Responses of Rat Spinal Dorsal Horn Neurons to Intracutaneous Microinjection of Histamine, Capsaicin, and Other Irritants

E. CARSTENS

Section of Neurobiology, Physiology, and Behavior, University of California, Davis, California 95616

Carstens, E. Responses of rat spinal dorsal horn neurons to intracutaneous microinjection of histamine, capsaicin, and other irritants. J. Neurophysiol. 77: 2499–2514, 1997. To investigate the spinal processing of cutaneous pruritic and algesic stimuli, single-unit recordings were made from wide-dynamic-range-type lumbar spinal dorsal horn neurons in pentobarbital-sodium-anesthetized rats. Neuronal responses were recorded to mechanical and noxious thermal stimuli, as well as to microinjection (1 μl) of histamine (0.01–10% = 9 × 10^{-3}–9 × 10^{-4} M), capsaicin (0.1% = 3.3 × 10^{-3} M), or other algesic chemicals into skin within the receptive field via intracutaneously placed needles. Most (84%) of the 89 neurons responded to intracutaneous (ic) microinjection of histamine with a brief phasic discharge followed by an afterdischarge of variable (s to min) duration. Ten minutes after ic microinjection of histamine (but not NaCl), there was a significant increase in the mean area of the low-threshold (but not high-threshold) portion of unit mechanical receptive fields. However, responses to graded pressure stimuli were not significantly affected after histamine. Responses did not exhibit significant tachyphylaxis when histamine microinjections were repeated at 5- or 10-min intervals. Unit responses significantly increased in a dose-related manner to microinjection of histamine at concentrations ranging across 4 orders of magnitude. Within 30 s after ic microinjection of the H1 antagonist cetirizine, unit responses to ic histamine delivered at the same skin site were significantly attenuated. Unit responses to histamine, as well as to noxious thermal stimulation, were significantly reduced after systemic administration of morphine (3.5 mg/kg ip) in a naloxone-reversible manner. Application of a mechanical rub, scratch, or a noxious heat stimulus during the unit’s ongoing response to ic histamine produced a brief and marked excitation, often followed by a period of reduced ongoing discharge. Unit responses to histamine were markedly suppressed by electrical stimulation in the midbrain periaqueductal gray. Most (79%) histamine-responsive units tested also responded to ic microinjection of capsaicin. After the initial microinjection of capsaicin, subsequent responses to histamine and capsaicin microinjections were significantly reduced. Units also responded to ic ethanol (capsaicin vehicle) in a dose-related manner, and showed tachyphylaxis to repeated ic ethanol at 80% but not at 8%. The mean response to 80% ethanol was significantly smaller than to 0.1% capsaicin. All units tested also responded to topical application of mustard oil (50%) and ic serotonin (30 μg). The results are discussed in terms of theories that attempt to reconcile psychophysical and clinical observations of pain and itch sensation.

INTRODUCTION

Itch can be defined as an unpleasant sensation associated with the desire to scratch (Rothman 1941). Although itch is normally a minor irritation associated with insect bites, etc., under pathological conditions such as atopic dermatitis the itching and associated severe scratching can become just as unbearable and debilitating as chronic pain, leading to depression and suicidal thoughts (Keel and Armstrong 1964). A better understanding of the underlying neural mechanisms therefore has potential clinical value (for recent reviews see Magee 1991, 1996; McMahon and Koltzenburg 1992).

Sensations of either burning pain or of itch can be elicited by application of algesic (e.g., capsaicin, the active chemical in red chili peppers) or pruritic (e.g., histamine) chemicals, respectively, to the skin (Keel and Armstrong 1964; Simone et al. 1987, 1991a). Although recent studies indicate that spinothalamic tract neurons are involved in signaling sensations of chemogenic burning pain induced, for example, by intracutaneous (ic) injection of capsaicin (Simone et al. 1991b), much less is known about neural mechanisms of itch as a sensation distinct from pain. In present study I attempt to address this question by assessing the sensitivity of spinal dorsal horn neurons to algesic and potentially pruritic chemical stimuli.

There are two main hypotheses concerning itch and its relation to pain. One, specificity, states that itch and pain sensations are transmitted separately by specific populations of spinal neurons receiving input from “itch receptors” or nociceptors, respectively. The other, intensity, states that itch is a subliminal form of pain, with itch signaled by a low frequency, and pain by a higher frequency, of firing in a common population of neurons in spinal cord (McMahon and Koltzenburg 1992). Although both itch and pain sensations appear to be transmitted via the spinothalamic tract (White and Sweet 1969), there is now considerable evidence against the intensity hypothesis. 1) Decreasing the intensity of a pain-producing stimulus does not lead to itch (Keel 1956). 2) Electrical stimulation at certain sites on the skin evokes itch, and increasing the frequency of stimulation leads to increased itch but not pain (Tuckett 1982). 3) Intra-neuronal electrical microstimulation of C fiber nociceptor afferents in conscious humans evokes pain that does not become itch at lower stimulus frequencies (Handwerker et al. 1991; Ochoa and Torebjörk 1989). 4) Conversely, itch can occasionally be elicited by intraneuronal electrical microstimulation, and increases but does not become painful when the stimulus frequency is increased (Schmidt et al. 1993). 5) The opiate analgesic morphine reduces pain but often evokes itch (Ballantyne et al. 1988; Hales 1980).

Although the concept of specificity is thus more consistent with experimental observations, specific itch receptors have not yet been unequivocally identified. Itch is thought to be mediated by a subpopulation of polymodal nociceptors that are sensitive to pruritic chemicals such as histamine or cow-
hage (Handwerker et al. 1991; Tuckett and Wei 1987), although recent data indicate that certain thermally and mechanically insensitive nociceptors with C fiber afferents respond to histamine (Schmelz et al. 1996) and might constitute an itch receptor. Variants of the specificity hypothesis have also been proposed. The selectivity hypothesis is similar to specificity, but additionally incorporates the inhibitory effect of nociceptive inputs on putative itch-signaling neurons, so that excessive activation of polymodal nociceptors will suppress itch and increase pain transmission. This is in agreement with common experience that pain and itch rarely coexist in the same skin area, and that scratching (a mild form of pain) suppresses itch. A fourth hypothesis, here called “occlusion,” is that pruritic stimuli activate a subset of chemosensitive nociceptors, which in turn activate a subpopulation of dorsal horn neurons to signal itch. When a noxious stimulus recruits more nociceptors, more nociceptive dorsal horn neurons are activated to signal pain; itch is suppressed by occlusion (Handwerker 1992).

