriction injury.

Capsaicin administered on the third day following the nerve injury failed to attenuate thermal hyperalgesia (Figure 1). In addition, capsaicin elicited more profound elevation in thermal response threshold in the injured side than the uninjured side in two dosing regimens (Figure 3). Different TRPV1 activities between the two hemispinal cords as reported previously could have accounted for the different magnitudes of responses between the two hind paws.<sup>7</sup> Augmented TRPV1 activity has been found to be associated with the efficacy of therapeutic strategies targeting TRPV1.<sup>8,9</sup> For instance, the TRPV1 antagonists provide a more profound attenuation of pain responses to noxious stimuli in rats with inflammatory pain, a state known to have increased TRPV1 activity.<sup>8</sup> The state of TRPV1 also determines the analgesic efficacy of a combination of capsaicin and N-(2,6-dimethylphenyl)-carbamoylmethyl triethylammonium bromide (QX-314), a membrane-impermeable sodium channel blocker.<sup>14</sup> The QX-314 blocks nociceptive sodium channels from inside the cell, but it relies on coadministered capsaicin to bind the TRPV1 receptors and to allow entry via the transmembrane channels. When a combination of capsaicin and QX-314 was locally applied in the hyperalgesic area arising from nerve injury, the analgesic efficacy of this combination positively correlated with the dynamic profile of local TRPV1 expression following nerve injury.<sup>14</sup>

In our study, we found that no significant alleviation of mechanical allodynia was achieved with intrathecal capsaicin, although a dramatic increase in paw withdrawal threshold was noted in several cases. This distinct effect on the responses to thermal and mechanical stimuli has also been documented with intrathecal administration of another TRPV1 agonist, resiniferatoxin. Using an acute inflammatory pain model in the rat, Jeffrey et al demonstrated that intrathecally administered resiniferatoxin significantly elevated thermal response threshold but not the mechanical response threshold in the inflamed paw.<sup>15</sup> The TRPV1 is predominantly expressed in small to medium diameter, unmyelinated C, and thinly myelinated A- $\delta$  fibers that transmit nociceptive signals. However, the TRPV1 immunoreactivity is also reported to be increased in the myelinated A- $\beta$  fibers after nerve ligation.<sup>16</sup>

The intrathecal administration of the TRPV1 antagonist, N-(4-tertiarybutylphenyl)-4-(3-chlorophenyl)-2-pyridinyl tetrahydroprazine-1(2H)-carboxamide (BCTC) and AS1928370, has been shown to significantly attenuate mechanical allodynia in two different models of neuropathic pain, implicating TRPV1 in the development of mechanical allodynia.<sup>7,9</sup> Nevertheless, the results of these two studies are not comparable to our study since the time courses during which the drug's effect was evaluated were very different. For example, with the CCI neuropathic pain model, Kanai et al demonstrated a

transient amelioration of mechanical allodynia within 1 hour of intrathecal BCTC administration; whereas, we tested the capsaicin's effect at least 12 hours after its administration.<sup>7</sup>

## Conclusion

In summary, our study indicates that the intrathecal administration of capsaicin effectively attenuates thermal hyperalgesia in a chronic neuropathic pain model. Capsaicin's antinociceptive efficacy positively correlates with the nerve injury-induced dynamic profile of spinal TRPV1 expression reported previously.

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## Disclosure

The authors report no conflicts of interest in this work.

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