Enhanced responses of lumbar superficial dorsal horn neurons to intradermal PAR-2 agonist but not histamine in a mouse hindpaw dry skin itch model

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Akiyama T, Carstens MI, Carstens E. Enhanced responses of lumbar superficial dorsal horn neurons to intradermal PAR-2 agonist but not histamine in a mouse hindpaw dry skin itch model. J Neurophysiol 105: 2811–2817, 2011. First published March 23, 2011; doi:10.1152/jn.01124.2010.—Chronic itch is symptomatic of many skin conditions and systemic diseases. Little is known about pathophysiological alterations in itch-signaling neural pathways associated with chronic itch. We used a mouse model of hindpaw chronic dry skin itch to investigate properties of presumptive itch-signaling neurons. Neurons in the lumbar superficial dorsal horn ipsilateral to hindpaw dry skin treatment exhibited a high level of spontaneous activity that was inhibited by scratching the plantar surface. Most spontaneously active units exhibited further increases in firing rate following intradermal injection of an agonist of the protease-activated receptor PAR-2, or histamine. The large majority of pruritogen-responsive units also responded to capsaicin and allyl isothiocyanate. For neurons ipsilateral to dry skin treatment, responses elicited by the PAR-2 agonist, but not histamine or mechanical stimuli, were significantly larger compared with neurons ipsilateral to vehicle (water) treatment or neurons recorded in naïve (untreated) mice. The spontaneous activity may signal ongoing itch, while enhanced PAR-2 agonist-evoked responses may underlie hyperkinesia (enhanced itch), both of which are symptomatic of many chronic itch conditions. The enhancement of neuronal responses evoked by the PAR-2 agonist, but not by histamine or mechanical stimuli, implies that the dry skin condition selectively sensitized PAR-2 agonist-sensitive primary afferent pruritogens.

protease-activated receptor; intradermal

CHRONIC ITCH ASSOCIATED WITH dermatitis, liver or kidney disease, HIV, and many other conditions represents a large and poorly treated medical condition worldwide (Carstens 2009). Recent studies are starting to elucidate the mechanisms of normal itch transmission, with emerging evidence for histamine-dependent and -independent forms of itch. For example, the tropical legume, cowhage (Mucuna pruriens), has seed pods with spicules that contain proteases (mucunain) that act at protease-activated receptor (PAR) subtypes PAR-2 and PAR-4 (Reddy et al. 2008) to elicit itch that is not attenuated by antihistamines (Johane et al. 2007). Histamine or cowhage activate largely non-overlapping populations of primary afferents (Schmelz et al. 1997; Namer et al. 2008) and spinothalamic tract neurons (Davidson et al. 2007), supporting the existence of parallel itch-signaling pathways.

Less is known about pathophysiological changes associated with chronic itch. Sensitization of itch-signaling pathways represents a potential mechanism for chronic itch of atopic dermatitis, where histamine elicits greater itch, and noxious stimuli elicit itch instead of pain in lesional skin (Ikoma et al. 2003, 2004). Peripheral sensitization of pruriceptors innervating lesional skin may result in increased spontaneous and evoked firing (Schmelz et al. 2003). Central sensitization of itch-signaling superficial dorsal horn neurons may also contribute to symptoms of chronic itch, although this has not yet been investigated. We addressed this issue by investigating the properties of superficial dorsal horn neurons in a mouse model of chronic dry skin itch (Miyamoto et al. 2002; Nojima et al. 2004; Akiyama et al. 2010a, 2010c). In this model, chronic dry skin is induced by twice-daily skin treatments with acetone and diethylether followed by water (AEW). When applied to the rostral back, AEW-treated mice exhibited increased hindlimb scratching directed to the dry skin area in a manner that was significantly attenuated by the µ-opioid antagonist naltrexone but not by histamine or mechanical stimuli, as well as increased epicutaneous thickness, decreased stratum corneum hydration, and increased transepidermal water loss (Miyamoto et al. 2002). AEW treatment of the hindpaw also resulted in a significant increase in transepidermal water loss, accompanied by spontaneous biting of the treated hindpaw that was significantly attenuated by the µ-opioid antagonist naltrexone but not by morphine, consistent with itch (Nojima et al. 2004; Akiyama et al. 2010c). Moreover, significantly more scratching was elicited by acute intradermal (id) injection of 5-HT or a PAR-2 agonist into AEW-treated skin compared with vehicle-treated or untreated skin (Akiyama et al. 2010a). For this reason, we hypothesized that chronic dry skin would sensitize itch-signaling pathways. The aim of the present study was to investigate if lumbar spinal neurons recorded in mice with dry hindpaw skin exhibit increased spontaneous firing as a manifestation of chronic ongoing itch, and enhanced responses to acute id injection of pruritogens.

