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Gabapentin produces antinociceptive effects on the spinal cord with simultaneous activation of descending facilitation in spinal nerve-ligated rats

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Abstract

Gabapentin has been proposed as one of several first-line agents to treat neuropathic pain. Although both spinal and supraspinal neuronal mechanisms participate in the antinociceptive effects of gabapentin, the supraspinal contribution to the effects of gabapentin at the spinal level remains unclear. We evaluated the role of descending modulation in the antinociceptive effects of gabapentin at the spinal level using continuous blockade of descending pathways in spinal nerve-ligated (SNL) rats. Tail flick (TF) latencies following sham operation or SNL operation were measured for 2 weeks. Rats were chronically implanted with both cervical and lumber intrathecal catheters, and a continuous cervical intrathecal infusion of 1% lidocaine was utilized for suppression of descending modulation. TF latencies following intrathecal administration of normal saline or 50 μg gabapentin were measured with/without descending modulation in SNL and sham-operated rats. TF latencies (percentage of the maximum possible effect) were significantly shortened in the 2 weeks following SNL operation. With descending modulation, intrathecal gabapentin did not prolong TF latencies in sham-operated rats, and prolonged TF latency only at the 60-min time point in SNL rats; 28.9±17.3% ($p<0.05$ compared with baseline). Without descending modulation, intrathecal gabapentin to sham-operated rats slightly prolonged TF latencies at 15 and 30 min compared with the saline group of sham-operated rats, but intrathecal gabapentin to SNL rats resulted in significant prolongation of TF latencies; 41.6±39.0% ($p<0.01$) to 68.2±37.4% ($p<0.001$). The results of this study indicate that gabapentin causes both apparent antinociception at the spinal level and simultaneous descending facilitation in neuropathic pain conditions.

Key words: gabapentin, descending pathway, spinal, tail-flick test, rat

Introduction

The anticonvulsant gabapentin is proposed as one of several first-line treatments for neuropathic pain.[1] Marked up-regulation of the $\alpha_2\delta$ subunit of voltage-dependent calcium channels (VDCCs) is evident in the dorsal root ganglion (DRG) and at the sensory nerve terminal in the spinal dorsal horn in neuropathic pain models.[2–4] Since gabapentin interacts with the

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$\alpha_2\delta$ subunit of VDCCs, $\alpha_2\delta$ subunits in the spinal cord have been implicated in the antinociceptive effects of gabapentin in neuropathic conditions.[5]

Supraspinal neuronal mechanisms are also involved in the effect of gabapentin at the spinal level. Although gabapentin has been presumed to activate the descending noradrenergic system,[6–9] Takasaki et al.[10] speculated that the antinociceptive effect of gabapentin may be mediated primarily by its spinal action and not by the brain. Thus, the contributions of supraspinal sites to the effects of gabapentin at the spinal level are still unclear. The aim of this study was to evaluate the role of descending supraspinal modulation in the antinociceptive effects of gabapentin at the spinal level in spinal nerve-ligated (SNL) rats.

In the preliminary experiments, we observed that decreased ipsilateral withdrawal latency and difficulty in immobilizing animals caused instability of paw-withdrawal latencies with repetitive von Frey testing in both conscious SNL and sham-operated rats. It has been well described that peripheral nerve injury-evoked dysfunction of pain-processing neurons in the central nervous system causes abnormal pain sensations in a distribution that does not coincide with the territories of nerves or posterior roots.[11–13] In this study, we used unconscious rats and assessed the long-term effects of spinal nerve-ligation on the tail-flick (TF) reflex for 2 weeks, and then evaluated the antinociceptive effects of intrathecal gabapentin at the level of the spinal cord with/without suppression of descending modulation by means of continuous cervical intrathecal lidocaine infusion (Table 1).

Materials and Methods

With the approval of the animal care and use committee of Kinki University Faculty of Medicine, Sprague-Dawley (slc : SD) rats purchased from Japan SLC, Inc. (Shizuoka, Japan) were utilized for the experiments. Animals were bred in the Life Science Research Institute, Kinki University Faculty of Medicine. They were maintained under controlled conditions (temperature 23±0.5°C ; humidity 55±5% ; 12/12 h light/dark cycle) and were fed a commercial diet of CE-2 (Clea Japan Inc., Tokyo, Japan), with tap water *ad libitum*. The experiments were performed between 13 : 00 and 17 : 00 hours under controlled conditions (temperature 23±0.5°C).

