Research report

Local administration of resveratrol inhibits excitability of nociceptive wide-dynamic range neurons in rat trigeminal spinal nucleus caudalis

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A R T I C L E   I N F O

Article history:
Received 4 March 2016
Received in revised form 28 May 2016
Accepted 6 June 2016
Available online 7 June 2016

Keywords:
Nociception
Resveratrol
Trigeminal spinal nucleus caudalis
Extracellular single-unit recording
Lidocaine
Local anesthetic agents
Complementary and alternative medicine

A B S T R A C T

Although we recently reported that intravenous administration of resveratrol suppresses trigeminal nociception, the precise peripheral effect of resveratrol on nociceptive and non-nociceptive mechanical stimulation-induced trigeminal neuron activity in vivo remains to be determined. The aim of the present study was to investigate whether local subcutaneous administration of resveratrol attenuates mechanical stimulation-induced excitability of trigeminal spinal nucleus caudalis (SpVc) neuron activity in rats, in vivo. Extracellular single-unit recordings were made of SpVc wide-dynamic range (WDR) neuron activity in response to orofacial mechanical stimulation in pentobarbital-anesthetized rats. Neurons responded to non-nocuous and nocuous mechanical stimulation applied to the orofacial skin. Local subcutaneous administration of resveratrol (1–10 mM) into the orofacial skin dose dependently and significantly reduced the mean number of SpVc WDR neurons firing in response to both non-nocuous and nocuous mechanical stimuli, with the maximal inhibition of discharge frequency in response to both stimuli being seen within 5 min. These inhibitory effects were no longer evident after approximately 20 min. The mean magnitude of inhibition by resveratrol (10 mM) of SpVc neuron discharge frequency was almost equal to that of the local anesthetic 1% lidocaine (37 mM). These results suggest that local injection of resveratrol into the peripheral receptive field suppresses the excitability of SpVc neurons, possibly via inhibition of Na⁺ channels in the nocicceptive nerve terminals of trigeminal ganglion neurons. Therefore, local subcutaneous administration of resveratrol may provide relief of trigeminal nociceptive pain, without side effects, thus contributing to the suite of complementary and alternative medicines used as local anesthetic agents.

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1. Introduction

Resveratrol (trans-3,4',5-trihydroxystilbene) is a natural polyphenolic compound found in large number of plants that are part of the human diet, including peanuts, mulberries, grapes and red wine. It is well known that resveratrol has a variety of biological actions, including cardiovascular protection, neuroprotection, and anticancer and anti-inflammatory effects (Fremont 2000; Pervaiz 2003). Because resveratrol has no known toxic side effects (Russo, 2007) and complementary and alternative medicines (CAM), such as herbal medicines and acupuncture, have been used for the treatment of persistent clinical chronic pain (Rao et al., 1999; Konvicka et al., 2008; Rosenberg et al., 2008), resveratrol may be a candidate therapeutic CAM analgesic agent.

The trigeminal spinal nucleus is an important relay station in the transmission of orofacial sensory information and it is functionally subdivided into three nuclei (from rostral to caudal): oralis, interpolaris and caudalis (Sessle, 2000). It is well known that the spinal trigeminal nucleus caudalis (SpVc) is most important relay stations for trigeminal nociceptive inputs from inflammation and tissue injury (Sessle, 2000; Takeda et al., 2012). Recently, Takehana et al.

Abbreviations: SpVc, trigeminal spinal nucleus caudalis; WDR, wide dynamic range; CAM, complementary and alternative medicine; TRP, transient receptor potential; TRPA1, TRP ankyrin 1; DRG, dorsal root ganglion; ANOVA, analysis of variance; TTX-S, tetrodotoxin sensitive; TTX-R, tetrodotoxin resistant.

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http://dx.doi.org/10.1016/j.brainresbull.2016.06.001
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(2016) reported that, in the absence of inflammatory or neuropathic pain, acute intravenous administration of resveratrol suppresses SpVc wide-dynamic range (WDR) neurons via both peripheral and central mechanisms. Therefore, resveratrol may be a potential CAM therapeutic agent for the treatment of trigeminal nociceptive pain without side effects.