In previous studies we have pruritic and algesic chemical effects on spinal neurons been compared. In one study, Wei and Tuckett (1991) reported some ventrolateral tract axons in cat spinal cord to respond to application of cowhage to the skin; algesic chemicals were not tested. It was recently reported (Li et al. 1995) that six of seven primate spinothalamic tract neurons responded to ic histamine, and that all additionally responded to ic capsaicin. Because of the relative absence of information about spinal mechanisms of itch versus pain, the responses of spinal dorsal horn neurons to pruritic and algesic chemical stimulation of the skin were investigated. The main hypothesis is that itch-signaling neurons should respond to pruritic stimuli such as histamine in a manner consistent with itch sensation. The following characteristics are proposed that one might expect of neurons signaling itch. 1) Graded responses to pruritogens, such as histamine, across a concentration range that evokes itch sensation in humans. 2) Response to histamine is blocked by peripheral H1 receptor antagonists (Ganellin and Parsons 1982). 3) Responses to pruritogens are (selectivity) or are not (occlusion) suppressed by noxious counterstimuli that have been shown to reduce itch sensation (Bickford 1937; Graham et al. 1951; Ward et al. 1996). 4) Mechanosensitive receptive fields should expand after application of the pruritogen. This stems from the observation that an area of spreading alloknesis (“itchy skin” in which itch is evoked by mechanical stimuli) develops around the site of intradermal injection of histamine in humans (Simone et al. 1991a). A correlate of alloknesis might be expansion of neuronal receptive fields, analogous to the idea that expanded receptive fields contribute to secondary mechanical allodynia following intradermal injection of capsaicin (LaMotte 1992). 5) Because itch, like pain, is under at least limited descending (e.g., volitional) control, itch-signaling neurons should be under descending modulation from the brain stem. 6) Responses to pruritic stimuli might be enhanced, rather than suppressed, by systemic administration of opiate analgesics. 7) Because the sensation of itch from pruritic stimuli is desensitized by pretreatment of the skin with capsaicin (Handwerker et al. 1987; Toth-Kasa et al. 1986), capsaicin may reduce responses of itch-signaling neurons to subsequent pruritic stimuli. In the present study these predictions have been experimentally tested in recordings from spinal dorsal horn neurons. An abstract of this work has appeared (Carstens 1996).

METHODS

Surgical and recording methods

Electrophysiological experiments were conducted with the use of 33 adult male Sprague-Dawley rats anesthetized with pentobarbital sodium (induction: 65 mg/kg ip; maintenance: 10–20 mg/kg by constant infusion through a cannula in the jugular vein). The lumbar spinal cord was exposed by laminectomy for single-unit recording, and the head and spinal column were rigidly fixed in a stereotaxic frame. A tungsten microelectrode (F. Haer, ~10 MΩ) was advanced into the cord, and unitary activity was amplified and displayed by conventional methods and fed to a computer for construction of peristimulus time histograms (PSTHs; binwidth: 1 s) with the use of Spike software in later experiments (Forster and Handwerker 1990). In some experiments a concentric bipolar electrode was positioned in the midbrain periaqueductal gray (PAG) for electrical stimulation (100-ms pulse trains at 100 Hz, 3 per s, 0–400 μA as monitored with a current probe).

Unit selection and receptive field mapping

Single units responsive to mild mechanical stimulation of the ipsilateral hindpaw were searched. In this initial study only wide-dynamic-range-type (multireceptive) units that additionally responded to noxious mechanical and thermal stimuli were selected. When a unit was isolated, its mechanosensitive receptive field on the hindpaw was carefully mapped with the use of four von Frey filaments whose bending forces ranged from 40 mg to 76 g. For each filament, the perimeter (isothreshold contour) of the field within which the unit responded to repeated application was determined by establishing the boundary at which the unit responded to 50% of repeated stimuli. Boundary points were determined at intervals of ~1–2 mm. Most units so tested had little or no spontaneous activity (SA) that might have interfered with the ability to detect evoked responses. Isothreshold contours were sketched onto a scale drawing of the hindpaw (area: 390 mm², mean of inked hindpaw impressions from 3 rats). Receptive field areas were measured by computerized planimetry. A potential drawback is that stronger mechanical stimuli may have activated the unit by stretching more sensitive skin areas. However, this was not a confounding factor because an expansion of low-threshold, but not high-threshold, receptive field areas was observed (see RESULTS). Additionally, responses of some of the units to application of a series of graded nonnoxious pressure stimuli were recorded with the use of von Frey filaments (range: 1.2–76 g). Each filament was applied at the same site in the low-threshold receptive field area for a duration of 5 s, with 5–10 s between successive stimuli. Responses were quantified as the total number of impulses during a 10-s period beginning with the stimulus.

Noxious thermal stimuli [usually 48°C, 5 s in duration, interstimulus interval (ISI) ≥2 min, from an adapting level of 35°C] were delivered to the center of the mechanosensitive receptive field with the use of a feedback-regulated Peltier thermode. In most experiments, one unit with a receptive field on the left paw, and a second unit on the other side of the cord with a receptive field on the right paw, were recorded. In some experiments two units with receptive fields on the same paw (plus 2 with receptive fields on the other paw for a maximum of 4 units per rat) were recorded. In these cases, the second unit on one side was only studied if its receptive field was spatially separate from that of the first (e.g., heel vs. toe) and ≥2 h had passed.
Chemical stimulation of the skin

