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Some Effects of Mustard Oil and Cinnamaldehyde on Spinal Neuronal Responses to Cutaneous Stimuli in Male Rats

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(Presented by Academy Member Tengiz Oniani)

ABSTRACT. Transient receptor potential (TRP) channels are being ardently pursued as targets for pain therapies. They play an important role in transducing thermal, mechanical and chemical stimuli for somatic sensation. Several TRP channels exhibit sensitivity to increases or decreases in temperature as well as chemical ligands that elicit similar thermal or painful sensations; these include mustard oil, cinnamaldehyde from cinnamon, menthol from mint, gingerol, camphor, capsaicin from chili peppers, eugenol from cloves, and others.

Mustard oil [allyl isothiocyanate (AITC)] and cinnamaldehyde (CA), agonists of the ion channel TRPA1 expressed in sensory neurons, elicit a burning sensation and heat hyperalgesia. In this work, we tested whether these phenomena are reflected in the responses of lumbar spinal wide-dynamic range (WDR) neurons recorded in anesthetized male rats. Responses to electrical and graded mechanical and noxious thermal stimulation were tested before and after cutaneous application of AITC or CA. Repetitive application of AITC initially increased the firing rate of 52% of units followed by rapid desensitization that persisted when AITC was reapplied 30 min later. Responses to noxious thermal, but not mechanical, stimuli were significantly enhanced irrespective of whether the neuron was directly activated by AITC. These findings indicate that AITC produced central inhibition and peripheral sensitization of heat nociceptors. CA did not directly excite WDR neurons, and significantly enhanced responses to noxious heat while not affecting responses to skin cooling or mechanical stimulation, indicating a peripheral sensitization of heat nociceptors.

Overall, the presented data with our behavioral results support the idea that thermo-sensitive TRPA1 channel represents a promising target for the development of analgesic drugs in relief of pain. *© 2012 Bull. Georg. Natl. Acad. Sci.*

Key words: *desensitization, dorsal horn, nociception, noxious heat, skin cooling, sensitization, spinal cord.*

The transient receptor (TRP) cation channels have been among the most intensively pursued drug targets for pain relief over the past few years. Pioneering research in the field of pain has established that a subset of TRP channels which are activated by temperatures (the so-called thermoTRP channels) are capable of initiating sensory nerve impulses following the detection of thermal and chemical stimuli [1-3]. Although pain is currently the most advanced TRP channel-related field, an increasing number of gene deletion studies in animals and genetic association investigations in humans have demonstrated that the pathophysiological roles of TRP channels extend well beyond the sensory nervous system [4].

The TRP cation channel superfamily is a diverse family of 28 cation channels that have varied physiological functions, including thermal sensation, chemo- and mechanosensation, magnesium and iron transport. Several TRP channels exhibit sensitivity to increases or decreases in temperature as well as chemical ligands that elicit similar thermal or painful sensations; these include mustard oil, cinnamaldehyde from cinnamon, menthol from mint, gingerol, camphor, capsaicin from chili pepper, eugenol from cloves, and others. The TRPA subfamily has only one known member (TRPA1) and its name refers to unusually high number of ankyrin repeats at the amino terminus of the channel protein [3-5].

It is known that mustard oil [allyl isothiocyanate (AITC)] and cinnamic aldehyde (CA) are agonists of the TRPA1 channel [6-8]. When applied to skin, they elicit burning pain, thermal hyperalgesia, and mechanical allodynia [9]. In the oral or nasal mucosa, AITC and CA elicit burning irritation that decreases (desensitizes) across trials of repeated application [10-12]. Lingual application of AITC or CA excites neurons in the trigeminal subnucleus caudalis (Vc) [13-15]. AITC excitation of Vc neurons exhibits a desensitizing temporal pattern while sensitizing responses to noxious heat [14].

Here we tested whether spinal wide-dynamic range (WDR) type dorsal horn neuronal responses to repeated cutaneous application of AITC or CA similarly exhibit a desensitizing pattern and whether their responses to mechanical and noxious thermal stimuli are enhanced after application of these chemicals, consistent with human psychophysical observations [9,11,12]. We presently focused on WDR neurons for two reasons. First, WDR neurons respond to innocuous mechanical as well as noxious thermal stimuli, allowing assessment of the effects of AITC and CA on both types of responses within the same neuronal population, which would not be possible with nociceptive-specific (NS) neurons. Second, available evidence indicates that WDR neurons are sufficient for pain perception and they are well suited to encode the intensity of noxious heat [16].

Methods

Animals and Surgery. Adult male Sprague–Dawley rats (450-600 g) were used. The experimental protocol was approved by the UC Davis Animal Use and Care Committee. Rats were housed in a room with controlled temperature (22±1°C) and lighting with unrestricted access to food and water.

Rats were anesthetized with sodium pentobarbital (65 mg/kg, intraperitoneal injection). A tracheostomy tube was implanted, the jugular vein or lateral tail vein was cannulated with PE-50 tubing for maintenance of pentobarbital anesthesia. Core body temperature was monitored rectally using a BAT-12 thermometer (Physitemp, Clifton, NJ) and maintained at 37±0.2°C with a lamp and heating pad. During recording, anesthesia was maintained by intravenous (iv) pentobarbital pump infusion. The L6–S1 intervertebral space was identified by palpation of the spinous processes and the posterior superior iliac spine, and a midline skin incision was made from approximately L6 to T11 spinous processes. The paraspinous muscles were dissected free from the L2–T12 spinous processes on both sides, and the transverse processes were exposed by scraping off attached connective tissue. L1 and T13 spinous processes were cut and