Previous reports suggest that resveratrol modulates neuronal excitability in both the peripheral and central nervous systems via voltage-dependent ion channels (sodium, potassium and calcium; Kim et al., 2005; Liew et al., 2005; Gao and Hu, 2005), as well as synaptic transmission via ligand-gated channels and various voltage-dependent ion channels (Gao et al., 2006; Lee et al., 2011). Kim et al. (2005) demonstrated that resveratrol inhibits tetrodotoxin-sensitive (TTX-S) and TTX-resistant (TTX-R) Na+ currents in acutely dissociated dorsal root ganglion (DRG) neurons. Furthermore, it has been shown, using the rat formalin test, that resveratrol induces peripheral antinociception via opening of several K+ channels (Grannados-Soto et al., 2002). In addition, recent findings suggest that resveratrol modulates the activity of transient receptor potential (TRP) channels, including being a potent inhibitor of TRP ankyrin 1 (TRPA1) channels both in vitro and in vivo (Yu et al., 2013). In turn, TRPA1 channels have been shown to modulate mechanotransduction via the generator potential in primary sensory neurons (Kwan et al., 2009). Together, these observations strongly suggest that local administration of resveratrol into the receptive field of SpVc WDR neurons may suppress the transmission of nociceptive pain in the periphery. Therefore, we hypothesized that local subcutaneous administration of resveratrol would attenuate both non-nociceptive and nociceptive stimulation-induced excitability of SpVc WDR neurons. However, the acute effects of resveratrol in vivo on nociceptive and non-nociceptive mechanical stimulation-induced SpVc WDR neuron activity have not yet been elucidated.

Therefore, the aim of the present study was to investigate whether local subcutaneous injection of resveratrol into the receptive field of SpVc WDR neurons could attenuate non-nociceptive and nociceptive stimulation-induced excitability of these neurons, in vivo. In addition, we compared the magnitude of suppression of trigeminal nociception between resveratrol and the clinically used local anesthetic lidocaine, a sodium channel blocker.

2. Materials and methods

The experiments reported herein were approved by the Animal Use and Care Committee of Azabu University and were performed in accordance with the ethical guidelines of the International Association for the Study of Pain (Zimmermann, 1983). Every effort was made to minimize the number of animals used and their suffering.

2.1. Extracellular single-unit recordings from SpVc WDR neurons

Electrophysiological recordings were made in 24 adult male Wistar rats (weighing 250–290 g). Each animal was first anesthetized with pentobarbital sodium (45 mg/kg, i.p.) and maintained with additional doses of 2–3 mg/kg per h pentobarbital sodium administered through a cannula inserted in the jugular vein, as required. The level of anesthesia was confirmed by the absence of the corneal reflex and a lack of response to paw pinching. Rectal temperature was maintained at 37.0 ± 0.5 °C with a homeothermic blanket during recording. Rats were then placed in a stereotaxic apparatus, and the activity of a single neuron from the SpVc region was recorded extracellularly. Single neuron activity was recorded using a glass micropipette filled with 2% Pontamine sky blue and 0.5 M sodium acetate in regions identified according to the stereotaxic coordinates of Paxinos and Watson (1986). Neuronal activity was amplified (DAM80; World Precision Instruments, Sarasota, FL, USA), filtered (0.3–10 kHz), monitored on an oscilloscope (SS-7672; Iwatsu, Tokyo, Japan) and recorded on a polygraph (8M14; NEC-Sanei Instruments, Tokyo, Japan). Recordings were analyzed off-line using a Power Lab and Chart 5 software (ADInstruments, Oxford, UK).