This was accomplished as follows. In most experiments, histamine and capsaicin (and in fewer cases, mustard oil) were delivered topically via cotton swab. Although mustard oil activated units by this means, histamine (up to 20%) and capsaicin (up to 1%) were usually ineffective, prompting the ic application of these chemicals. In early experiments, a 30.5-gauge needle was inserted into the skin and injections were made from a 1-ml syringe. However, this method usually activated the unit mechanically because of movement of the needle during injection. Therefore a microinjection system was developed in which the 30.5-gauge needle, connected via chemical-filled PE 20 tubing to a Hamilton 5- or 10-µl microsyringe, was positioned intrataneously and left there. Up to three or four needles could be positioned within 1 mm of each other in the receptive field center (1 toe or a circumscribed area on the plantar surface of the paw). It was attempted to systematically position the needle nearly parallel to the skin, with the tip extending ~1 mm into the dermis just below the epidermis. Needle placement evoked unit responses that often persisted for tens of seconds. Chemicals were subsequently microinjected only after the unit’s firing rate had returned to the previous baseline level. A standard volume of 1 µl was microinjected over a 1- to 2-s period. This did not mechanically activate units, as judged by an absence of response in most cases when an equivalent volume of vehicle (0.9% NaCl) was microinjected. Chemicals were as follows: histamine (0.01–10% = 9 × 10^{-19}–9 × 10^{-4} M in 0.9% NaCl; Sigma), capsaicin (0.1% = 3.3 × 10^{-3} M in 80% ethanol; Sigma), mustard oil (50% in paraffin oil; Fluka), and in some experiments serotonin [HCl or creatinine sulfate; 3 or 30 µg/µl (0.3% or 3% = 1.4 × 10^{-1} or 1.4 × 10^{-2} M) in 0.9% NaCl; Sigma], nicotine (5–10% = 3 or 30 × 10^{-3} M NaCl; Sigma), and the H₁ antagonist cetirizine dihydrochloride (Zyrtec, 0.01–0.1% = 0.0001–0.001 mg/µl in 0.9% saline; UCB Chemie). Unit responses were quantified by counting the total number of action potentials during the 60-s period following the onset of the chemical (or heat) stimulus.

Because up to four ic needles were placed near one another, there was concern that inflammation might develop. Indeed, swelling was sometimes observed around the injection area toward the end of experiments. However, it usually developed over a period of hours, whereas unit recordings were usually completed in <2 h. Furthermore, no systematic increase or decrease in successive neuronal responses to repeated histamine injections or noxious heat was observed, arguing against sensitizing or desensitizing effects associated with developing inflammation that might have confounded the results.

Experimental design and data analysis

After determining the unit’s mechanical receptive field and responsiveness to heat, the following sequence of tests ensued.

EXPANSION OF RECEPTIVE FIELD AND RESPONSE TO NONNOXIOUS STIMULI. This test was conducted on the first unit recorded in an experiment; the skin had received no prior stimuli. After the initial receptive field size was mapped, vehicle (0.9% NaCl) was microinjected intrataneously at the center of the receptive field, and the receptive field size was redetermined 10 min later. Histamine was then microinjected at the same site and the receptive field was remapped 10 min later to test for expansion. The 10-min waiting period was selected on the basis of the report that the area of spreading allonknesis peaks 10 min after ic histamine in human psychophysical studies (Simone et al. 1991a). In some experiments the histamine injection was not preceded by the vehicle control injection. To determine whether histamine affected unit responses to nonnoxious stimuli, each unit’s responses to a series of graded von Frey filaments were recorded before, and again 10 min after, histamine. At this stage additional tests were conducted, although not necessarily in the following sequence.

TACHYPHYLAXIS. Histamine microinjections were repeated at a 5- or 10-min ISI to determine whether responses progressively decreased.

DOSE-RESPONSE RELATIONSHIP. Four different concentrations of histamine (0.01–10%) were microinjected via separate needles, with ≥5 min between successive injections.

H₁ RECEPTOR ANTAGONIST. After three successive responses to repeated ic histamine (10%, 5-min ISIs) were recorded, the peripherally acting H₁ receptor antagonist cetirizine (0.01%; 1 µl) (Simons 1993; Simons and Simons 1991), was microinjected ic 30 s before the next subsequent histamine microinjection via a needle whose tip was placed as close as possible to that of the histamine needle. Responses to histamine continued to be recorded at 5-min intervals to evaluate the time course of any effect of cetirizine.

MORPHINE. If responses to repeated histamine injections were stable (i.e., within ~20% of the mean of 3 trials), the opiate analgesic morphine was administered systemically (3.5 mg/kg ip). Twenty minutes later, histamine was microinjected again. Naloxone (1–3.5 mg/kg ip) was then administered and histamine was microinjected again 20 min later. The unit’s response to noxious thermal stimulation was also tested before and ~20 min after morphine, and again ~20 min after naloxone.

COUNTERSTIMULATION. Mechanical rub (cotton swab) or scratch (wooden stick) or noxious thermal (48–52°C, 5 s) stimuli were delivered before and immediately after histamine microinjection to determine whether they affected the histamine-evoked response. The rub stimulus was delivered by manually moving a cotton swab back and forth (excursion 5 mm) against the skin within the mechanosensitive receptive field. Five such movements were made at a rate of one per second for a total stimulus duration of 5 s. This evoked a nonpainful rubbing sensation when delivered to human skin. The scratch stimulus was delivered in an identical manner, except that the flat end of a wooden stick (~0.5 mm diam) was moved against the skin. This evoked a mildly painful scratching sensation when delivered to human skin. Every attempt was made to apply rub and scratch stimuli with uniform pressure. In some experiments a noxious heat stimulus (48–52°C, 5 s in duration) was similarly delivered 5 s after ic histamine to determine whether heat affected the neuronal response to histamine.

DESCENDING MODULATION. In three experiments electrical stimulation was performed in the midbrain PAG either during or just founded the results. Before a unit’s response to histamine microinjection. Electrolytic lesions made at the stimulation (and in a few cases recording) sites were verified in postfixed 50-µm tissue sections counterstained with cresyl violet.

CHEMORESPONSIVENESS AND CAPSAICIN DESENSITIZATION. In many experiments the responsiveness of the unit to capsaicin microinjected via a separate cannula placed near the histamine injection site was tested. In a smaller number of experiments, the effects of topical application of mustard oil (n = 6) or ic microinjection of serotonin (n = 4) or nicotine (n = 2) were tested. A subjective attempt was made to deliver chemicals in concentrations evoking an approximately equivalent sensory rating magnitude when applied to the investigator’s tongue (capsaicin 0.1%, histamine 10%, serotonin 30 µg/µl, nicotine 5–10%). Histamine was microinjected 10 min after ic capsaicin to determine whether the histamine response was reduced by prior capsaicin. Similarly, capsaicin was microinjected again 10 min later to determine whether the response was affected by prior capsaicin.