Procedure of intrathecal catheterization

For intrathecal drug administration, rats were simultaneously implanted with indwelling cervical and lumbar intrathecal catheters (Fig. 1). The subarachnoid space was cannulated with 2 polytetrafluoroethylene (PTFE)-lined polyethylene tubes (0.3 mm O.D. and 0.11 mm I.D. ; Microspinal Catheter, Hakko Co. Ltd., Nagano, Japan) by application of the modified method of Sakura et al.[14] and Jensen and Yaksh.[15] In brief, 8-week-old rats were anesthetized by intraperitoneal injection of pentobarbital sodium. The catheters were passed through the same slit in the atlanto-occipital membrane and one was extended 3 cm caudally to the level of the lower-cervical spinal cord and the other 11 cm caudally to the level of the lumbar spinal cord. The free

Table 1 Subjects and methods

Experiments		
	Subjects	Methods
1. Changes in TF latencies after spinal nerve ligation		
	Sham-operated rats	TF testing at 0, 7 and 14 days after spinal
	SNL rats	nerve-ligation or sham-operation
2. Changes in TF latencies following intrathecal administration of gabapentin with descending modulation		
	Sham-operated rats	TF testing following lumbar intrathecal
	SNL rats	administration of gabapentin or normal saline
3. Changes in TF latencies following intrathecal administration of gabapentin without descending modulation		
	Sham-operated rats	TF testing following lumbar intrathecal
	SNL rats	administration of gabapentin or normal saline with suppression of descending modulation by means of continuous cervical intrathecal lidocaine infusion

TF : tail flick, SNL rats ; spinal nerve ligated rats

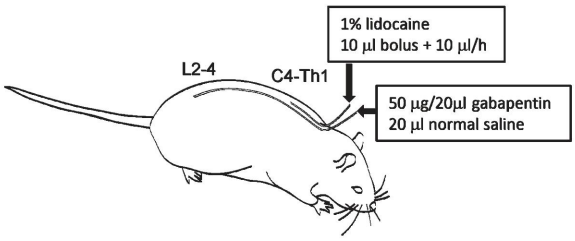

Fig. 1 Cervical and lumbar intrathecal catheterization. Two polytetrafluoroethylene (PTFE)-lined polyethylene tubes were implanted into the subarachnoid space through a slit in the atlanto-occipital membrane. One was extended 3 cm caudally to the lower-cervical level and the other 11 cm caudally to the lumbar level. A 10 μl bolus followed by 10 μl/h continuous infusion of 1% lidocaine was infused through the cervical intrathecal catheter to suppress descending modulation. Then, 50 μg/20 μl gabapentin or 20 μl normal saline was injected into the lumbar intrathecal catheter.

ends of the catheters were fixed in the subcutaneous tissue to avoid dislodgement. The catheters were filled with normal saline and the ends were heat sealed. One week later, rats that exhibited any evidence of sensory or motor dysfunction were excluded from the study.

Upon completion of the experimental series, 3 of the catheterized animals were killed by intraperitoneal injection of an overdose of pentobarbital sodium. On removal of vertebral bone, the cervical intrathecal catheter tips were found to be located between C4 and Th1, and the lumbar intrathecal catheter tips were located between L2 and L4.

Procedure of spinal nerve ligation

One week after intrathecal catheterization, 16 animals underwent SNL surgery using the methods of Kim and Chung,[16] and another 16 animals were sham-operated. Briefly, the left L5 and L6 spinal nerves were isolated and tightly ligated with 6-0 silk thread in the SNL rats, and were not ligated in the sham-operated rats, under intraperitoneal pentobarbital anesthesia. Hemostasis was confirmed and the wound was sutured. Behavioral testing was carried out on postoperative day 7. The 9-week-old SNL rats that exhibited mechanical allodynia in the left paw-withdrawal reflex against stimulation using calibrated von Frey filaments (6 g) (Touch Test™ Sensory Evaluator; Stoelting Co., Wood Dale, IL, USA) were considered to be neuropathic. Sham-operated rats that exhibited motor deficiency (such as paw dragging or limping) or SNL rats that failed to exhibit subsequent mechanical allodynia were excluded from any further testing.