MATERIALS AND METHODS

Experiments were conducted using 52 ICR mice (Harlan, Oxnard, CA) (25–45 g) under a protocol approved by the UC Davis Animal Care and Use Committee.

Dry skin model. To induce chronic dry skin on the hindpaw, we followed a previously reported procedure (Nojima et al. 2004; Akiyama et al. 2010c). In most experiments (n = 40), one or both hindpaws were wrapped with gauze soaked with a mixture of acetone and diethylether (1:1) for 15 s, followed immediately by distilled water for 30 s (referred to as AEW treatment), twice daily for 10–12 days. In the remainder of experiments (n = 12), one hindpaw was treated with AEW and the other hindpaw was identically treated with distilled water only for 45 s (designated as W treatment) as a control. All mice were fitted with a plastic Elizabethan collar (diameter 11 cm) placed around the chest just beneath the forelimbs to prevent any biting or licking of the treated hindpaw(s).
Electrophysiological recording. Following the final treatment day, the mouse was anesthetized with pentobarbital sodium (60 mg/kg ip) and prepared for single-unit recording from the lumbar spinal cord as previously detailed (Akiyama et al. 2009a). In the first set of experiments using AEW-treated mice, a tungsten microelectrode was driven into the superficial lumbar dorsal horn ipsilateral to the AEW treatment, and a spontaneously firing extracellular action potential was isolated. No chemical search stimuli was used. Recording depths were restricted to <300 μm below the surface to record superficial units matching our previous study (Akiyama et al. 2009a). Unit activity was amplified, digitized, and displayed on computer using a Powerlab (AD Instruments, Colorado Springs, CO) interface. Once isolated, most units were tested for mechanosensitive responsiveness and effect of scratching the plantar surface on ongoing activity. Scratching was accomplished by moving a brush bristle approximating the size of a mouse toenail in a back-and-forth motion across the ventral surface of the hindpaw at a frequency of ~2 Hz, excursion of ~5 mm, and force of 300 mN for a period of 60 s. Mechanical receptive fields were determined by the ability of light brush (with a cotton whisk) or pinch (with forceps) stimuli to reproducibly elicit an increase in ongoing activity when applied within but not outside a circumscribed region of skin. It should be noted that accurate determination of receptive fields was impeded by high levels of spontaneous activity in some units. Units were classified as wide dynamic range (WDR) if they responded at higher firing rate to pinch than brushing. They were classified as nociceptive specific (NS) if they responded to pinch but not light touch. Units insensitive to touch or pinch were classified as mechanically insensitive. Units were then tested for responsiveness to intradermal (id) microinjection of either histamine (Sigma-Aldrich, St. Louis, MO) or the PAR-2 agonist SLIGRL-NH2 (Quality Controlled Biochemicals, Hopkinton, MA; GenScript, Piscataway, NJ) (both 50 μg in a volume of 1 μl of saline) with all id injections made over a 1- to 2-s period in the receptive field area that was always within the treatment area on the ventral hindpaw surface. Although mechanosensitive receptive fields were not mapped for mechanically insensitive units, id injection within the plantar treatment area activated such units, implying the presence of a chemosensitive receptive field there. The response to the first chemical stimulus was recorded for at least 26 min, after which the other chemical was microinjected id via a separate 30-gauge needle. The order of injection of histamine and the PAR-2 agonist was counterbalanced across experiments. Unit activity was recorded for another 20–30 min following the second chemical microinjection. Units were then tested with topical hindpaw application of allyl isothiocyanate (AITC; mustard oil, Sigma; 75% in mineral oil, 2 μl) and id microinjection of capsaicin (Sigma; 3.3 mM in 1 μl of ethanol-water vehicle). In many experiments, the vehicle was also tested either by id microinjection of saline (0.9%, 1 μl) or topical application of mineral oil (vehicle for AITC).