CONTROLS. In most cases 0.9% saline was microinjected ic to control for volumetric effects (see above). The capsaicin vehicle, 80% ethanol, was also given ic as a control and proved to excite...
all units tested. Therefore a lower dose of ethanol was also tested (8%) to examine the dose-response relationship, and repeatedly delivered ethanol was used (8% or 80%) to test for tachyphylaxis as described above for histamine.

Mean group values (expressed as number of impulses per 60 s) were compared with the use of paired t-tests with P < 0.05 taken as significantly different. Unit SA, if present, was not subtracted from stimulus-evoked responses unless otherwise stated. The histamine dose-response relationship was subjected to a one-factor analysis of variance (ANOVA) with P < 0.05 taken as significant.

RESULTS

Unit sample

Results are based on a total of 89 wide-dynamic-range-type units that responded to innocuous tactile as well as noxious mechanical and thermal stimuli. Mechanical receptive fields on the ipsilateral hindpaw varied in size, spanning most or all of the ventral paw (33% of units), one-half of the paw including four to five digits (3%), or smaller areas restricted to three digits (19%), two digits (23%), or one digit (22%). Examples of receptive fields are shown in many of the figures. All units responded to noxious pressure stimuli, usually at thresholds <1.2 g, and responded at higher frequencies to increasing pressure (see below). Most units initially displayed no (45% of units) or low levels of (<1 Hz; 27%) spontaneous firing, whereas the remainder fired spontaneously at rates of 1–5 Hz (9%) or higher (19%) up to a maximum of ~15–20 Hz. Recording sites ranged from 62 to 794 μm (401.6 ± 185 μm, mean ± SD) below the cord surface, which corresponds to the superficial and middle layers of the dorsal horn. There were no discernible differences in unit properties as a function of depth in the dorsal horn, so results from all units were pooled.

Response to histamine

Of the 89 units, 75 (84%) showed clear-cut increases in firing rate to ic microinjection of histamine. Most units responded in a biphasic manner to low or intermediate-strength von Frey hairs were usually about the same size, ranging from a few toes to the entire hindpaw, whereas those mapped with the weakest (40 mg) were considerably smaller. An example is shown in Fig. 2A. Effects of histamine on receptive field area were therefore analyzed only for the largest and smallest iso-threshold contours. In eight experiments, vehicle (0.9% NaCl, 1 μl) was first microinjected into the center of the lowest-threshold area and the receptive field was remapped 10 min later. This did not change receptive field areas (Fig. 2A). Histamine was then microinjected at the same site and the receptive field was remapped 10 min later. The low-threshold area usually expanded considerably, whereas the high-threshold area usually expanded only slightly in size (Fig. 2A). In Fig. 2B, mean receptive field areas are plotted for eight units to show the significant increase in the low-threshold (162%), but not high-threshold, receptive field area following histamine. An expansion in low-threshold receptive field area was verified in an additional nine units in which the histamine injection was not preceded by the vehicle (NaCl) control injection. Overall there was a statistically significant increase in the low-threshold area following histamine for all units tested (mean: 173%, range: 102–303%; n = 17; P = 0.0001), whereas the high-threshold area was not significantly affected (mean: 113.5%) after histamine.

Unit responses to graded nonnoxious pressure stimuli were usually not affected after ic histamine despite receptive field expansion. Figure 3A shows a typical example. The initial receptive field is shown in the drawing, and the PSTHs show the unit’s increasing responses to graded pressure stimuli. Figure 3B shows that the receptive field expanded after ic histamine, but the unit’s responses to graded pressure were essentially unchanged. Similar results were obtained in 7 of 13 units, whereas in three cases responses to pressure were enhanced by >30%, and in three cases they were reduced by >30%, after histamine. In Fig. 3C, mean responses of all 13 units are plotted versus stimulus pressure to show a significant (P = 0.0001, ANOVA), logarithmically increasing stimulus-response relationship that was not significantly changed after ic histamine.

Response to repeated histamine

Histamine microinjections were repeated to determine whether there was a tachyphylaxis in subsequent responses. When repeated at a 5- or 10-min ISI, successive responses were frequently stable in size. An example is shown in Fig. 4 (top 3 PSTHs). The responses of separate populations of units to histamine microinjections at a 5- or 10-min ISI, respectively, are collectively shown in Fig. 5, A and B. Although some individual units showed either a decrement (tachyphylaxis) or an increase (sensitization) in successive responses, the mean changes at either ISI were small (Fig. 5, A and B, thick lines) and not statistically significant. Figure 5B, right data point, shows the mean population response to control vehicle (saline) microinjection, which was
significantly lower compared with histamine-evoked responses.

**Dose-response relationship**

Unit responses to histamine increased across the concentration range employed (0.01–10%), with a response threshold near 0.01%. Figure 6 shows PSTHs of responses of an individual unit to histamine microinjections at the four different concentrations. The peak response increased with histamine concentration up to 1%, and the response duration increased across the dose range. Figure 7 shows averaged responses of 12 units to histamine at each concentration, and illustrates the dose-related posthistamine increase in response frequency and duration. To estimate the overall contribution of background firing level to the histamine-evoked responses, mean responses of the 12 units are plotted in Fig. 8 with SA subtracted (Fig. 8A; mean number of impulses per 60 s before histamine subtracted from mean impulses per 60 s posthistamine) or not (Fig. 8B). Figure 8A shows individual (thin lines) and mean (thick line) neuronal responses corrected for background firing. The dose-related increase was statistically significant (ANOVA, \( P = 0.0004 \)). In Fig. 8B, mean responses are plotted with background activity included, and additionally mean SA levels are shown. To determine whether there was a progressive overall increase in SA during the course of investigation of the unit, SA was measured for 60 s before the initial microinjection of histamine in each unit (Fig. 8B, leftmost bar), and again >5 min after the final histamine microinjection in the series (Fig. 8B, rightmost bar). The small increase in mean SA shown in Fig. 8B was not statistically significant.

**\( H_1 \) receptor antagonist**

Responses of each of 10 units to ic histamine were reduced or abolished by ic cetirizine. An example is shown in Fig.
and did not enter the systemic circulation in a concentration sufficient to exert a more prolonged antihistaminic effect.