removed, and a bilateral laminectomy was performed at both levels under a dissection microscope. The dura was removed and warm agar was poured over the spinal cord. Vertebral clamps on the transverse processes of T12 and L2 were used to stabilize the animal in a stereotaxic frame (Kopf Instruments, Tujunga, CA). Needle electrodes were placed in both forelimbs to monitor electrocardiographic (ECG) activity. In 21 rats the sciatic nerve was exposed for electrical stimulation. A 3.5-cm midline incision was made in the postero-lateral upper hindlimb at the level of the biceps femoris muscle. The semitendinosus and biceps femoris muscles were separated using blunt dissection techniques and the semimembranosus muscle was reflected with fine forceps and microscissors. The left sciatic nerve was isolated above the bifurcation of the tibial and common peroneal nerve and a strip of paraffin wax was wrapped beneath the nerve. After placement in the stereotaxic frame, the sciatic nerve was positioned onto a hooked parallel bipolar electrode (FHC, Bowdoinham, ME) and bathed in warmed mineral oil intestinal lubricant. During trials with electrical stimulation a neuromuscular blocker (pancuronium, 0.1 mg iv) was administered and the animal was ventilated using a positive-pressure pump (Harvard Apparatus, Holliston, MA). End-tidal CO_2 was monitored by a Datex 254 gas analyzer (Datex-Ohmeda, Tewksbury, MA) and maintained between 3.0 and 4.0% by adjustment of tidal volume and/or respiratory rate.

Stimulation and recording. An 8-11-MΩ Teflon-coated tungsten microelectrode (FHC) was advanced into the dorsal horn of the spinal cord using a hydraulic microdrive to record single-unit activity of dorsal horn neurons. Units isolated for study were always at depths <1 mm. Action potentials were amplified and displayed by conventional means, and sent to a computer for storage and analysis using a Powerlab interface and Chart 5.0 software (AD Instruments, Oxford, UK).

Single units were searched for and isolated using innocuous mechanical stimulation of the plantar surface of the ipsilateral hindpaw. Units were chosen with receptive field areas on the plantar surface of the toes, corresponding to approximately L5 spinal cord. Only units that responded to graded non-noxious (brushing, 4–12 g von Frey) and noxious (76 g von Frey, pinch) mechanical and noxious thermal (42, 46, and 50°C) stimuli were considered for further study (WDR neurons). For mechanical stimulation, a series of graded von Frey filaments (4, 12, and 76 g) were applied in ascending order. Each stimulus was applied for 10 s at a 1.5-min interstimulus interval to the center of the receptive field.

Thermal stimuli were delivered to the center of the receptive field using a Peltier device (Physitemp NTE-2A) mounted to a micromanipulator. The thermode temperature was controlled by computer, and stimuli were delivered at a rate of about 12.5°C/s from an adapting temperature of 35°C with an accuracy of ±0.1°C. In the initial studies with AITC (n=27 rats), 46°C and 50°C stimuli were used, whereas in later studies with CA (n=14 rats), 42, 46, and 50°C stimuli were used. In several experiments, a cooling stimulus (from 35°C to 10°C over a 30 sec period) was also delivered.

Chemical application. Ten minutes after completion of the mechanical and thermal (and electrical, if included) stimulation series, 60 s of baseline activity was recorded before application of either AITC, CA, or mineral oil (vehicle control). AITC (allyl isothiocyanate; 2 μl, 75% in mineral oil; Fluka, St. Louis, MO), cinnamaldehyde (CA; in mineral oil; Sigma–Aldrich), or mineral oil was then topically applied to the center of the receptive field area at 1 min intervals for 10 min using a Hamilton microsyringe attached to PE-50 tubing. Eleven minutes after the last AITC or CA droplet was applied, the von Frey and thermal stimulation series were repeated. The thermal probe was replaced at the same hindpaw location using millimeter coordinates on the micromanipulator to which the thermal probe was mounted. Thermal stimulation was always initiated 2 min after