Procedure of suppression of descending modulation

Continuous cervical intrathecal lidocaine infusion was utilized for suppression of descending modulation, as described by Takasugi et al.[17] The rats received a 10 μl bolus followed by 10 μl/h continuous infusion of 1% lidocaine through the cervical intrathecal catheter via a micro-syringe pump (ESP-64; Eicom Corp., Kyoto, Japan).

After completion of the experiment, 10 μl of 1% lidocaine was injected intrathecally, all rats revealing motor and sensory paralysis in the upper limbs with intact nociceptive reflexes in the lower limbs and tail.

Procedure of tail-flick test

The TF test was used to evaluate antinociceptive effects of the drugs. The Tail-Flick Unit (Model 7360; Ugo Basile, Varese, Italy) was utilized and TF latency was measured following the methods of Takasugi et al.[18] In brief, each rat was placed in a plastic box (22×6.5×6.5 cm) that had 2 holes in the front wall, one for administration of oxygen and anesthetic gases and the other for gas sampling, and a hole in the distal wall through which the tail protruded. Under inhalational anesthesia with 1% isoflurane in oxygen, for elimination of the decrease in TF latency due to the learning effect in conscious animals,[18] a radiant heat intensity setting of IR20 (161.5 mW/cm^2) was used. Different points along the distal 5 to 6 cm of the tail were exposed and a 10-s cut-off was used to minimize the risk of tissue damage. A 10-s interval was maintained between measurements. The mean of the last 5 TF latencies of 7 consecutive measurements was used as the representative value.

To analyze changes in antinociceptive effects, TF latency was converted to represent the percentage of the maximum possible effect (%MPE) according to the following formula:

%MPE = (test latency − baseline latency)/(cut-off time − baseline latency) × 100

Changes in TF latencies after spinal nerve ligation

Sham operation and SNL surgery, respectively, were performed in 2 groups of 10 rats each, followed by TF testing at 0, 7 and 14 days postoperatively to observe changes in TF latency following SNL surgery. At the same time points, the paw withdrawal reflex against stimulation

using calibrated von Frey filaments (6 g) was tested to ascertain developing mechanical allodynia in the SNL rats.

Changes in TF latencies following intrathecal administration of gabapentin with descending modulation

TF testing was performed in 16 sham-operated and 16 SNL rats divided into 2 groups of 8 animals each, receiving gabapentin or normal saline, respectively, without injection of 1% lidocaine, to assess the effects of gabapentin on TF latency in SNL rats with descending modulation. Gabapentin (gabapentin, G117250; Toronto Research Chemicals Inc., North York, ON, Canada) or normal saline was intrathecally administered through the lumbar catheter. According to previous reports that the ED_{50} of gabapentin with intrathecal administration is 49.5 μg in SNL rats,[19] 50 μg gabapentin was dissolved in 20 μl normal saline.

The rats were placed in the boxes and exposed to 1% isoflurane in oxygen for 20 min, and baseline TF latencies were measured. Then, the respective drugs were injected through the lumbar intrathecal catheters of rats in each group, and each rat was tested for 60 min at 15-min intervals.

Changes in TF latencies following intrathecal administration of gabapentin without descending modulation

TF testing was performed in 16 sham-operated and 16 SNL rats divided into 2 groups of 8 animals each, receiving gabapentin or normal saline, respectively, with injection of 1% lidocaine for descending inhibition, to assess the effects of gabapentin on TF latency in SNL rats without descending modulation. After measurement of baseline TF latencies under isoflurane inhalation, a 10 μl bolus of 1% lidocaine was administered through the cervical intrathecal catheter, followed by 10 μl/h continuous infusion. Five minutes later, TF latencies were measured and saline or gabapentin, at the same doses as described above, was injected through the lumbar intrathecal catheter of rats in both groups, and TF testing was performed for 60 min at 15-min intervals.

Statistical Analysis

Data are expressed as the mean ±S.D. TF latency changes over time were compared using one-way repeated measures ANOVA followed by post-hoc Dunnett's multiple comparison test, and comparisons among groups were analyzed by the unpaired t-test. Statistical analysis was performed using Prism 5 for Windows Ver. 5.01 (GraphPad Software Inc., San Diego, CA, USA). The significance level was set at $P<0.05$.