The second set of experiments used mice (n = 12) treated with AEW on one hindpaw and W on the opposite hindpaw. The W treatment was done to control for effects of repeated handling and treatment over the 10- to 12-day period. Moreover, in these experiments, a histamine or PAR-2 agonist was injected id (0.1 μl) as a search stimulus as in our previous studies (Akiyama et al. 2009a). The rationale for using a pruritogen search stimulus was to ensure that neurons on both the AEW- and W-treated sides received the identical sequence of stimuli. The side (AEW or W) and chemical (histamine or PAR-2 agonist) for the initial search stimulus was counterbalanced across experiments. After a unit was isolated using the chemical search strategy, the same sequence of stimuli was delivered as described above except that mechanical stimuli were tested after (but not prior to) chemical stimuli. After completion of the test series on the first side, the same procedure was used to isolate and record responses of a neuron on the opposite side of the spinal cord. This allowed us to compare responses of neurons on the AEW- and W-treated sides from the same animal.

Data analysis. Unit activity was usually quantified as number of action potentials in 1-min intervals, and displayed in peristimulus time histogram (PSTH) or line-graph format with either 1-s or 60-s bins. Group responses at 1-min intervals after a given stimulus were compared with activity 1 min before the stimulus by paired t-test or repeated measures ANOVA (SPSS 9.0; SPSS, Chicago, IL), with P < 0.05 set as significant. A response was considered to be a 30% or greater increase in spike counts/min. To compare responses of units ipsilateral to AEW treatment with those ipsilateral to W treatment, or units from untreated animals, spontaneous activity during the 1-min prestimulus period was subtracted. Baseline-corrected responses were compared between AEW-treated (no search stimulus) and untreated mice (isolated using histamine or PAR-2 agonist search stimuli), or between neurons on AEW- and W-treated sides (both isolated using histamine or PAR-2 agonist search stimuli), by two-tailed unpaired t-tests with P < 0.05 set as significant. Responses to histamine and the PAR-2 agonist were also compared with unit activity during the first minute following id saline using an unpaired t-test.

Histology. At the conclusion of recordings, an electrolytic lesion was made. The spinal cord was postfixed in 10% buffered formalin and cut in 50-μm frozen sections to identify the lesion sites under the light microscope.

RESULTS

Unit characterization. Recordings were made from a total of 79 units in 52 mice ipsilateral to the AEW- or W-treated hindpaw. They were located primarily in the superficial dorsal horn at a mean depth of 110.7 μm ± 9.3 SE below the surface. In 33 animals receiving AEW treatment, recording sites were histologically localized to the superficial dorsal horn with most in lamina I (Fig. 4, inset; Fig. 5A, inset). All units ipsilateral to the AEW treatment exhibited spontaneous activity ranging from 0.4 to 18.6 Hz with a mean of 4.59 Hz ± 0.52 (SE). This was significantly greater (P < 0.001) compared with the low level of spontaneous activity of 40 superficial dorsal horn units recorded in naïve mice (1.1 ± 0.2 Hz) (Akiyama et al. 2009a) and that of 11 superficial dorsal horn units ipsilateral to W-treated skin (1.2 ± 0.4 Hz).

Due to the spontaneous firing of the present units, it was not always possible to accurately map mechanosensitive receptive fields. This was compounded by the observation that mechanical scratching of the hindpaw usually inhibited ongoing firing. Nevertheless, 32% (11/34) of units gave graded responses to light brushing and pinch and were classified as WDR, while 44% (15/34) responded to pinch but not light brushing and were classified as NS. Eight units (24%) unresponsive to mechanical stimuli were classified as mechanically insensitive. Percentages of neurons tested with histamine, PAR-2 agonist, and pinch are shown in the Venn diagram of Fig. 1. The vast majority (79%) of pruritogen-responsive neurons also responded to noxious stimuli (pinch, capsaicin, AITC), while 21% responded to histamine and/or the PAR-2 agonist but not to pinch.

Responses to pruritic and noxious stimuli. Nearly all units ipsilateral to AEW treatment, identified by their spontaneous firing, responded to pruritogens. When histamine was tested first, all eight units responded. When the PAR-2 agonist was tested first, 17/18 units responded. Figure 2 shows an example of a unit ipsilateral to AEW treatment. It exhibited spontaneous firing that was inhibited by scratching the ipsilateral plantar surface, a phenomenon observed in all presently tested units and to be reported in detail separately. Firing of the unit in Fig.
Fig. 1. Venn diagram shows overlapping populations of spinal neurons responsive to histamine (Hist+), PAR-2 agonist (PAR-2+), or noxious pinch (Noci). Numbers indicate percentages of neurons within each region (n = 24 units tested with all 3 stimuli). White and light gray: mechanically insensitive units responsive to histamine and/or PAR-2 agonist. Darker gray shades: pinch-responsive wide dynamic range (WDR) and nociceptive-specific (NS) units that also responded to histamine or PAR-2 agonist (dark gray) or both (medium gray). Black: theoretical population of WDR and NS units that did not respond to histamine or PAR-2 agonist.