2.2. Experimental protocols

Extracellular recordings of SpVc WDR unit activity were performed as described previously (Takeda et al., 2000, 2012; Takehana et al., 2016). Briefly, mechanical stimulation was used as a search stimulus to identify the receptive field quickly and to avoid sensitization of peripheral receptors. Single units that responded to stimulation of the left side orofacial skin (whisker pad) with a brush and a set of von Frey hairs (Semmes-Weinstein Monofilaments; North Coast Medical, Gilroy, CA, USA) were identified. Noxious pinch stimulation was applied to the orofacial area with forceps that evoked a pain sensation when applied to a human subject. After identification of WDR SpVc neurons responding to whisker pad stimulation, we determined whether there was spontaneous discharge. The threshold for mechanical stimulation was determined by using non-nociceptive and nociceptive mechanical stimulation (5 s) with von Frey hairs (2, 4, 6, 10, 15, 26 and 60 g) applied at 5 s intervals. The mecanorceptive field of neurons was mapped by probing the facial skin with von Frey hairs, and then outlined on a life-sized drawing of a rat on tracing paper. WDR neuron discharges induced by mechanical stimulation were quantified by subtracting background activity from evoked activity. Spontaneous discharge frequencies were determined over 2–5 min. If no discharge was recorded, the cell was deemed a silent neuron. Mean firing rates of SpVc WDR neurons evoked by mechanical stimulation were compared before and after drug administration. Because previous studies have demonstrated that WDR neurons in the SpVc region have an important role in the mechanism underlying hyperalgesia and referred pain associated with orofacial pain (Takeda et al., 2000, 2005, 2012; Nishikawa et al., 2004) and that the discharge of these neurons is suppressed by intravenous resveratrol administration (Takehana et al., 2016), the focus of the present study was on the effects of resveratrol on SpVc WDR neuronal activity; we did not examine nociceptive-specific neurons. Post-stimulus histograms (bin = 100 ms) were generated in response to each stimulus. The effects of subcutaneous resveratrol (0.05 mL; 1, 5 and 10 mM) and lidocaine (1% and 2% Xylocaine; equivalent to 37 and 74 mM, respectively), administered through a Hamilton microsyringe, were evaluated 5, 10, 20, 30 and 40 min after administration because the peak effect and recovery were thought to occur within this time frame. Resveratrol was dissolved in dimethyl sulfoxide to create a stock solution of 20 mM. The stock solution was stored at −20 °C until use. The stock solution was diluted to the desired concentrations using saline immediately before use. Mean spontaneous and mechanical stimulation-induced discharges rates, and the mechanical threshold before and after subcutaneous administration of resveratrol were analyzed in the present study.

2.3. Identification of recording sites

The location of the recording sites for SpVc WDR neuron activity was identified as described previously (Takeda et al., 2000, 2012; Takehana et al., 2016). Briefly, at the end of the recording sessions, rats were deeply anesthetized and anodal direct current (DC; 30 μA, 5 min) was passed through the recording micropipette. The rats were perfused transcardially with saline and 10% formalin. Frozen coronal sections (30 μm) were cut and stained with hematoxylin–eosin. Recording sites were identified as blue spots.
on the coronal sections, and electrode tracks were constructed in combination with micromanipulator readings.

2.4. Data analysis

Values are expressed as the mean ± SEM. Statistical analysis was performed using two-way repeated-measures analysis of variance (ANOVA) followed by the Tukey–Kramer or Dunnnett’s test as post hoc tests for electrophysiological data. Two-sided P < 0.05 was considered significant.

3. Results

3.1. Activity of SpVc WDR neurons innervating the facial skin

Extracellular single-unit activity was recorded from 24 neurons in the SpVc. The effects of subcutaneous injections of resveratrol were tested on 15 SpVc neurons, whereas the remaining nine neurons were used to examine the effects of subcutaneous lidocaine injection on neuron excitability. These SpVc neurons responded to non-noxious and noxious mechanical stimulation and exhibited a somatic receptive field in the orofacial area (mainly the whisker pad; Fig. 1A), as described previously (Takeda et al., 2000, 2012; Takehana et al., 2016). In addition, all these neurons responded to mechanical stimulation of the receptive field innervated by ophthalmic and maxillary branches. Three of 24 units exhibited spontaneous discharge. As shown in Fig. 1B, recording sites were found in Layers I–II (n = 5; 21%) and III–V (n = 19; 79%), at a depth of 130–780 μm in the SpVc (obex from −0.25 to −2.0 mm). There were no obvious differences in the location of the recording sites between the resveratrol- and lidocaine-injected groups (Fig. 1B). Typical examples of SpVc WDR neuronal unit responses are shown in Fig. 1C. Graded mechanical stimulation was applied to the most sensitive area of the receptive field, which resulted in an increase in the firing frequency of SpVc WDR neurons in proportion to stimulus intensity. Typical examples of the action potential waveforms evoked by mechanical stimulation are shown in Fig. 1C (inset). The mean mechanical stimulation-induced spike threshold was 2.6 ± 1.2 g (n = 24). Every neuron recorded belonged to the WDR category of neurons (Takeda et al., 2012).