Results

Changes in TF latencies after spinal nerve ligation

Alterations in TF latencies (%MPE) for 2 weeks following sham operation or SNL operation are shown in Figure 2. There were no significant differences between baseline TF latencies in sham-operated rats and SNL rats, these being 5.6±0.3 sec and 5.6±0.2 sec, respectively. Sham-operated rats had similar TF latencies to the baseline at 7 and 14 days postoperatively: −5.0±5.2% and −5.6±10.7%, respectively. In contrast, SNL rats had significantly shortened TF latencies compared with those of sham-operated rats at 7 and 14 days postoperatively: −27.0±8.3% ($p<0.001$ compared with sham-operated rats) and −28.9±5.3% ($p<0.001$), respectively.

Changes in TF latencies following intrathecal administration of gabapentin with descending modulation

Alterations in TF latencies (%MPE) following lumbar intrathecal injection of normal saline or gabapentin in the sham-operation and SNL groups are shown in Figures 3A and 3B, respectively. In sham-operated rats, although TF

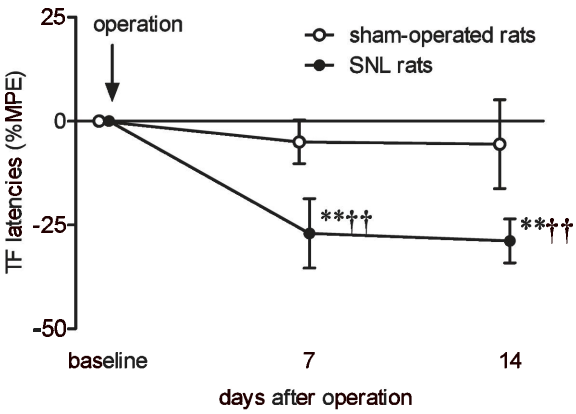

Fig. 2 Comparison of alterations in TF latencies (%MPE) following sham operation or SNL operation. TF latencies in sham-operated rats remained stable, whereas those in SNL rats were significantly shortened. Data are presented as the mean ±S.D. (n=10). **: $p<0.01$ vs sham-operated rats (unpaired t-test). ††: $p<0.01$ vs baseline (Dunnett's multiple comparison test).

latencies in the gabapentin group were slightly prolonged at 15 min and 60 min compared with those in the normal saline group, intrathecal injection of both normal saline and gabapentin did not alter TF latencies during the observation period.

In the SNL rats, TF latencies in the normal saline group remained stable during the observation period. There were no significant alterations in TF latencies between groups until 45 min after injection. At 60 min, significant prolongation of TF latency was observed in the gabapentin group (28.9±17.3%, $p<0.05$), significantly longer than in the normal saline group (3.4±15.8%).

Changes in TF latencies following intrathecal administration of gabapentin without descending modulation

Alterations in TF latencies (%MPE) following lumbar intrathecal injection of normal saline and gabapentin under suppression of descending modulation by 1% lidocaine in the sham-operation and SNL groups are shown in Figures 4A and 4B, respectively. In the sham-operated rats, at 5 min after cervical intrathecal administration of lidocaine, TF latencies in the sham-operated normal saline group were shortened (−31.9±14.1%, $p<0.001$ compared with baseline) and