2 increased following id injection of the PAR-2 agonist, and again following subsequent injection of histamine and 5-HT, capsaicin, and AITC. Figure 3 shows a WDR unit that gave graded responses to brush and pinch, and additionally responded to histamine, the PAR-2 agonist, and 5-HT. Interestingly, it responded to capsaicin with an initial increase followed by inhibition of activity for 3 min, a pattern observed in 4/18 units following capsaicin and 3/19 units following AITC.

Averaged responses of tested units ipsilateral to AEW treatment are shown in Fig. 4. The vast majority of units responded to histamine, the PAR-2 agonist SLIGRL-NH2, 5-HT, AITC, and capsaicin, regardless of stimulus order. Most units tested responded to brushing or pinching, and none of the units responded to control id injection of saline or topical mineral oil. Mean responses to histamine, the PAR-2 agonist, 5-HT, AITC, capsaicin, brush, and pinch were all significantly greater for at least the first minute postinjection compared with pre-stimulus baseline (P < 0.05, paired t-tests), as well as compared with the first minute following id saline (P < 0.05 for all comparisons, unpaired t-test). Histologically localized recording sites were in the superficial dorsal horn (Fig. 4, inset).

AEW treatment enhanced responses to PAR-2 agonist but not histamine. To determine the effect of AEW treatment on pruritogen-evoked responses, we made two comparisons. The first compared response of units ipsilateral to AEW treatment, and isolated by their spontaneous activity, with units recorded in untreated mice and isolated using a pruritogen search stimulus. The level of spontaneous activity prior to the pruritic stimulus was subtracted. There was no significant difference between neuronal responses to id histamine in AEW-treated compared with naïve groups. However, units ipsilateral to AEW treatment exhibited significantly larger responses to the PAR-2 agonist over the first 2 min postinjection compared with units recorded in untreated (naïve) animals.

Comparison of units isolated by spontaneous firing in AEW-treated mice with units isolated by a chemical search stimulus in untreated mice presents two potential confounding factors. First, use of the search stimulus might have reduced neuronal responses to the subsequently applied pruritogen (e.g., tachyphylaxis). Second, untreated animals did not receive the same handling and treatment compared with the AEW-treated mice. For these reasons, we conducted additional experiments in which mice received AEW treatment on one hindpaw and W treatment on the other. We then recorded from units on both the AEW- and W-treated sides, using a histamine or PAR-2 agonist search stimulus to isolate the units. The results were very similar to those described above. Thus, units isolated by a histamine search stimulus on either the AEW- or W-treated side exhibited similar responses to histamine that did not differ significantly. For units isolated by the PAR-2 search stimulus, those ipsilateral to AEW treatment exhibited significantly larger responses to the PAR-2 agonist over the first 2 min postinjection compared with those ipsilateral to W treatment. Moreover, the mean responses to histamine injected into dry skin and recorded under the two experimental conditions (presence and absence of search stimulus) were not significantly different [respective mean peak responses 1-min posthistamine: 421 spikes/min ± 117 SE (n = 9) vs. 433.5 ± 198 (n = 6), P > 0.1, unpaired t-test] nor was there any significant difference between histamine-evoked responses in naïve vs. W-treatment conditions [253 ± 540 SE (n = 19) vs. 195 ± 117 (n = 5)]. The same was true for PAR-2 agonist-evoked responses. For this reason, data from the two experimental conditions were pooled and are shown in Fig. 5. There was a statistically nonsignificant trend toward enhancement of neu-
ronal responses to histamine injected into dry skin (Fig. 5A); however, a power calculation based on the observed effect size did not warrant the large sample size necessary to establish a significant treatment effect. In contrast, id injection of the PAR-2 agonist into dry skin elicited significantly larger responses over the first 3 min postinjection compared with responses of units in mice receiving PAR-2 agonist injections in untreated or vehicle-treated skin (Fig. 5B). Finally, responses during the first minute postinjection under each AEW or control treatment condition were significantly different compared with the first minute postsaline (P < 0.05 for all, unpaired t-test).