**Suppression by morphine**

Because successive mean histamine-evoked responses did not decrement significantly (Fig. 5), it was possible to investigate the effect of systemic morphine on these responses. An example is shown in Fig. 10, A and B. The unit’s responses to histamine (Fig. 10A, top) and noxious heat (Fig. 10B, top) were recorded, and then morphine was injected systemically (3.5 mg/kg ip). At 20 min postmorphine, the unit’s responses to histamine microinjection (Fig. 10A, middle)

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**Fig. 3.** Responses to graded nonnoxious mechanical stimuli and lack of effect of ic histamine. A: PSTHs of dorsal horn unit’s responses to von Frey pressure stimuli at the indicated bending forces. Drawing shows low-threshold (black) and high-threshold (gray) receptive field on left hindpaw before ic histamine. Arrow: site of stimulus application. B: responses of unit in A to identical pressure stimuli, 10 min after ic histamine (arrow in drawing in A). Drawing shows receptive field that has expanded in size. C: mean responses of 13 units vs. stimulus force, before (●, Control) and after (∅) ic histamine.

**Fig. 4.** Example of unit responses to repeated histamine microinjections. Shown are PSTHs (binwidth: 1 s) of a unit’s responses to ic microinjection (at time indicated by ▼) of histamine (HIS, top 3 traces), NaCl (4th trace), and capsaicin (CAP, bottom 2 traces). Note the nearly complete absence of response to 2nd capsaicin injection. Drawing at top left shows microinjection site (●) and extent of receptive field on left hindpaw (stippling). Drawing at top right shows unit recording site in mid-dorsal horn.
heat (Fig. 10B, middle) were almost totally abolished. Responses recovered after systemic naloxone (Fig. 10, A, bottom and B, bottom). Mean data for the unit population are shown in Fig. 10C. After morphine, the population responses to histamine and heat were significantly reduced (to 29% and 55% of control for histamine and heat, respectively) compared with predrug conditions ($P = 0.0021, P = 0.0091$ for histamine and heat, respectively) or postnaloxone conditions ($P = 0.0027, P = 0.02$ respectively).

**Effect of counterstimuli on response to histamine**

In 14 units it was tested whether application of a nonnoxious rub or a noxious scratch or heat stimulus affected unit responses to histamine. Qualitative evidence was obtained that such counterstimuli summed with histamine-evoked responses, often followed by a variable depressant effect. The unit shown in Fig. 11, A–D, responded to histamine (Fig. 11A), and to rub and scratch stimuli applied to the mechano-sensitive receptive field (Fig. 11B). The responses evoked by the rub and scratch stimuli summed with the histamine-evoked response, followed by what appeared to be a brief reduction in ongoing activity (Fig. 11B). This unit also responded to noxious heat (Fig. 11D). The heat-evoked response summed with that evoked by histamine (Fig. 11E), followed by a reduction in firing (compare Fig. 11, C and E). Similar results were obtained in two additional units, whereas in three cases there was no evidence of any subsequent reduction in firing following heat. Another unit is shown in Fig. 11, F and G. Rub and scratch stimuli evoked responses that summed with the response to histamine, followed by periods of reduced activity (compare Fig. 11, F and G). This pattern was seen in a total of seven units, whereas in four other units the rub- and scratch-evoked responses summed with the histamine-evoked response without any subsequent reduction in firing.

**Descending suppression**

In three units it was additionally tested whether the response to histamine was affected by electrical PAG stimulation. The example in Fig. 12, top PSTH, shows that a brief episode of PAG stimulation superimposed during the unit’s response to histamine caused a near total suppression of

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**FIG. 5.** Dorsal horn unit responses to repeated ic histamine microinjections. Graphs: individual (thin lines) and mean (thick line) unit responses evoked by 3 successive injections of histamine (His-1, His-2, and His-3). A: 5-min interstimulus intervals (ISIs) for population of 14 dorsal horn units. B: 10-min ISI, for a separate population of 13 units. Right data point shows mean response to vehicle (saline). Asterisk: significantly different from His-2 ($P = 0.04$). Error bars: means ± SE.

**FIG. 6.** Example of dose-related increase in dorsal horn unit responses to different concentrations of ic histamine. A–D: PSTHs of 1 unit’s responses to ic histamine (●) at indicated concentrations. Drawing in A shows receptive field (gray) and site of histamine microinjection (●) on right hindpaw.
firing that recovered quickly after termination of the PAG stimulation. Figure 12, bottom PSTH, shows that when PAG stimulation began coincident with the histamine microinjection, the response was delayed for several seconds after termination of PAG stimulation. A similar near total suppression of histamine-evoked responses by PAG stimulation was also observed in the other two units.

**Chemoresponsiveness and capsaicin desensitization**

Twenty-nine histamine-responsive units were tested for their response to ic microinjection of capsaicin near the histamine microinjection site, and 23 (79%) responded. Examples are shown in Figs. 4, 13, and 16B. After capsaicin, the initial phasic response developed significantly more slowly (time to peak: $10.5 \pm 8.1$ s, mean ± SD; range: 3–30 s) compared with histamine ($P = 0.025$), and then declined (decay to 1/2 peak: $10.3 \pm 7$ s, mean ± SD; range: 2–25 s). The firing rate declined to the precapsaicin level in <2 min in half of the units ($62.3 \pm 20.4$ s, mean ± SD; range: 30–90 s), whereas the increased firing rate persisted beyond 2 min in the remainder. The magnitude of the mean capsaicin-evoked response was similar to that of histamine (Fig. 15), possibly reflecting a near maximal firing capacity of the units as well as the attempt to match histamine and capsaicin concentrations according to subjective sensory magnitude.

Topical application of mustard oil evoked a prolonged response in each of six histamine-sensitive units (2 tested also responded to capsaicin). An example is shown in Fig. 13. Responses to mustard oil were of slower onset ($27.3 \pm 15.3$ s, mean ± SD), decayed to half of the maximal rate more slowly ($40.5 \pm 20.3$ s, mean ± SD), and in all cases persisted >2 min. However, this slower time course is due at least partly to the time of diffusion of topically applied mustard oil through the skin.