3.2. Effects of local resveratrol injections on the excitability of SpVc WDR neurons

Fig. 2 shows a typical example of the effects of local subcutaneous injection of resveratrol (10 mM) on the excitability of SpVc WDR neurons in response to non-noxious mechanical stimulation. Five minutes after subcutaneous injection of 10 mM resveratrol into the center of the receptive field, non-noxious (6 and 10 g) mechanical stimulation-evoked SpVc WDR neuronal activity was inhibited, with activity returning to control levels within approximately 20 min (Fig. 2A–C). The size of the receptive field decreased slightly after resveratrol injection, from 18.1 ± 0.2 to 15.7 ± 0.3 mm², but not significant. No obvious changes in the mechanical threshold were observed after resveratrol administration. The effects of resveratrol on non-noxious mechanical stimulation-evoked SpVc WDR neuron activity are summarized in Fig. 3. Mean firing rates of non-noxious mechanical stimulation-evoked SpVc WDR neurons decreased significantly after resveratrol injection compared with prior to injection (Fig. 3; before vs after; 6 g, F = 6.4; 10 g, F = 7.7; n = 5; P < 0.05), and returned to control levels within 20 min (after resveratrol vs recovery; 10 g, F = 7.4, n = 5; P < 0.05). Resveratrol (1–10 mM) exhibited significant dose-dependent suppression of non-noxious mechanical stimulation-evoked SpVc WDR neuron firing (Fig. 4; 1 mM vs 10 mM; 6 g, F = 30.1; 10 g, F = 12.7; n = 5; P < 0.05). No obvious changes in spontaneous firing were observed after local injection of resveratrol. Local injection of vehicle had no significant effect on either spontaneous or non-noxious, noxious mechanical and pinch stimulation-evoked SpVc WDR neuron activity (n = 3; Fig. 2D).
3.3. Effects of resveratrol on the excitability of SpVc WDR neurons in response to noxious stimuli

Fig. 2 also shows typical examples of the effects of subcutaneous injection of 10 mM resveratrol into the receptive field on the excitability of SpVc WDR neurons in response to noxious mechanical and noxious pinch stimulation. Noxious mechanical (15–60 g) stimulation-evoked SpVc WDR neuron activity was inhibited 5 min after injection of resveratrol, but neuron activity returned to control levels within approximately 20 min (Fig. 2A–C). Similarly, SpVc WDR neuron activity in response to noxious pinch stimulation was inhibited 5 min after resveratrol injection, with responses returning to control levels within 20 min (Fig. 2A–C).

As shown in Fig. 3, the mean firing rates of SpVc WDR neurons evoked by noxious mechanical and pinch stimulation decreased significantly after injection of resveratrol compared with control (Fig. 3; before vs after: 15 g, F = 6.9, P < 0.05; 60 g, F = 31.2, P < 0.01; pinch, F = 7.9, P < 0.05; n = 5). Resveratrol (1–10 mM) suppression of noxious mechanical stimulation- and noxious pinch-evoked SpVc WDR neuron firing was dose dependent (Fig. 4; 1 mM vs 10 mM; 15 g, F = 9.4; 60 g, F = 12.9; pinch, F = 12.5; n = 5; P < 0.05). The size of the receptive field decreased slightly after resveratrol injection, from 16.5 ± 0.4 to 13.9 ± 0.5 mm², but not significant. Local administration of vehicle had no significant effect on either spontaneous or evoked (non-noxious, noxious mechanical, and pinch stimulation) activity of SpVc WDR neurons (n = 3; Fig. 2D).