We also compared unit responses to brush and pinch between AEW-treated and W-treated sides. Figure 6 shows that mean responses to each stimulus were not significantly different between groups.

**DISCUSSION**

We presently identified neurons in the lumbar superficial dorsal horn ipsilateral to hindpaw AEW treatment exhibiting high rates of spontaneous activity that we postulate is due to ongoing pruriceptive input from the chronic dry itchy skin. Nearly all units tested responded to id injection of histamine, the PAR-2 agonist SLIGRL-NH2, and 5-HT. Each of these mediators is associated with itch in human skin (Fjellner and Hagermark 1979; Simone et al. 1987; Steinhoff et al. 2003) and elicits dose-dependent scratching behavior (Akiyama et al. 2009c; Tsujii et al. 2008) and excitation of superficial dorsal horn neurons (Akiyama et al. 2009a,b) in untreated ICR mice. The spontaneous firing of presently recorded units was significantly attenuated by scratching the skin. All of these observations are consistent with a role for these spinal neurons in conveying itch sensation to higher centers. These units exhibited enhanced response to PAR-2 agonist, but not histamine and mechanical stimuli, suggesting peripheral sensitization of pruriceptive primary afferents that respond to the PAR-2 agonist. This is consistent with a report showing enhanced scratching behavior and calcium responses of DRG cells elicited by a PAR-2 agonist and 5-HT, but not histamine, in mice with dry skin treatment (Akiyama et al. 2010a).

**Comparison with previous studies.** The proportions of WDR, NS, and mechanically insensitive units isolated in AEW-treated mice by their spontaneous activity (Fig. 1) were similar to those of histamine- and PAR-2 agonist-responsive units recorded in naïve mice using the same methods, except that the latter were identified by a chemical search strategy (Akiyama et al. 2009a). Furthermore, the proportions of pruritogen-responsive units that additionally responded to noxious
stimuli were similar in AEW-treated and naive mice (79 and 84%, respectively). Previous studies in other species are generally consistent with this. Primate spinothalamic tract neurons that responded to id histamine or cowhage all additionally responded to capsaicin (Davidson et al. 2007). In the cat, 50% of histamine-responsive lamina I spinothalamic tract neurons tested also responded to AITC (Andrew and Craig 2001). A large majority of units responded to both histamine and the PAR-2 agonist in both AEW-treated and naive mice (84 and 81%, respectively) (Akiyama et al. 2009a). This differs from a recent study reporting that primate spinothalamic tract neurons usually respond to either histamine or cowhage, but not both (Davidson et al. 2007), and that approximately one-third of Vc neurons innervating mouse cheek skin respond to both histamine and the PAR-2 agonist, while two-thirds respond to one but not the other (Akiyama et al. 2010b). This difference may reflect the species and/or methodological differences and/or glabrous skin vs. hairy skin as previously discussed (Akiyama et al. 2009a). Finally, we assume that the majority of spinal WDR and NS neurons is unresponsive to pruritogens (Fig. 1). This is supported by our recent study using an algogen (AITC) as a search stimulus to isolate nociceptive neurons (Akiyama et al. 2010b); only a minority of these (13–41%) also responded to the pruritogens histamine, PAR-2 agonist, or 5-HT.

We presently did not determine if the recorded neurons have ascending projections, and thus cannot state whether they participate in ascending sensory pathways or function as local interneurons. Nevertheless, in patients suffering from atopic dermatitis, nocturnal scratching can occur during various stages of sleep (Aoki et al. 1991; Ebata et al. 1999), suggesting that neural circuits controlling limb scratch movements can operate subconsciously and hence independently of itch sensation. It is probable that the search strategy used in the present study would isolate both projection and non-projection neurons responsive to pruritogens. Moreover, since lumbar lamina I neurons contribute only sparsely to the spinothalamic tract in this species. Thus, it would be useful in future studies to identify the rostral projections of pruritogen-responsive lamina I neurons, and to determine if projection and non-projection neurons have similar functional properties.