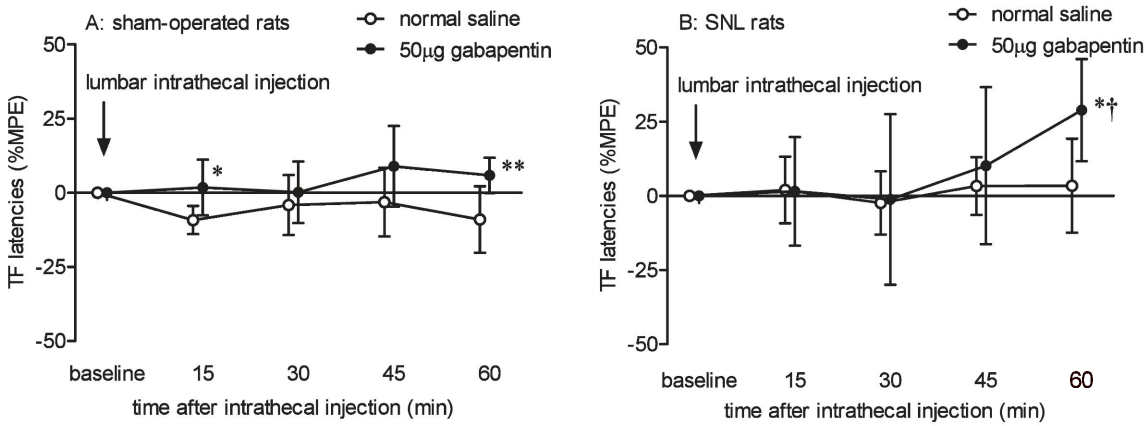

Fig. 3 Comparison of alterations in TF latencies (%MPE) following administration of gabapentin or normal saline with descending modulation in sham-operated (A) and spinal nerve-ligated (SNL) rats (B). In SNL rats, there were no differences in TF latencies between groups except at the 60-min time point. Data are presented as the mean ±S.D. (n=8). *: $p<0.05$, **: $p<0.01$ vs normal saline (unpaired t-test), ††: $p<0.01$ vs baseline (Dunnett's multiple comparison test).

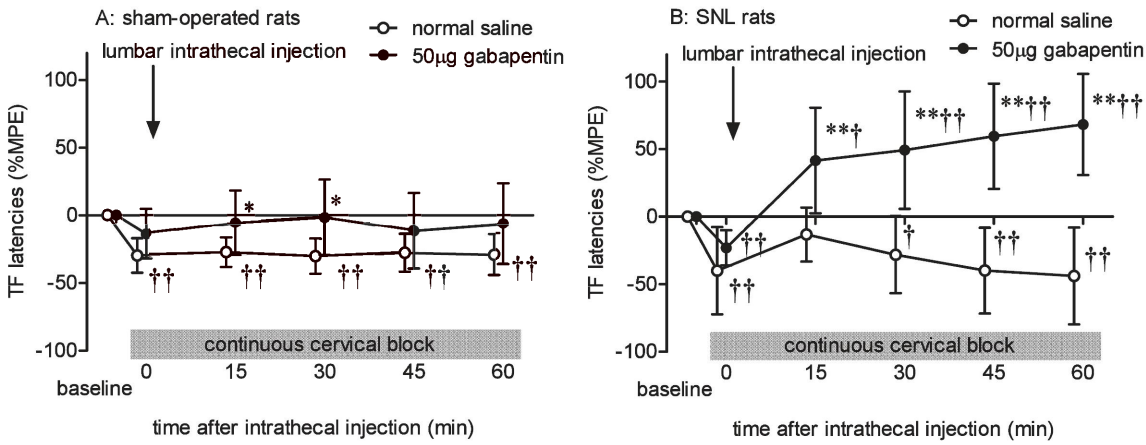

Fig. 4 Comparison of alterations in TF latencies (%MPE) following administration of gabapentin or normal saline without descending modulation in sham-operated (A) and spinal nerve-ligated (SNL) rats (B). Drugs were injected into the lumbar intrathecal catheter following continuous cervical lidocaine infusion. In SNL rats, TF latencies in the normal saline group remained shortened, whereas those in the gabapentin group were prolonged after lumbar injection. Data are presented as the mean ±S.D. (n=8). *: $p<0.05$, **: $p<0.01$ vs normal saline (unpaired t-test), †: $p<0.05$, ††: $p<0.01$ vs baseline (Dunnett's multiple comparison test).

remained stable during the observation period. On the other hand, there were no significant changes in TF latencies in the sham-operated gabapentin group. Although TF latencies in the gabapentin group tended to be longer than in the normal saline group, the differences were significant only at 15 and 30 min.

In SNL rats without descending modulation, at 5 min after cervical intrathecal administration of lidocaine, TF latencies in both the normal saline and gabapentin groups of SNL rats were shortened: $-40.0\pm32.3\%$ and $-23.1\pm13.1\%$, respectively. Thereafter, TF latencies in the normal saline group remained almost stable during the observation period. On the other hand, TF latencies in the SNL-operated gabapentin group were gradually prolonged during the observation period: from $41.6\pm39.0\%$ at 15 min to $68.2\pm37.4\%$ at 60 min ($p<0.01$ and $p<0.001$ compared with the baseline, respectively).

Discussion

Shortened TF latencies were ascertained for 2 weeks following SNL operation. TF latencies following lumbar intrathecal gabapentin did not obviously change under descending modulation in both SNL and sham-operated rats. With suppression of descending modulation by 1% intrathecal lidocaine administration, TF latencies in the gabapentin group of sham-operated rats were only slightly prolonged at 15 min and 30 min compared with the saline group of sham-operated rats, but were significantly prolonged in the gabapentin group of SNL rats.