3.4. Comparison of the effects of resveratrol and lidocaine on noxious stimulus-induced SpVc WDR neuron activity

Finally, the magnitude of the inhibition of noxious stimulation-induced SpVc WDR neuron excitability by resveratrol and lidocaine was compared. Typical examples of the effects of 1% lidocaine (37 mM; injected subcutaneously into the center of the receptive field) on the excitability of SpVc WDR neurons in response to non-noxious, noxious mechanical, and noxious pinch stimulation are shown in Fig. 5A. Responses of SpVc WDR neurons to non-noxious and noxious mechanical stimulation were inhibited 5–10 min after lidocaine injection, and the inhibition was relatively long-lived compared with that seen after resveratrol injection (40 vs 20 min, respectively). Please compare to Figs. 2 C and 5 C. Similarly, SpVc WDR neuron activity in response to noxious pinch stimulation was inhibited 5 min after injection of lidocaine, with responses returning to control levels within 40 min (Fig. 5A–C). The effects of lidocaine on non-noxious and noxious mechanical stimulation-evoked SpVc WDR neuron activity are summarized in Fig. 5D. After injection of 1% lidocaine, there was a significant decrease in mean firing rates of non-noxious and noxious mechanical stimulation-evoked SpVc WDR neurons compared with rates prior to lidocaine injection. Firing rates returned to control levels within 40 min (Fig. 5; lidocaine vs recovery; 6 g, F = 10.4, P < 0.05; 10 g, F = 19.5, P < 0.01; 15 g, F = 34.7, P < 0.01; 60 g, F = 25.5, P < 0.01; Pinch, F = 10.1, P < 0.05, n = 5).

Although the duration of the inhibitory effect of 1% lidocaine on SpVc WDR neuron responses to noxious stimuli was significantly longer than that of 10 mM resveratrol (resveratrol vs lidocaine; 18.0 ± 2.7 vs 41.0 ± 3.6 min, F = 21.1, n = 5, P < 0.01), a comparison of the mean magnitude of inhibition of SpVc WDR nociceptive transmission showed no significant differences between 10 mM resveratrol and 37 mM lidocaine (Fig. 6), with the inhibition by resveratrol of SpVc neuronal discharge frequency being almost equal to that of the sodium channel blocker lidocaine (37 mM).

4. Discussion

The present study provides evidence that subcutaneous local injection of resveratrol into the peripheral receptive field suppresses the excitability of SpVc neurons, possibly by inhibiting sodium channels in the nociceptive nerve terminals of trigeminal ganglion neurons. Therefore, local injection of resveratrol may act in a manner similar to injection of a local anesthetic agent, providing relief from trigeminal nociceptive pain without side effects. As such, resveratrol may be a candidate CAM.

4.1. Subcutaneous resveratrol suppresses SpVc neuronal activity

Recently, we reported that in the absence of inflammatory or neuropathic pain, acute intravenous resveratrol administration suppressed the activity of SpVc WDR neurons and therefore resveratrol may be a candidate CAM therapeutic agent for the treatment of trigeminal nociceptive pain without side effects (Takehana et al., 2016); the results of that study suggested that resveratrol suppresses trigeminal nociceptive pain via both peripheral and central effects. In the present study, we investigated whether local subcutaneous injection of resveratrol into the receptive field could attenuate non-noxious and noxious mechanical stimulation-induced excitability of SpVc WDR neurons in vivo. The main findings of the present study are that: (i) the mean firing rate of SpVc WDR
Fig. 5. Effects of subcutaneous administration of 1% lidocaine (37 mM) into the peripheral receptive field on responses of spinal trigeminal nucleus caudalis (SpVc) wide-dynamic range (WDR) neurons to non-noxious, noxious mechanical, and noxious pinch stimulation. (A–C) Typical examples of SpVc WDR neuronal activity in response to non-noxious (6 and 10 g), noxious (15 and 60 g) mechanical, and noxious pinch stimulation before (A) and 5 (B) and 40 min (C) after 1% lidocaine administration (37 mM). Receptive field of whisker pad in the facial skin. Blacken area indicates the location and size of receptive field. (D) Time course of the effects of local 1% lidocaine on mean firing frequency of SpVc WDR neurons responding to non-noxious, noxious mechanical, and noxious pinch stimulation. *P < 0.05 for before vs 5 min after 1% lidocaine administration; **P < 0.05 for 5 vs 40 min after 1% lidocaine administration. n = 5.