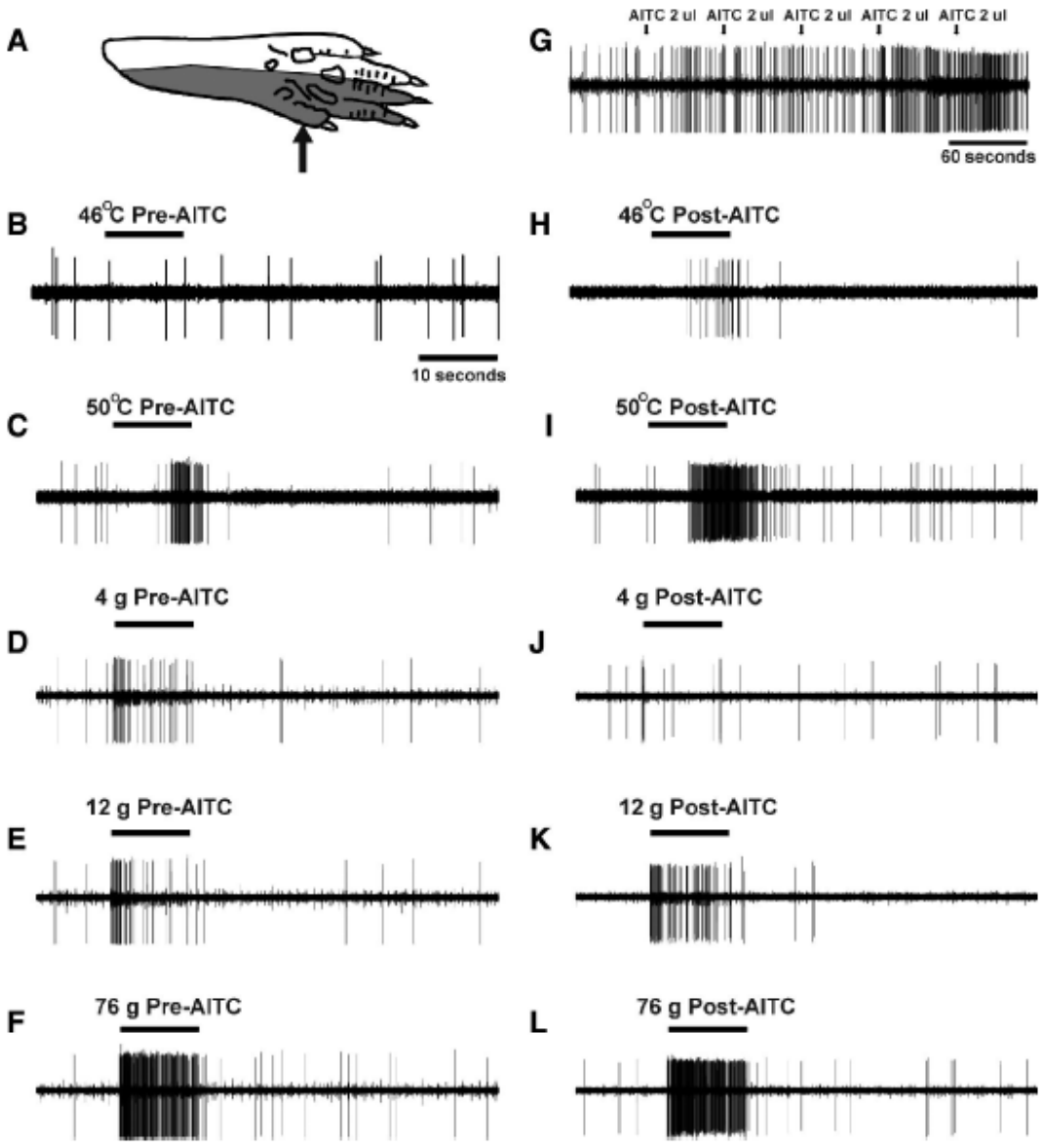

Fig. 1. Example of allyl isothiocyanate (AITC) sensitive lumbar spinal wide dynamic range (WDR) neuron. *A*: shaded area shows extent of mechano-sensitive receptive field on lateral hindpaw. Arrow: site of AITC application. *B* and *C*: raw spike traces of response to 46°C and 50°C heat stimuli before AITC application. *D–F*: responses to graded mechanical stimulation at indicated von Frey bending forces. *G*: spike trace of activity during repeated application of AITC (75%, 2 μl droplets) at 1 min intervals (arrows). *H–L*: spike traces of responses to graded noxious heat (*H*, *I*) and mechanical stimulation (*J–L*) after sequential application of AITC.

replacement of the thermal probe. Application of AITC or CA was repeated after a 10 min wait period. Thus, 30 min had passed between the last AITC or CA application of trial 1 and the first AITC or CA application of trial 2. On completion of the experiment the animal was killed by overdose of pentobarbital, administered intravenously.

In 14 experiments electrical stimulation of the sciatic nerve was performed. In these plus an additional 5 experiments, the hindpaw receptive field was also stimulated electrically by percutaneous needle electrodes. Constant-current stimulus trains of 16 pulses (0.7 ms duration) at 1 Hz were delivered with an S48 stimulator (Grass, West Warwick, RI). We presently

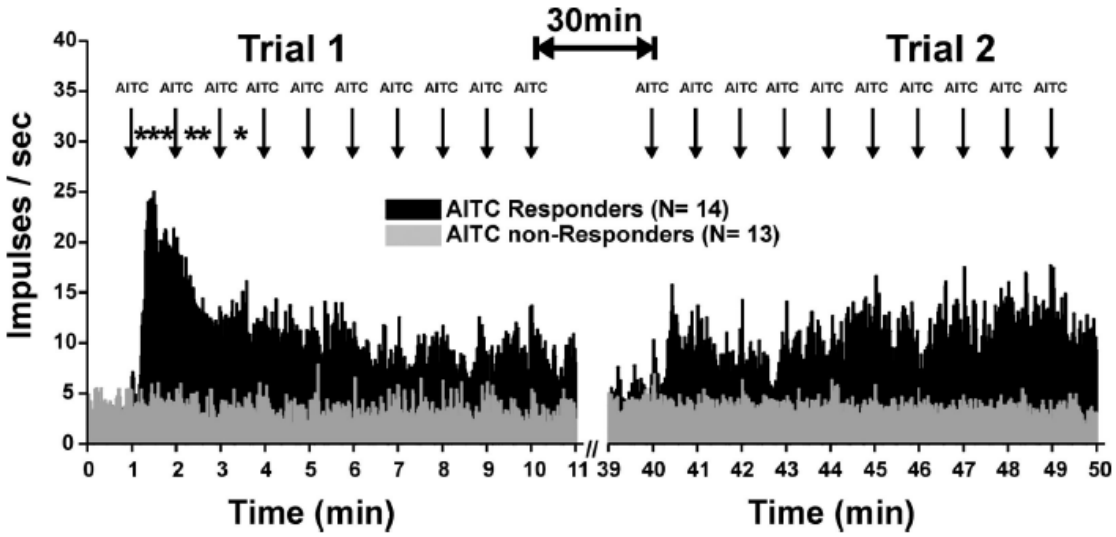

Fig. 2. Desensitization of responses to repeated application of AITC. Shown are averaged peristimulus time histograms (PSTHs, 1-s bin width) of unit firing during repeated application of AITC (75%, 2 μl droplets) at 1-min intervals (arrows) for 10 min to the center of the receptive field area on the ipsilateral hindpaw. Black PSTHs: 14 WDR units that exhibited increased firing during the initial application of AITC. Gray PSTHs: 13 units unresponsive to AITC. Error bars are omitted for clarity. Left-hand PSTHs: responses to the first trial of sequential AITC application. Right-hand PSTHs: responses to second trial of sequential AITC application starting 30 min after the end of the first trial. *, **, ***: significantly different compared with the initial 60 s baseline period before the first application of AITC ($P<0.05$, $P<0.005$, $P<0.0005$, respectively).

counted all C-fiber and after-discharge activity occurring in the 100- to 1,000 ms latency period. The stimulus intensity was adjusted for each unit to be threefold that of the C-fiber threshold.

Data analysis. The spontaneous firing rate was calculated as the sum of the total number of action potentials that occurred for 30 or 60 s before each stimulus. Responses to von Frey and thermal stimuli were quantified by summing the total number of action potentials recorded during the 10 s stimulus period, and subtracting the spontaneous firing rate per 10 s (30 s total/3). The after-discharge was quantified as the total number of action potentials during the 30 s after the offset of the stimulus. Spontaneous firing, evoked responses, and after-discharge to each mechanical and thermal stimulus were compared pre- versus post-treatment for each treatment group (AITC, CA, and mineral oil) using paired *t*-test. Responses to AITC, CA, and mineral oil were quantified by summing the total spikes during the 60 s interval after each application. Each sum was compared with the sum of the total spikes during the 60 s preceding the first application (baseline) using univariate ANOVA with post hoc Dunnett's two-sided *t*-test. A P value of <0.05 was taken to be significant. Statistical analyses were performed using SPSS 9.0 software. All data are means ±SE unless otherwise noted.