Both spinal and supraspinal neuronal mechanisms participate in the antinociception of gabapentin at the spinal level, and descending modulation of persistent pain involves both inhibition and facilitation.[20,21] We chemically dissociated the lumbar spinal cord from supraspinal neuronal modulation by means of continuous cervical infusion of lidocaine[17] to evaluate the antinociceptive effect of gabapentin at the spinal level. Since the results of experiments under cervical lidocaine administration showed persistently shortened TF latencies in both sham-operated and SNL rats with normal saline injection, we hypothesized that descending inhibition dominates over descending facilitation under both normal and neuropathic conditions with regard to supraspinal modulation.

During suppression of descending modulation, significant antinociceptive effects of gabapentin were evident in SNL rats as compared to sham-operated rats, and the effect of gabapentin gradually increased. These findings indicate that the effect of gabapentin at the spinal level is more obvious under neuropathic conditions than under normal conditions.

Gabapentin has been reported to act on supraspinal structures and to stimulate noradrenergic descending inhibition under neuropathic conditions.[8,9,22,23] Suppression of descending inhibition causes behavioral hypersensitivity, manifested as shortened latency in the TF test.[17] In this study, the antinociceptive effect of intrathecal gabapentin, seen as prolonged TF latency, was only apparent at 60 min under supraspinal modulation in SNL rats, whereas significant prolongation of TF latencies occurred from 15 min when supraspinal modulation was inhibited by 1% lidocaine. Descending facilitation from the brainstem promotes spinal neuronal hyperexcitability and behavioral hypersensitivity;[24] therefore, the results of this study may indicate that supraspinal facilitative mechanisms invalidate the antinociceptive effects of gabapentin at the spinal level. Saga and Wilcox[25] reported that intrathecal water-soluble contrast media were distributed to the brain at 15 min after injection in dogs. Thus, we speculate that the lumbar intrathecally administered, highly water-soluble gabapentin promptly spread in the spinal canal to the supraspinal structures and produced descending facilitation. It is also possible that the gradually increasing antinociception of gabapentin at the spinal level exceeded facilitation 60 min after intrathecal administration.

Takasaki et al.[10] speculated that the brain is not the primary site of the antinociceptive action of gabapentin, at least in acute herpetic pain, since gabapentin was effective in relieving nociceptive behaviors in acute herpetic pain mice when given intrathecally, but not intraventricularly or intracisternally. From the results of our study, we further postulate that gabapentin has profiles of obvious antinociception at the spinal level and simultaneous descending pronociception from supraspinal structures under neuropathic conditions.

Gabapentin increases the concentration and rate of GABA synthesis in the brain.[5,26,27] Neurons of the spinally projecting noradrenergic nucleus, the locus coeruleus, are under inhibitory

GABAnergic control.[28] Further, increased GABAnergic activity in the rostral ventromedial medulla facilitates descending serotonergic projections that promote dorsal horn neurons.[29] Thus, although the mechanism of supraspinal control of gabapentin is not clear from our experiments, this evidence raises the possibility that elevation of GABA levels in the brain by gabapentin may contribute to the activation of descending facilitatory pathways and attenuation of descending inhibitory pathways.

The limitations of the present study are as follows. First, the withdrawal reflex with intrathecal gabapentin may not be comparable to that with systemic administration. We believed that intrathecal administration of gabapentin was preferable to systemic administration to assess the effect of the drug in the spinal cord since systemic administration may have affected not only the spinal cord or central nervous system but also peripheral organs. Second, all rats in the gabapentin group received a single intrathecal dose. It cannot be rejected that the effects of variable doses of gabapentin on supraspinal structures are not comparable. Hayashida et al.[9] reported that intracerebroventricular gabapentin produced a dose-dependent increase in the withdrawal threshold to paw pressure in paw incision model rats. Thus, larger doses of intrathecal gabapentin raise the possibility of facilitating descending inhibitory pathways.

Our findings indicate that gabapentin causes both apparent antinociception at the spinal level and simultaneous descending facilitation under neuropathic pain conditions. Although gabapentin is proposed as one of several first-line treatments for neuropathic pain[1], the maximal tolerable dose of gabapentin administered as a single agent has an insufficient therapeutic profile.[30–34] Our results suggest that one of the reasons for the insufficient therapeutic profile of systemic gabapentin might be the activation of descending facilitation. Complete elucidation of the supraspinal effects of gabapentin on descending modulation, however, requires further investigation.

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