4.2. Peripheral mechanism: suppression of SpVc WDR neuron excitability by local subcutaneous resveratrol

Recently, Meng et al. (2015) reported that, in vitro, mechanical stimuli induce mechanosensitive currents via mechanosensitive channels such as the TRPA1 channel to trigger mechanotransduction in trigeminal neurons innervating the inner walls of the

neurons in response to both non-noxious and noxious mechanical stimuli was dose-dependently reduced by local injection of resveratrol (1–10 mM); (ii) resveratrol inhibition of the discharge frequency in response to both non-noxious and noxious mechanical stimuli was reversible (within ~20 min); and (iii) local injection of vehicle had no significant on non-noxious or noxious mechanical or pinch stimulation-evoked SpVc WDR neuron activity.
anterior eye chamber. In addition, TRPA1 channels have been shown to modulate mechanotransduction in primary sensory neurons (Kwan et al., 2009) and it has been reported that resveratrol is a potent inhibitor of TRPA1 channels in vitro and in vivo (Yu et al., 2013), suggesting that resveratrol attenuates the generator potential and inhibits action potential firing via the mechanical transduction process. Moreover, resveratrol has been reported to modulate Na⁺ and K⁺ currents in DRG neurons, which are associated with the generation of action potentials (Kim et al., 2005; Grannados-Soto et al., 2002). Specifically, Kim et al. (2005) showed that resveratrol predominantly inhibits Na⁺ currents in the acutely dissociated DRG neurons, indicating that resveratrol inhibits the generation of action potentials. In addition, it has been reported that resveratrol inhibits both TTX-S and TTX-R Na⁺ currents in acutely dissociated primary afferent sensory (DRG) neurons and TTX-R Na⁺ currents appear to be selectively expressed in nociceptive (small- and medium-sized) DRG neurons, corresponding to Aβ-/C-primary afferent trigeminal ganglion neurons (Cummins et al., 1999; Takeda et al., 2005). Because TTX-S Na⁺ currents were relatively more sensitive to the inhibitory effects of resveratrol than TTX-R Na⁺ currents (Kim et al., 2005), it can be speculated that local administration of resveratrol may attenuate the non-nociceptive primary afferent (trigeminal ganglion) neurons, subsequently inhibiting non-nociceptive stimulation-evoked SpVc WDR neuronal activity. However, further studies examining the effects of resveratrol on the excitability of non-nociceptive and nociceptive trigeminal ganglion neurons are needed to confirm this possibility.

Together, the results suggest that resveratrol inhibits the excitability of peripheral terminals of trigeminal nerves by modulating both transduction (generator potential) and generation (initiating action potentials) mechanisms.

Previously, antinociceptive effects of resveratrol following intravenous administration were observed with doses as low as 10 mM, with no further increases in effect observed with higher doses (Takehana et al., 2016). In the present study, following the local administration of 10 mM resveratrol, the drug entered the subcutaneous space and was diluted in the extracellular fluid to a calculated local concentration of approximately >100 μM; this concentration had a significant effect on the sensory terminals of trigeminal ganglion neurons. Indeed, a previous in vitro study showed that 100 μM resveratrol had the maximum inhibitory effect on the amplitude of TTX-S Na⁺ currents (~60%; Kim et al., 2005). In this study, we found that there was no significant difference in magnitude of the inhibitory effect on the SpVc neuronal discharge frequency between the 10 mM and 20 mM resveratrol (data not shown). Therefore it can be speculated that the maximum inhibitory effect was obtained with 10 mM resveratrol.