Results

Response to AITC application. In the first series of experiments, 27 units were tested for responses to repeated application of AITC and 14 (52%) responded. The example in Fig. 1*G* shows a buildup of firing to the initial AITC stimuli. The mean responses are shown in Fig. 2 for units excited by repeated application of AITC [Fig. 2, left, black peristimulus time histograms (PSTHs)] and for those unaffected by AITC (gray PSTH). For the responsive units, the mean firing rate during the first three stimulus applications was significantly greater compared with pre-AITC baseline but then declined to a level that was not significantly different from baseline (Fig. 2, left). After a 30-min rest period, AITC

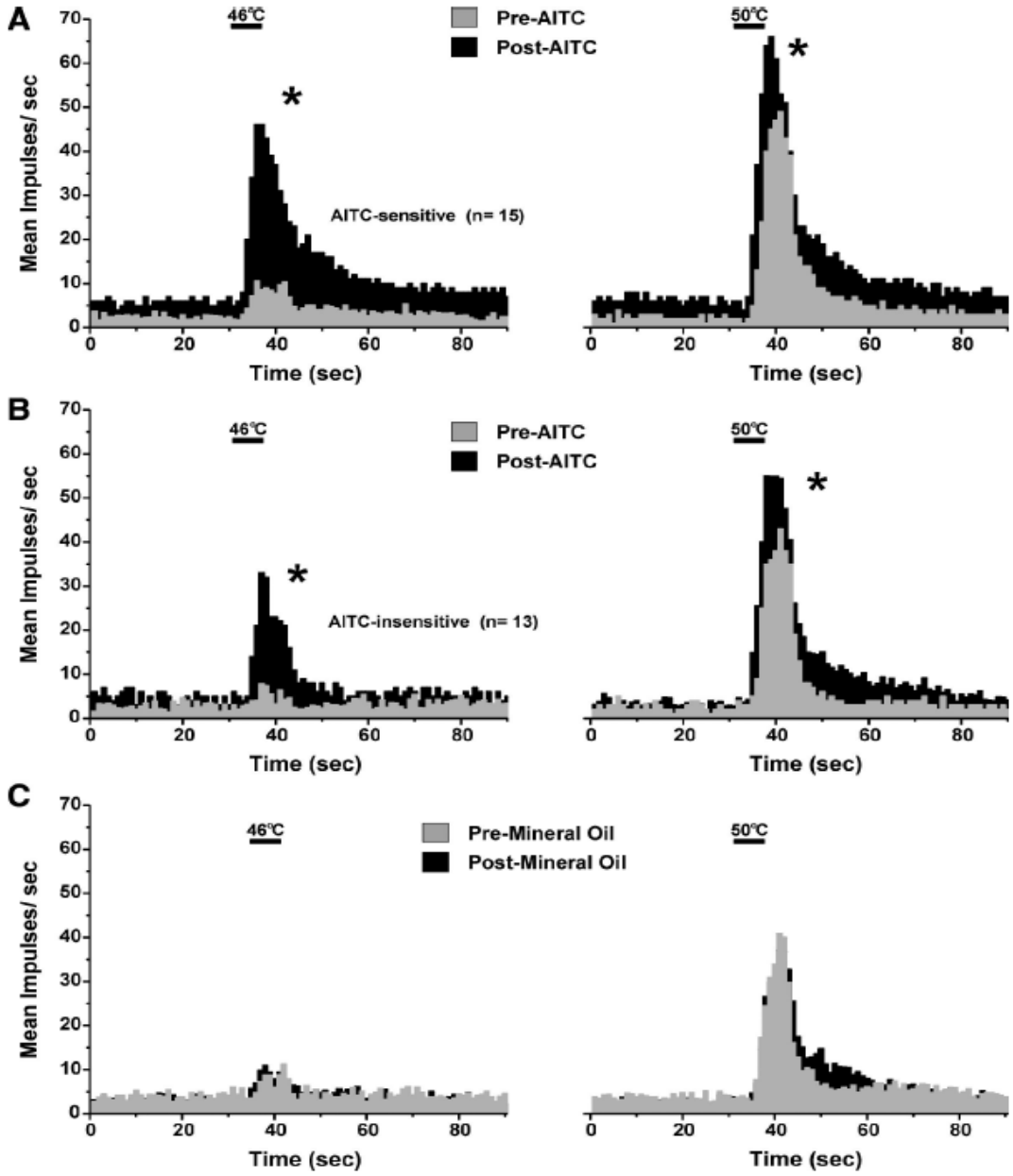

Fig. 3. AITC sensitization of WDR responses to noxious heat stimulation. *A*: responses to 46°C and 50°C heat stimuli, before (gray PSTHs) and 11 min after the end of sequential application of AITC (black PSTHs) for AITC-sensitive WDR units. Pre and post-AITC responses are aligned to the heat stimulus (indicated by horizontal bars). Error bars omitted for clarity. *: post-AITC response significantly different from pre-AITC ($P<0.05$). *B*: format as in *A* for 13 AITC-insensitive WDR units. *C*: format as in *A* for 10 separate WDR units receiving sequential application of mineral oil (vehicle control).

was reapplied in the same manner. Although there was a trend toward an increased firing rate, this did not reach statistical significance relative to pre-AITC baseline (Fig. 2, right).

All units were tested for responses to graded (46°C and 50°C) heat before and after AITC. Figure 1 shows one unit's responses before AITC (Fig. 1, B and C) and their marked enhancement post-AITC (Fig. 1, *H* and *I*). Figure 3*A* shows averaged responses to heat stimuli before (gray PSTHs) and after AITC (black PSTHs) for units that were directly activated by AITC. Responses to both 46 and 50°C were sig-

nificantly enhanced post-AITC. Units unresponsive to AITC similarly exhibited a significant enhancement of heat-evoked responses post-AITC (Fig. 3B). Vehicle (mineral oil) application had no effect on heat-evoked responses in a separate group of 10 units (Fig. 3C).