Ic Microinjection of serotonin (30 μg) evoked a response in four of four histamine-responsive units, two of which also responded to capsaicin (Fig. 14). Microinjection of nicotine (5% and 10%) also evoked responses in both of two histamine-responsive units (Fig. 14).

**FIG. 7. Dose-related increase in dorsal horn unit responses to ic histamine: population data.** A–D: PSTHs (binwidth: 1 s) of averaged responses of 12 dorsal horn units to histamine (↓) at indicated concentrations. Error bars: means ± SE.
After the initial capsaicin microinjection, responses to subsequent microinjections of histamine and capsaicin were markedly reduced. Examples are shown in Figs. 4 and 13. The mean responses to the second histamine and capsaicin microinjections were significantly reduced (to 33% and 32% of control for histamine and capsaicin, respectively) compared with the first injections of each ($P < 0.005$ and 0.001 for histamine and capsaicin, respectively; Fig. 15). This suggests that a single application of capsaicin was sufficient to desensitize cutaneous receptors to subsequent capsaicin (self-desensitization) and histamine (cross-desensitization). It could not be determined whether prior application of histamine affected the unit’s response to capsaicin because of the capsaicin self-desensitization. Only 3 of 17 units previously receiving histamine did not respond to subsequent capsaicin.

**Ethanol**

Because capsaicin was dissolved in ethanol, itself an irritant (Green 1988), it was tested whether units responded to ic microinjection of ethanol. Each of the 12 units tested responded. An example is shown in Fig. 16A. In this unit, which is typical of all cases, capsaicin evoked a larger response compared with that evoked by ethanol (Fig. 16B). Mean responses are plotted in Fig. 16C to show the significant difference ($P < 0.05$) in responses to capsaicin versus 80% ethanol. In this group, the mean response to 10% histamine was again comparable with that evoked by capsaicin.

All units also responded to a lower dose (8%) of ethanol. The mean response to 8% ethanol was significantly smaller ($P = 0.012$) than that to 80% ethanol (Fig. 16C). It was also investigated whether successive unit responses to repeated injections of ethanol exhibited tachyphylaxis. Figure 17A shows that unit responses to repeated 8% ethanol tended to decline, but this was not significant. Successive mean responses to repeated 80% ethanol, however, decreased significantly (to 56% and 58% of control; $P < 0.05$; Fig. 17B).

**Discussion**

The present results show that a large majority of dorsal horn wide-dynamic-range-type neurons respond to ic microinjection of histamine within the receptive field. Neuronal response magnitude and duration increased across a range of histamine concentrations known to elicit itch sensation in humans (Simone et al. 1987), and responses were reduced or blocked by the H1 receptor antagonist cetirizine. Furthermore, unit responses to histamine were suppressed by the opioid analgesic morphine in a naloxone-reversible manner. After histamine, neuronal low-threshold mechanical receptive fields increased significantly in size, possibly providing a functional basis for allodynia (itchy skin). Histamine-evoked responses were suppressed by stimulation in the midbrain PAG, an area associated with analgesia. Peripheral mechanical or noxious thermal stimuli evoked excitatory responses that appeared to sum with that evoked by histamine, usually followed by a period of reduced ongoing activity. Finally, a large majority of neurons also responded to other irritants (capsaicin, serotonin, mustard oil, and ethanol). Neuronal responses to histamine and capsaicin were significantly reduced after prior application of capsaicin.
Do neuronal responses to histamine mirror itch sensation?

In the present study, most units responded to ic histamine with a rapid phasic discharge followed by a prolonged lower-frequency afterdischarge that usually dissipated within tens of seconds to a few minutes. The rapid onset of neuronal responses contrasts somewhat with the onset of human sensation of itch, which developed more slowly after ic or subcutaneous injection (Simone et al. 1991a) or epicutaneous iontophoretic application (Handwerker et al. 1987) of histamine, reached a peak >1 min later, and persisted for >10 min. The magnitude and duration of neuronal responses increased across a range of histamine concentrations in a manner corresponding well with magnitude estimates of human itch elicited by a similar range of histamine concentrations delivered intracutaneously (Simone et al. 1987). Furthermore, spontaneous neuronal firing was increased, albeit not significantly, 5 min after the last in a series of histamine microinjections. However, human itch sensation persists up to 30 min following high-dose histamine (Simone et al. 1987). Thus the time course of human itch sensation is longer than that of histamine-evoked dorsal horn neuronal responses in rats. Possible explanations for this discrepancy are as follows: 1) itch sensation requires recruitment of neural itch-signaling mechanisms beyond the dorsal horn, 2) species differences, 3) anesthesia, 4) differences between glabrous (used in these studies) versus hairy skin, which is often used in human studies, or 5) histamine in rodents is algesic rather than pruritic (see below).

Earlier psychophysical studies reported larger amounts (100 μl) of intradermally injected histamine to evoke pain (Broadbent 1955), whereas more recent studies in which a range of doses was used (0.1–100 μg in 10 μl) reported primarily sensations of itch (Handwerker et al. 1987; Melton and Shelly 1950; Simone et al. 1987, 1991a). The itch sensation evoked by histamine and other pruritic chemicals (e.g., serotonin, substance P, and vasoactive intestinal polypeptide) is in nearly all cases prevented by pretreatment with H₁ receptor antagonists (Hagermark 1992; Heyer and Magerl 1995; Magerl 1991), suggesting a common action via histamine released by mast cell degranulation. Out data showing a reversible attenuation of ic histamine-evoked responses following local application of the peripherally acting H₁ antagonist cetirizine (Simons 1993; Simons and Simons 1991) are consistent with this.

In the present study, the ic doses of histamine employed (0.1–100 μg in 1 μl) are likely to have produced a localized activation of nociceptors. In this regard it is interesting that intradermal injections of substance P, serotonin, and the mast cell degranulator compound 48/80, but not capsaicin or formalin, evoked behavioral scratching directed toward the injection site in mice and rats (Berendsen and Broekkamp 1991; Kuraishi et al. 1994, 1995). Histamine (up to 300 μg/100 μl = 3%) did not evoke significant scratching in mice (Kuraishi et al. 1995) but did so in hairless guinea pigs (Woodward et al. 1995). If one assumes that scratching reflects itch sensation (see Magerl 1991 for discussion), then these inconsistent behavioral data raise the question of whether ic histamine in rodents is a pruritic or rather an algesic stimulus. For this reason ic serotonin, which is colocalized with histamine in rodent mast cell granulocytes (Hagermark 1992), was also tested. Like histamine, serotonin also excited the smaller number of units tested. Serotonin can evoke pruritis in humans, although it is much weaker than histamine (Hagermark 1992). Clearly more work is needed, particularly in developing a behavioral animal model that differentiates itch from pain, to establish whether histamine, serotonin, or other substances such as platelet-activating factor (Woodward et al. 1995) are reliable pruritogens in rodents.