Noxious stimulus-evoked inhibition. Scratching temporarily relieves experimentally evoked itch in normal subjects (Kosteletzky et al. 2009) and in patients suffering from chronic pruritus (Yosipovitch et al. 2003, 2007). It was recently reported that cutaneous scratching reduced histamine-evoked activity of primate spinothalamic tract neurons (Davidson et al. 2009), suggesting that itch relief may involve scratch-evoked central inhibition of itch-signaling neurons. We presently observed that the spontaneous firing of superficial dorsal horn

Fig. 6. Responses to mechanical stimuli. Bar graph plots peak number of action potentials per second with preceding baseline activity subtracted, for AEW-treated (n = 10 for brush, n = 26 for pinch) and W-treated mice (n = 4 for brush, n = 9 for pinch). Error bars: SE.
neurons recorded in dry skin-treated mice was inhibited by scratching within the hindpaw treatment area. Moreover, some units exhibited a transient increase followed by a marked and more prolonged reduction in firing immediately after application of capsaicin (Fig. 3) or AITC. This may be relevant to observations that AITC can reduce histamine-evoked itch (Ward et al. 1996) and that histamine-evoked itch is attenuated in the area of allodynia produced by prior capsaicin (Brull et al. 1999).

Sensitization of itch-signaling neurons. We presently observed significantly heightened spontaneous activity in superficial dorsal horn neurons ipsilateral to dry skin treatment. This might reflect spontaneous firing in pruriceptive primary afferent fibers that were sensitized by the dry skin condition (Schmelz et al. 2003). In addition, when baseline firing was accounted for, superficial dorsal horn neurons ipsilateral to AEW treatment exhibited significantly larger responses to id injection of the PAR-2 agonist SLIGRL-NH2 compared with neurons ipsilateral to W treatment or neurons recorded in untreated animals (Fig. 5B). In contrast, responses to histamine were not significantly different between AEW- and W-treated sides or in neurons from untreated animals. However, there was a trend toward enhancement of histamine-evoked responses from dry skin (Fig. 5A). These findings suggest that the dry skin treatment results in a differential peripheral sensitization of pruriceptives. Recent behavioral data from our laboratory are consistent with this. AEW treatment resulted in a significant enhancement of scratching elicited by the PAR-2 agonist SLIGRL-NH2 as well as 5-HT, whereas there was a trend toward increased scratching elicited by histamine that did not reach statistical significance (Akiyama et al. 2010a). Furthermore, dorsal root ganglion (DRG) cells from AEW-treated mice exhibited enhanced calcium responses to application of the PAR-2 agonist and 5-HT, whereas there was a nonsignificant trend toward increased responses to histamine. These data argue for a differential peripheral sensitizing effect of dry skin on pruriceptive afferent fibers that respond to PAR-2 agonists or 5-HT, but less so for histamine.

The above-mentioned observations presuppose the existence of separate populations of PAR-2 agonist- and histamine-sensitive afferents. Current evidence is consistent with this possibility. Mechanically insensitive C-fiber afferents preferentially respond to histamine but not cowhage (Schmelz et al. 1997; Namer et al. 2008). In contrast, C-fiber polymodal nociceptors readily respond to cowhage with lesser responses to histamine (Johanek et al. 2008). Cowhage spicules contain proteases (mucunain) that act at PAR-2 and -4 receptors to elicit itch (Reddy et al. 2008). Thus, PAR-2 agonists may selectively excite C-polymodal nociceptors that also respond to noxious mechanical stimuli such as pinch. However, we presently did not observe any enhancement of pinch-evoked responses of pruriceptive dorsal horn neurons (Fig. 6). Thus, if the differential enhancement of neuronal responses to the PAR-2 agonist but not histamine is attributed to peripheral sensitization of polymodal nociceptors, the sensitization is stimulus specific, i.e., for chemical (PAR-2 agonist) but not mechanical activation.

Current evidence indicates that gastrin-releasing peptide (Sun and Chen 2007; Sun et al. 2009) and substance P (Carstens et al. 2010) may play important roles in the transmission of itch signals from pruriceptives to superficial dorsal horn neurons. Future studies should address possible mechanisms by which primary afferents might be differentially sensitized under pathophysiological conditions associated with chronic itch. We recently reported that scratching behavior associated with AEW treatment was significantly attenuated by local application of a PAR-2 antibody and systemic administration of a 5-HT2 antagonist, suggesting roles for endogenous 5-HT and proteases in the differential sensitization of pruriceptive afferent fibers (Akiyama et al. 2010a).

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DISCLOSURES
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