The WDR units typically exhibited graded responses to increasing bending forces of punctate von Frey stimuli (Fig. 1, D–F), which were minimally affected post-AITC (Fig. 1, J–L). Figure 4 shows averaged responses to graded mechanical stimuli before (gray PSTHs) and about 11 min after AITC (black PSTHs), for AITC-sensitive (Fig. 4A) and AITC-insensitive units (Fig. 4B). There were no significant differences in responses pre-versus post-AITC. Similarly, responses pre- and post-vehicle (mineral oil) application were not significantly different (Fig. 4C). Finally, responses of units to low-threshold brushing of skin in the center of the mechano-sensitive receptive field with cotton were not significantly different pre-versus post-AITC application.

Response to CA application

In a separate group of 14 units, repeated application of CA did not significantly affect any unit's firing rate. Similar to AITC, responses to graded noxious heating were significantly enhanced post-CA applications. Figure 5 shows an individual example (compare A–C with D–F), and Fig. 6A shows averaged responses that are overlaid to emphasize the progressive increase after the first (light gray PSTHs; post-CA 1) and second applications of CA (black PSTHs; post-CA 2) compared with pre-CA (dark gray PSTH). Mean responses after both the first and second trials of CA application were significantly different from pre-CA at each stimulus temperature (paired *t*-test, $P<0.05$).

At the same time, Figure 5 shows a typical example in which responses to graded von Frey stimuli were similar before (Fig. 5, G–I) and after CA (Fig. 5, J–L). Figure 6B shows averaged responses to graded von Frey stimuli with no significant change after the first or second application of CA compared with pre-CA.

Discussion

A main finding of this study is that both AITC and CA sensitized dorsal horn WDR neuronal responses to noxious heat while not significantly affecting their responses to other stimuli. This heat sensitization was observed irrespective of whether the AITC or CA directly excited the neuron. Furthermore, electrically evoked responses of the WDR units were either unaffected, or reduced, after application of the irritant to the skin. These data therefore support a peripheral site of heat sensitization by the TRPA1 agonists and argue against a central sensitizing action.

Roughly, 50% of WDR dorsal horn units responded directly to topical application of AITC with an initial increase in firing that desensitized over a 3-min period despite continued application of AITC. A previous study reported a similar fraction (53%) of mainly WDR dorsal horn neurons to be directly activated by 4% AITC applied adjacent to the mechanosensitive receptive field in decerebrate spinalized rats [17]. The desensitizing response pattern observed presently was similar to that of responses of neurons in trigeminal subnucleus caudalis (Vc) to lingual application of AITC [14-15], as well as the desensitizing temporal pattern of irritancy ratings elicited by lingual AITC in humans [12]. The lack of response of the other half of the WDR units to topical AITC suggests that our application strategy using a high concentration (75%) and low volume (2 μl) did not have non-specific excitatory or toxic effects. On reapplication, AITC did not evoke a significant increase in WDR neuronal firing, consistent with self-desensitization reported for AITC irritancy on the tongue that lasts >10 min in humans [12]. However, Vc neurons overcome AITC self-desensitization more quickly [14], possibly due to a more rapid clearance rate in the oral mucosa compared with hindpaw skin. Consistent with this, it was shown that a 10-fold higher concentration of capsaicin is required on facial skin versus