Receptive field expansion following histamine

After ic histamine, units’ low-threshold but not high-threshold receptive field areas expanded significantly; that

![Fig. 10. Morphine suppression of unit responses to histamine and to noxious heat. A: PSTHs of unit’s responses to ic histamine before drug (top), 20 min after systemic administration of morphine (middle), and after systemic naloxone (bottom). Drawing shows histamine microinjection site (×) in mechanical receptive field (gray) of left hindpaw. B: PSTHs of same unit’s responses to noxious heat stimulus, before and after morphine and naloxone (same format as in A). C: mean responses of 12 units to histamine (black bars) and heat (white bars) predrg, 20 min after systemic administration of morphine (3.5 mg/kg ip), and after systemic naloxone. Asterisks: significantly different from pre- and postnal levels (see text for P values). Error bars: means ± SE.](http://jn.physiology.org/ by 10.220.32.247 on November 2, 2016)
is, a portion of the high-threshold field contiguous with the low-threshold area became more sensitive posthistamine. This was not associated with a significant change in mechanical sensitivity at the center of the low-threshold field. Previous studies have reported expansion of dorsal horn unit receptive fields over a similar time course following noxious stimulation such as ic injection of capsaicin (e.g., Simone et al. 1991b). Such receptive field expansion may be associated with secondary mechanical hyperalgesia and allodynia that develops around the site of noxious stimulation (LaMotte et al. 1991). Injection of histamine ic evokes itch and the development of a region of “alloknesis” (itchy skin) in skin surrounding the injection site (Simone et al. 1991a). The maximum area of alloknesis was reached 10 min after histamine (Simone et al. 1991a), at which time dorsal horn unit low-threshold receptive field areas were presently observed to have expanded significantly.

Both the mechanical hyperalgesia following ic capsaicin (LaMotte et al. 1991) and alloknesis following histamine (Simone et al. 1991a) were prevented by prior local anesthesia of skin at the injection site. Furthermore, neither the field of hyperalgesia nor that of alloknesis spread beyond a thin barrier of locally anesthetized skin. These observations suggest that spreading hyperalgesia and alloknesis depend partly on a peripheral neurogenic mechanism. LaMotte (1992) hypothesized that cutaneous chemoreceptors with widely branching afferent fibers are activated by a noxious stimulus. These chemoreceptors send afferent fibers into the spinal cord to sensitize spinal dorsal horn neurons. Part of the central sensitization process may involve expansion of cutaneous mechanical receptive fields, such that mechanical stimulation at any point within the area of secondary hyperalgesia more effectively activates a larger number of nociceptive neurons, thus enhancing pain transmission. By analogy, if the present histamine-sensitive dorsal horn units signal itch, then expansion of their low-threshold mechanosensitive receptive fields following histamine may provide a basis for alloknesis. However, such a mechanism does not appear to
involve increased mechanical sensitivity at the center of the receptive fields of dorsal horn neurons.

**Suppression by morphine and descending pathways**

In the present study, neuronal responses to histamine as well as noxious heat were significantly suppressed, rather than enhanced, after systemic administration of morphine in a naloxone-reversible manner. The results with histamine are not consistent with observations that itch is refractory to or even enhanced by opioids in humans (Ballantyne et al. 1988; Bernstein and Swift 1979; Hales 1980), and that itch can be reduced by naloxone (Bernstein et al. 1982). Possible explanations for the discrepancy between the data of this study and clinical observations include species differences, anesthesia, and an algesic rather than pruritic role for histamine in rodents. The present results are in agreement with the finding that systemic morphine reduced the number of neurons in the rat lumbar dorsal horn exhibiting c-fos immu

**Summation and suppression of responses to histamine by counterstimuli**

Rubbing, scratching, or noxious heat stimuli delivered within the receptive field evoked excitatory responses that summed with the histamine-evoked discharge. This is not surprising, because wide-dynamic-range-type neurons were selected that respond to innocuous and noxious mechanical stimuli and to noxious heat. In the present study nonnociceptive neurons were not examined, because they do not receive input from chemosensitive polymodal nociceptors with C fiber afferents and therefore would not be expected to respond to histamine.

After excitation of the unit by the mechanical or noxious thermal stimulus, a period of reduced ongoing firing was observed in a majority of cases. Such a reduction in histamine-evoked spinal activity might be relevant to the common experience that itch can be relieved by rubbing or scratching the itchy skin area, and to psychophysical data showing that itch sensation induced by histamine can be suppressed for prolonged periods by noxious stimuli including heat, mustard oil, and electrical stimulation (Bickford 1937; Graham et al. 1951; Ward et al. 1996). Itch is also blocked by cooling the skin (Bromm et al. 1995; Fruhstorfer et al. 1986; Murray and Weaver 1975). It was observed that cooling the skin to 5°C reduced dorsal horn unit responses to ic histamine in some cases, but more data are needed to verify this finding.

That noxious mechanical and thermal inputs evoke excitatory responses superimposed on the histamine-evoked discharge could be taken as evidence favoring the occlusion hypothesis of itch (Handwerker 1992). In this regard, epicutaneous iontophoretic application of histamine, which nor-
DORSAL HORN<Unit Responses to Histamine

FIG. 13. Example of nonselective unit responses to chemical irritants. PSTHs (top to bottom): unit’s responses to noxious heat, ic histamine, topical mustard oil, ic capsaiacin, and ic histamine. Note near absence of response to histamine following capsaiacin (bottom). Histamine and capsaiacin microinjection sites were within 1 mm of each other at site indicated by dot on drawing of receptive field (gray) on left hindpaw.

mally evokes itch, evoked instead a burning pain sensation in skin that had been pretreated with the algesic chemical bradykinin (Koppert et al. 1993). Interestingly, itch sensation was suppressed for some time after the burning sensation had subsided. This suggests that the suppression of itch by pain may involve an active inhibitory mechanism with a longer time course than that expected for occlusion. It is unclear at what level of the nervous system this postulated inhibition might occur.