4.3. Functional significance of suppression of nociceptive stimulation-induced excitability of SpVc neurons following local injection of resveratrol

It is well known that the SpVc nucleus is an important relay station for trigeminal nociception, including for the orofacial region. Because SpVc WDR neurons contribute to the mechanism of hyperalgesia and/or referred pain associated with dental pain (Takeda et al., 2000, 2005, 2012; Nishikawa et al., 2004), only the effect of resveratrol on SpVc WDR neuronal activity was evaluated in the present study and nociceptive specific neurons were not tested. Following tissue injury and inflammation of the area innervating the orofacial area, changes in the properties of these neurons lead to pathological pain, such as hyperalgesia and allodynia (Iwata et al., 1999; Takeda et al., 2012). In addition, we reported previously that temporomandibular joint inflammation-induced hyperexcitability of SpVc WDR neurons contributes to the ectopic mechanical allodynia innervating the facial skin (Takeda et al., 2005, 2012). Thus, the results of the present study suggest that local subcutaneous resveratrol administration may attenuate the excitability of SpVc WDR neurons associated with the trigeminal area and tissue injury/inflammation. However, further studies are needed to confirm this.

The voltage-gated Na⁺ channel blocker lidocaine is the most representative and widely used form of local anesthetic. In the present study, we compared the mean magnitude of inhibition of SpVc WDR nociceptive transmission between resveratrol and 1% and 2% lidocaine. The mean magnitude of inhibition of SpVc neuronal discharge frequency was almost equal between resveratrol (10 mM) and 1% lidocaine (37 mM), indicating that the potency of the inhibitory effect of nociceptive transmission was four-fold higher for resveratrol than 1% lidocaine. However, the duration of the suppression of SpVc WDR neuron activity was significantly shorter for resveratrol than lidocaine. Although the precise mechanism underlying the difference in the magnitude and duration of inhibition of neuronal activity by resveratrol and lidocaine remains unknown, there are several possible explanations. First, it can be postulated that the reason why a lower concentration of resveratrol inhibits SpVc WDR neuron activity than lidocaine is that local injection of resveratrol suppresses the excitability of SpVc neurons, possibly by suppressing Na⁺ channels and/or mechanosensory channels, such as TRPA1 channels, in the nociceptive nerve terminals of trigeminal ganglion neurons. Second, the fact that the duration of the inhibitory effect of resveratrol was relatively shorter than that of lidocaine may be due primarily to differences in the affinity of the two drugs for Na⁺ channels (Kim et al., 2005). However, further studies are needed to clarify this point.

Finally, until recently CAM such as herbal medicines and acupuncture have been used for the treatment of persistent clinical chronic pain (Rao et al., 1999; Konvicka et al., 2008; Rosenberg et al., 2008). In addition, diet and dietary supplementation can potentially affect conditions associated with pain (Shir et al., 2001; Ernest, 2003; Tall and Raja 2004). Interestingly, resveratrol has no known toxic side effects (Russo 2007), and so it could be a candidate CAM for use as a therapeutic analgesic agent. Because incisions associated with surgery cause acute pain and surgery has been identified as a potential major cause of chronic pain (Perkins and Kehlet 2000; Kehlet et al., 2006), it can be speculated that resveratrol may effectively reduce clinical pain, such as postoperative pain (Locher-Claus et al., 2005; Tillu et al., 2012). There are some clinical reports that patients with trigeminal neuralgia, local and intravenous administration of lidocaine effectively attenuates of intensity of pain.
including allodynia and hyperalgesia (Kanai et al., 2006; Han et al., 2008; Stavrakou et al., 2014). Present study indicated that local injection of resveratrol may act in a manner similar to injection of a local anesthetic agent. Thus, local injection of resveratrol may provide relief from trigeminal nociceptive pain, including trigeminal neuralgia without side effects, and so resveratrol may be a candidate CAM therapeutic agent.

References