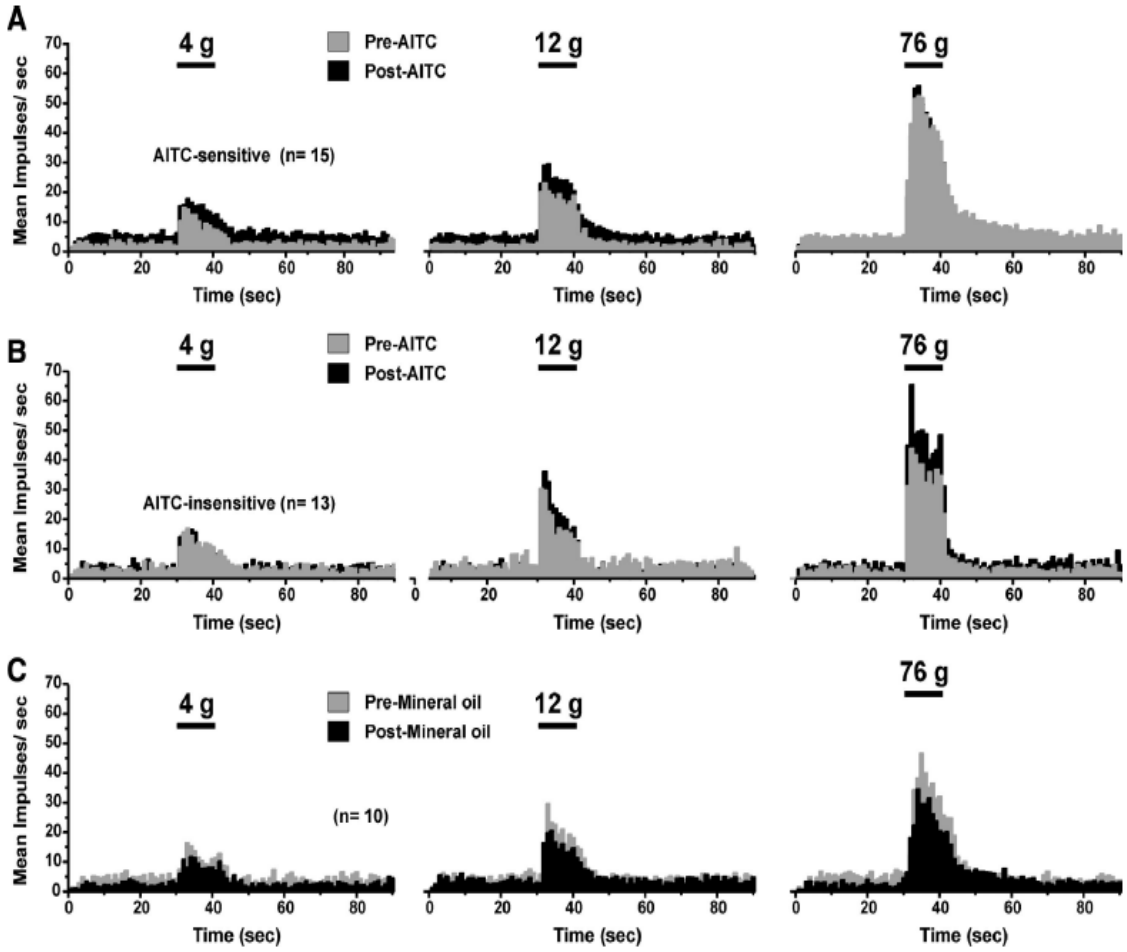

Fig. 4. Averaged responses to mechanical stimuli after application of AITC or mineral oil (control) to the receptive field area. *A*: averaged PSTHs of responses of AITC-sensitive neurons to stimulation with von Frey filaments with bending forces of 4, 12, and 76 g stimuli, from left to right, pre- (gray PSTHs) and 10-min post application of AITC (black PSTHs). Error bars omitted for clarity. *B*: format as in *A* for mechanically evoked responses of AITC-insensitive neurons pre- and post-AITC application. *C*: format as in *A* for mechanically evoked responses of 10 different WDR neurons pre- and post application of mineral oil (vehicle control).

tongue to elicit equivalent burning sensations and that the time course of desensitization was much slower on the face than on the tongue [18].

The mechanism underlying AITC self-desensitization could involve a peripheral or central site of action. Peripherally, repeated application of AITC may lead to desensitization of TRPA1 expressed in nociceptive endings. AITC self-desensitization was recently reported to occur by a calcium- and calcineurin-independent mechanism in an *in vitro* assay of peptide release from skin–nerve biopsies [19]. Alternatively, central inhibition might contribute to the reduced response of WDR neurons to repeated application of AITC. However, such a proposed central inhibition was insufficient to prevent AITC and CA enhancement of WDR neuronal responses to noxious heat.

CA did not directly excite the WDR units recorded presently, whereas lingual application of CA readily excited Vc neurons [15], presumably due to the lower diffusion barrier presented by the lingual epithelium compared with hindpaw skin. It is likely that the amount of CA that reached the sensory nerve endings in the hindpaw epithelium was insufficient to elicit action potentials, although it was sufficient to induce heat sensitization, presumably

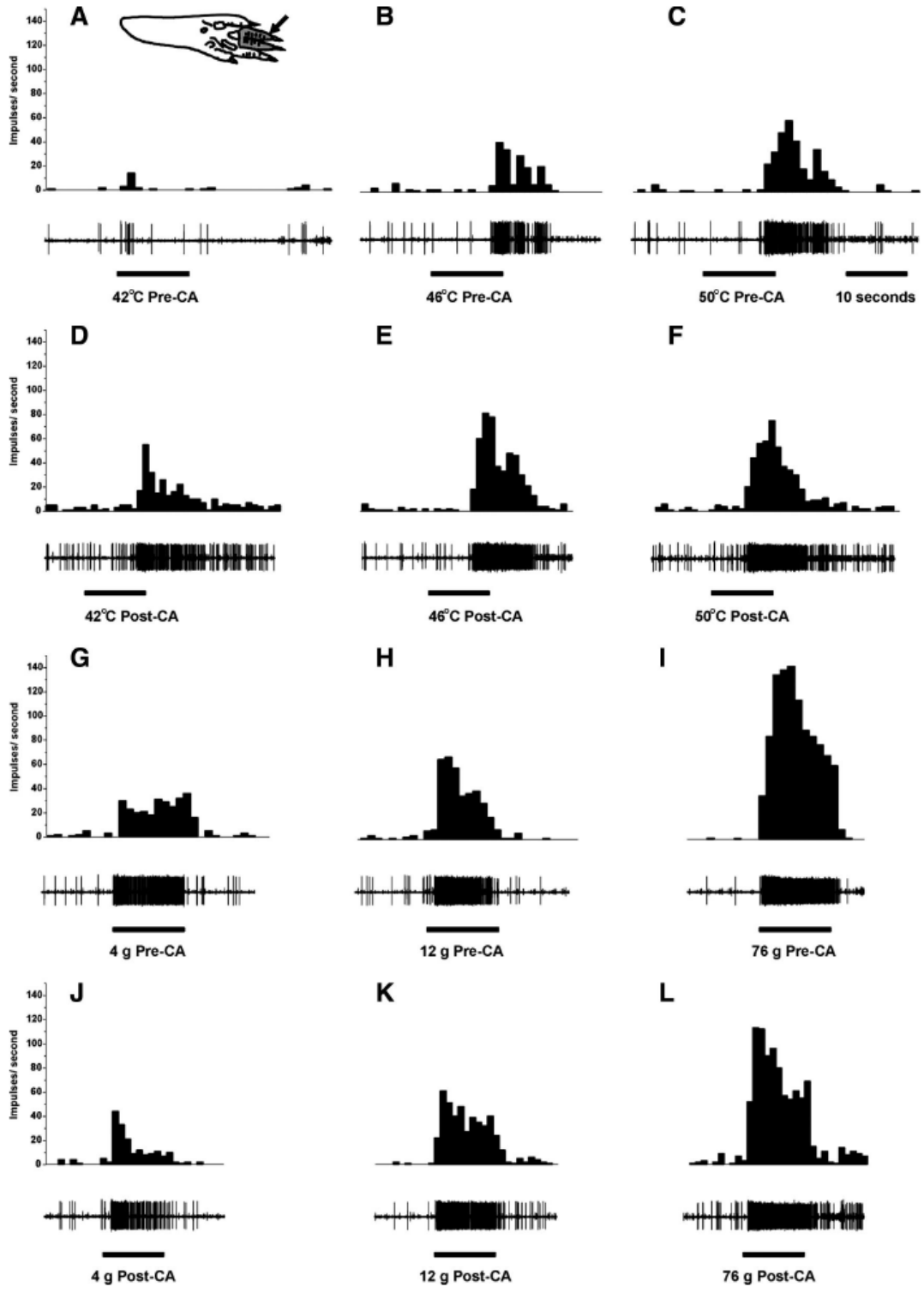

Fig. 5. Example of cinnamaldehyde (CA) heat sensitization of individual WDR neuron. A–C: spike traces (*bottom*) and PSTHs (1-s bin width) above, of responses to 42°C (A), 46°C (B), and 50°C (C) before CA. Inset in *A* shows receptive field on toes 3 and 4. Arrow: site of CA application. D–F: responses to same series of graded noxious heat stimuli post-CA. G–I: responses to graded mechanical von Frey stimuli: 4 g (G), 12 g (H), and 76 g (I), respectively, pre-CA. J–L: responses to graded mechanical von Frey stimuli post-CA.