Chemoresponsiveness and desensitization by capsaiacin

Most (79%) of the histamine-responsive units also responded to ic capsaiacin. Capsaiacin-evoked responses peaked significantly more slowly compared with those evoked by histamine. This may reflect a difference in time course of nociceceptor activation by these agents; it was attempted to match concentrations of histamine and capsaiacin according to subjective sensory magnitude. Each of the units tested

FIG. 15. Capsaiacin self-desensitization and cross-desensitization to histamine. Bar graph: mean unit responses to ic microinjection of histamine (black bars) and capsaiacin (white bars) at 10-min intervals, before (His-1, Cap-1) and after (His-2, Cap-2) 1st capsaiacin injection. Error bars: means ± SE. Asterisks: responses significantly smaller compared with His-1 (P = 0.0085) and Cap-1 (P = 0.0088), respectively. Error bars: means ± SE.
FIG. 16. Response to ethanol. A: dorsal horn unit’s response to ic ethanol 80% microinjected at site indicated by dot in drawing of receptive field (gray) on right hindpaw. B: response of unit in A to ic capsaicin. C: mean responses of 11 units to ic ethanol (EtOH; 8% and 80%), capsaicin (0.1%), and histamine (10%). Asterisk: responses significantly different (P < 0.05). Error bars: means ± SE.

Also responded to topical application of mustard oil and to ic serotonin, nicotine, and ethanol. This apparent lack of selectivity in neuronal responses to chemical irritants may reflect their afferent nociceptive input. In a recent human microneurographic study it was reported that a fraction of polymodal nociceptors responded to epicutaneous histamine iontophoresis sufficient to evoke itch (Handwerker et al. 1991). All histamine-sensitive nociceptors also responded to mustard oil, which evoked burning pain. In earlier work a lack of nociceptor selectivity to chemical irritants was also reported (e.g., Foster and Ramage 1981).

After the initial microinjection of capsaicin, there was a significant reduction in subsequent responses to capsaicin (self-desensitization) or histamine (cross-desensitization). The magnitude of this effect (reduction to 32% of control) was greater than the tachyphylaxis observed with repeated injections the capsaicin vehicle, 80% ethanol (to 56% of control). Capsaicin self-desensitization (Green 1989, 1991; Green and Shaffer 1993) and cross-desensitization to histamine (Handwerker et al. 1987; Toth-Kasa et al. 1986) have previously been reported in human psychophysical experiments. The mechanism by which a single microinjection of capsaicin produces desensitization to subsequent irritants is unclear. It might involve a toxicological action (Holzer 1991) or specific binding of capsaicin with vanilloid receptors (Szallasi 1994) that reside on polymodal nociceptors, to open cation channels (Petersen and LaMotte 1993; Wood et al. 1988) to possibly engage intracellular second-messenger systems via Ca\(^{2+}\) influx. Recent studies have shown that Ca\(^{2+}\) influx is required for both neurotoxic (Chard et al. 1995) and desensitizing (Cholewinski et al. 1993) actions of capsaicin on cultured dorsal root ganglion neurons.

It is uncertain whether prior application of histamine affects subsequent perceptual responses to histamine or capsaicin. In the present study, mean unit responses did not exhibit a significant tachyphylaxis to histamine microinjections repeated at 5- or 10-min intervals, although a few individual units exhibited tachyphylaxis or sensitization.

**Theoretical basis of itch and pain**

Except for their sensitivity to histamine, the characteristics of the presently recorded dorsal horn neurons are fully con-

FIG. 17. Tachyphylaxis to repeated ic ethanol. A: individual (thin lines) and mean (thick line with error bars) responses of 7 units to repeated ic ethanol 8% at a 5-min ISI. B: as in A, for responses of 11 units to ic ethanol 80%. Asterisk: significantly different from trial 1 (P < 0.05). Error bars: means ± SE.
sistent with a nociceptive role and only partially fulfilled
expectations for itch-signaling neurons (see INTRODUCTION).
Thus virtually all of the histamine-sensitive wide-dynamic-
range-type neurons also responded to capsaicin and other
irritants. Low-threshold mechanical receptive fields ex-
panded after histamine injection, and histamine-evoked re-
sponses were suppressed by descending pathways. In addi-
tion, application of capsaicin desensitized subsequent re-
sponses to histamine. Contrary to the proposed expectations,
however, the time course of histamine-evoked responses ap-
peared to be shorter compared with that of itch sensation.
Furthermore, responses to histamine appeared to summate with coincident mechanical or noxious thermal stimuli, fol-
lowed frequently by a period of reduced firing. Finally, histo-
mine-evoked responses were suppressed, rather than facili-
tated, by systemic morphine. The latter two findings, in par-
cular, are not consistent with the selectivity hypothesis of
itch and would appear to be most parsimonious with the occlusion hypothesis (Handwerker 1992; Koppert et al. 1993).
According to this idea, pruritic stimuli activate a subpopulation of chemosensitive polymodal nociceptors, which in turn excites a subset of dorsal horn neurons to signal itch. Noxious stimuli recruit a larger population of nociceptors and dorsal horn neurons, including the subset activated by histamine, whose total output signals pain and simultaneously occludes itch (see Handwerker 1992 for de-
tails). It is presently unclear what distinguishes the subset of itch-signaling neurons from the larger population.

Another interpretation of the present results is that the responses evoked by histamine are more reflective of pain rather than itch, particularly under the present experimental conditions (barbiturate anesthesia) in rodents. Itch might be signaled by a restricted subset of neurons, not presently encountered, that are selectively activated by pruritogens in a manner consistent with itch sensation. In the present work, nociceptive-specific neurons were not studied, and it is con-
ceivable that a subpopulation of this class might participate in signaling itch. In this regard it is interesting that certain thermally and mechanically insensitive C fiber afferents re-
corded in humans were recently reported to respond to hista-
mine delivered iontophoretically to the skin (Schmelz et al. 1996). If there were a specific itch pathway consisting of spinal neurons receiving input exclusively from this type of chemonociceptor, such neurons would not have been en-
countered with the present search strategy.

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