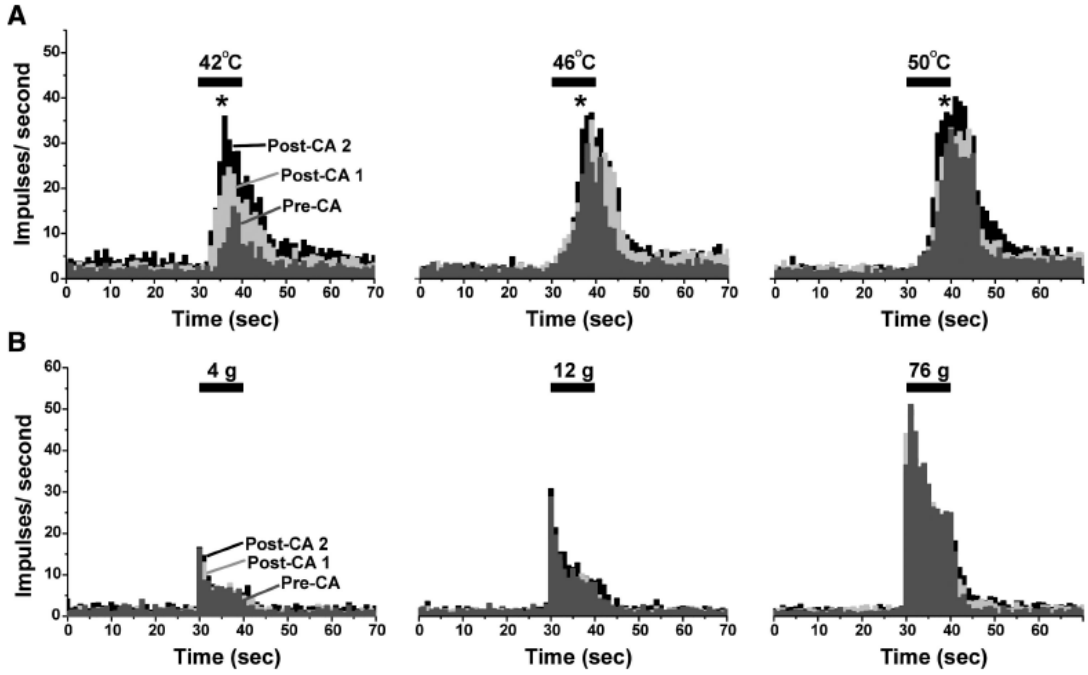

Fig. 6. CA sensitization of WDR responses to noxious heat but not mechanical stimuli. *A*: averaged PSTHs of responses of 13 units to 42°C (*left*), 46°C (*middle*), and 50°C (*right*) heat stimuli (black bars), before (dark gray PSTH) and after the first (post-CA 1; light gray PSTH) and second (post-CA 2; black PSTH) application of CA. Error bars omitted for clarity. *: significant difference between pre-CA and both post-CA 1 and post-CA 2 ($P<0.05$). *B*: averaged PSTHs of same units in *A* to 4 g (*left*), 12 g (*middle*), and 76 g (*right*) mechanical stimuli (black bars), before and after CA (format as in *A*).

by the same peripheral mechanism as suggested for AITC. In contrast, AITC strongly excited about 50% of WDR cells, with a resultant depression of electrically evoked neuronal responses presumably by activation of spinal inhibitory circuits by the stronger afferent drive.

Furthermore, AITC sensitized WDR neuronal responses to noxious heat, irrespective of whether AITC directly activated the unit. CA also sensitized responses to heat even though it did not directly excite WDR units. Previous studies of WDR neurons in lamina V of mice, reported significant enhancement of neuronal responses to 40°C (but not 45°C or 49°C) [20,21], and a significant enhancement of after-discharge responses to 41°C and 45°C [22] after application of AITC (10%, 60 μl) to the hindpaw. Lamina I nociceptive-specific (NS) neuronal responses to heat were also enhanced post-AITC [20,21]. Our results are generally consistent, in that AITC more strongly enhanced rat WDR neuronal responses to the lower stimulus temperatures (42°C and 46°C) compared with the highest (50°C). Two previous studies reported no change in noxious heat-evoked responses of rat and mouse WDR neurons after AITC (50 or 100%) was applied adjacent to the receptive field [23-24]. AITC sensitizes responses of mechanoheat- sensitive C-fiber afferents to noxious heating [25]. Because AITC did not enhance WDR neuronal responses to mechanical or electrical C-fiber stimuli, the most parsimonious explanation is that AITC applied within the cutaneous receptive field sensitized peripheral nociceptors to result in primary hyperalgesia. TRPA1 is coexpressed with the heat-sensitive channel TRPV1 in primary sensory neurons [26], so AITC enhancement of nociceptor responses to noxious heat might involve a cellular mechanism by which activation of TRPA1 enhances the thermal sensitivity of TRPV1. Another possibility is that AITC causes release of inflammatory mediators that in turn lower the thermal activation threshold of TRPV1 [27,28], resulting in

the observed enhancement of responses, particularly to 42°C and 46°C.

Neither AITC nor CA affected WDR neuronal responses to graded pressure or light brushing of the mechanosensitive receptive field. This is partially consistent with recent studies showing that AITC significantly enhanced murine deep dorsal horn WDR neuronal responses to only the weakest mechanical stimulus while having no significant effect on responses to stronger stimuli [21]. However, other studies have shown significant enhancement of neuronal responses to innocuous mechanical stimuli, and expansion of receptive fields, in rats and mice after application of AITC adjacent to the mechano-sensitive receptive field of spinal WDR or NS neurons [17,23,24,29]. Such enhancement was seen in decerebrate spinalized rats [17], although another study reported the AITC-induced mechanical enhancement to be significantly attenuated in spinalized rats [23], implicating involvement of descending facilitatory pathways. The present lack of effect of AITC or CA on mechanically evoked responses of WDR neurons indicates that our method of intermittent application of small (2 μl) volumes of these agents did not produce sufficient afferent drive to engage segmental or suprasegmental pronociceptive networks.

Our recent behavioral investigations showed that unilateral intraplantar injection of CA (5–20%) induced a significant, concentration-dependent reduction in latency for ipsilateral paw withdrawal from a noxious heat stimulus in mail rats (heat hyperalgesia). The highest dose of CA also significantly reduced the contralateral paw withdrawal latency. CA significantly reduced mechanical withdrawal thresholds of the injected paw (mechanical allodynia) and was more profound, with no effect contralaterally. Bilateral intraplantar injections of CA resulted in a significant cold hyperalgesia (cold plate test) and a weak enhancement of innocuous cold avoidance (thermal preference test) [30,31]. These results support a role for TRPA1 in cold detection, as the TRPA1 agonist CA enhanced cold sensitivity in two behavioral assays [32].

However, these behavioral findings are inconsistent with presented here electrophysiological data showing that neither CA nor AITC had any significant effect on mechanical sensitivity of spinal WDR neurons. The mismatch between our behavioral observation of a CA-induced increase in mechanosensitivity and lack of CA effect on neuronal mechanosensitivity may involve the route of administration of this substance [30-32].

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ადამიანისა და ცხოველთა ფიზიოლოგია

მდოგვის ზეთისა და დარიჩინის ალდეჰიდის ზოგიერთი ეფექტი მამრი ვირთაგვების ზურგის ტვინის ნეირონების პასუხებზე კანის გაღიზიანებისას

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 # მოლეკულური და სამედიცინო გენეტიკის დეპარტამენტი, თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი

(წარმოდგენილია აკადემიის წევრის თ. ონიანის მიერ)

უკანასკნელი წლების გამოკვლევათა თანახმად გარდამავალ რეცეპტორულ პოტენციალთა (გრპ- TRP) არხები მიიჩნევიან ტკივილის სამკურნალო სამიზნეებად. ეს არხები მნიშვნელოვან როლს ასრულებენ თერმული, მექანიკური და ქიმიური ტკივილის შეგრძნებების აღმოცენებაში. ზოგიერთი TRP არხი მგრძნობელობას ავლენს მაღალი ან დაბალი ტემპერატურის, ისევე როგორც რიგი ქიმიური ნივთიერებების მიმართ, რომლებიც აღძრავენ თერმულ ან ტკივილის შეგრძნებას. მათ მიეკუთვნება მდოგვის ზეთი, დარიჩინის ალდეჰიდი, პიტნის შემცველი მენთოლი, კაპსაიცინი (შეიცავს ცხარე წიწაკა), მიხაკის ზეთი და სხვა.

მდოგვის ზეთის შემცველი აქტიური ნივთიერება ალილ-იზოთიოციანატი (აითც) და დარიჩინის ალდეჰიდი (და) წარმოადგენენ TRPA1 იონური არხის აგონისტებს. ექსპრესირდებიან რა სენსორულ ნეირონებში, ისინი იწვევენ მწველ შეგრძნებასა და სითბურ ჰიპერალგეზიას. წარმოდგენილ შრომაში ჩვენ შევისწავლეთ თუ როგორ აისახება ეს რეაქციები ზურგის ტვინის ე.წ. ფართო დიაპაზონის დინამიური (wide dynamic range-WDR) ნეირონების პასუხებზე მამრ ვირთაგვებში. ელექტრული, ზრდადი მექანიკური და მტკივნეული სითბური სტიმულაციის შედეგად აღმოცენებული პასუხები შესწავლილ იქნა კანზე აითც-სა და და-ის მოქმედებამდე და მოქმედების შემდეგ. აითც-ის განმეორებითი აპლიკაცია თავდაპირველად იწვევდა ნეირონების განმუხტვათა სიხშირის ზრდას, რომელსაც მოსდევდა სწრაფი დესენსიტიზაცია. ეს უკანასკნელი შენარჩუნებული იყო აითც-ის ხელახალი აპლიკაციის შემდეგაც 30 წუთის ინტერვალით. პასუხები მტკივნეულ სითბურ, მაგრამ არა მექანიკურ სტიმულებზე სარწმუნოდ იყო გაზრდილი, მიუხედავად იმისა, იყო თუ არა ნეირონი პირდაპირ აქტივირებული აითც-ის ზემოქმედებით.

მიღებული შედეგები მიუთითებენ, რომ აითც იწვევს ცენტრალურ შეკავებას ზურგის ტვინის დონეზე და თერმული ნოციცეპტორების პერიფერიულ სენსიტიზაციას. დარიჩინის ალდეჰიდი არ იწვევს WDR ნეირონების უშუალო აგზნებას, თუმცა სარწმუნოდ ზრდის პასუხებს მტკივნეულ გაცხელებაზე. ამასთან იგი არ რეაგირებს გაციებასა და მექანიკურ სტიმულებზე. ეს უკანასკნელი ფაქტები მიუთითებენ სითბური ნოციცეპტორების პერიფერიულ სენსიტიზაციაზე.

ამრიგად, წარმოდგენილი მონაცემები, ჩვენი ქცევითი ექსპერიმენტების შედეგების გათვალისწინებით, ამყარებენ მოსაზრებას, რომ თერმო TRPA1 იონური არხი წარმოადგენს იმედის მომცემ პერიფერიულ სამიზნეს ახალი ტიპის ანალგეზიური პრეპარატების სინთეზისთვის.

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