

The development of cutaneous allodynia during a migraine attack

Clinical evidence for the sequential recruitment of spinal and supraspinal nociceptive neurons in migraine

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Summary

Recently, we showed that most migraine patients exhibit cutaneous allodynia inside and outside their pain-referred areas when examined during a fully developed migraine attack. In this report, we studied the way in which cutaneous allodynia develops by measuring the pain thresholds in the head and forearms bilaterally at several time points during a migraine attack in a 42-year-old male. Prior to the headache, he experienced visual, sensory, motor and speech aura. During the headache, he experienced photo-, phono- and odour-phobia, nausea and vomiting, worsening of the headache by coughing or moving his head, and cutaneous pain when shaving, combing his hair or touching his scalp. Comparisons between his pain thresholds in the absence of migraine and at 1, 2 and 4 h after the onset of migraine revealed the following. (i) After 1 h, mechanical and cold allodynia started to develop in the ipsilateral head but not in any other site. (ii) After 2 h, this allodynia increased on the ipsilateral head and spread to the contralateral head and ipsilateral forearm. (iii) After 4 h, heat allodynia was also detected while mechanical and cold allodynia continued to increase. These clinical

observations suggest the following sequence of events along the trigeminovascular pain pathway of this patient. (i) A few minutes after the initial activation of his peripheral nociceptors, they became sensitized; this sensitization can mediate the symptoms of intracranial hypersensitivity. (ii) The barrage of impulses that came from the peripheral nociceptors activated second-order neurons and initiated their sensitization; this sensitization can mediate the development of cutaneous allodynia on the ipsilateral head. (iii) The barrage of impulses that came from the sensitized second-order neurons activated and eventually sensitized third-order neurons; this sensitization can mediate the development of cutaneous allodynia on the contralateral head and ipsilateral forearm at the 2-h point, over 1 h after the appearance of allodynia on the ipsilateral head. This interpretation calls for an early use of anti-migraine drugs that target peripheral nociceptors, before the development of central sensitization. If central sensitization develops, the therapeutic rationale is to suppress it. Because currently available drugs that aim to suppress central sensitization are ineffective, this study stresses the need to develop them for the treatment of migraine.

Keywords: migraine; headache; allodynia; sensitization; pain

Abbreviations: QST = quantitative sensory testing; VFH = von Frey hairs

Introduction

Migraine is a neurological disorder that affects ~27 million women and 10 million men in the USA (Stewart *et al.*, 1992). Although the causes of migraine are unknown, it is generally thought that the pain originates from chemical

activation of sensory nerves that supply intracranial blood vessels and the meninges (Moskowitz *et al.*, 1988). Based on this concept, we applied chemical irritants to rats' dura for a brief period and reported that this irritation altered

the electrophysiological properties of first-order meningeal perivascular pain-sensitive neurons for a period of 1–2 h (Strassman *et al.*, 1996), and second-order brainstem trigeminal neurons that receive convergent input from the dura and facial skin for up to 10 h (Burstein *et al.*, 1998). The altered first- and second-order trigeminovascular neurons became more sensitive to innocuous mechanical stimuli such as dural indentation with forces <1 g and mild periorbital skin brushing or heating. Based on these studies, we proposed that sensitization of meningeal perivascular pain-sensitive neurons can explain the worsening pain during coughing or bending over, and the throbbing pain of migraine (Anthony and Rasmussen, 1993). We also proposed that the enhanced responses of brainstem trigeminal neurons represent a state of central sensitization. Because central sensitization is believed to be the underlying mechanism of cutaneous allodynia (Simone *et al.*, 1991; Torebjork *et al.*, 1992; McMahon *et al.*, 1993; Ren and Dubner, 1993; Woolf and Doubell, 1994; Koltzenburg *et al.*, 1995; Woolf *et al.*, 1995; Magerl *et al.*, 1998), we predicted that cutaneous allodynia must be present in migraine patients during migraine attacks.

Concurring with this prediction, previous studies reported tenderness of scalp and pericranial muscles during an attack (Tfelt-Hansen *et al.*, 1981; Lous and Olesen, 1982; Drummond, 1987; Jensen *et al.*, 1988, 1993; Gobel *et al.*, 1992; Jensen, 1993). To investigate this phenomenon further, we used quantitative sensory testing (QST) techniques to compare cutaneous pain thresholds of patients during migraine with their pain thresholds in the absence of migraine (Burstein *et al.*, 2000). We found that in most cases (79%), patients experienced increased skin sensitivity within the referred pain area on the ipsilateral head; their pain thresholds to cold, heat or mechanical stimulation decreased significantly. Unexpectedly, increased skin sensitivity of many patients (67%) extended to the other side of the head and/or the forearms.

Because the detection of cutaneous allodynia is a time-consuming process that uses repeated QSTs of multiple modalities in multiple skin sites, it was done at only one time point (Burstein *et al.*, 2000). This time point, 4 h from onset of the attack, was chosen to allow sufficient time for the full development of the allodynia. While a 4-h time point allowed us to conclude that central sensitization contributes to migraine pain, it did not provide the information needed to identify the order of the involved neurons.

In the present study, we were able to document the spatial and temporal spread of allodynia and its expression (i.e. the order in which cold, heat and mechanical allodynia develops in each site at each time point) in a patient who was willing to delay treatment and endure the repeated tasks of QST during an acute migraine attack. We argue that in this patient, the incremental spread of the allodynia provides evidence of a sequential spread of central sensitization from first-order neurons that innervate the meninges to second-order neurons that receive convergent input from the meninges and facial

skin to third-order neurons that process sensory information from the head and forearms.

Material and methods

This study was carried out in accordance with the ethical standards of the Committee on Clinical Investigation on Human Experimentation at Beth Israel Deaconess Medical Center and with the Helsinki Declaration of 1975, as revised in 1983. The patient gave informed consent to participate in the study.

Experimental protocol

The patient was examined in the Pain Management Center at Beth Israel Deaconess Medical Center twice, once on June 3, 1998 during a 10-day migraine-free period, and a second time on December 4, 1998 while experiencing an untreated migraine headache. Each examination included relevant medical history, documentation of neurological symptoms and repeated QSTs that determine his pain thresholds to cold, warm and mechanical stimulation of the left forearm ventral skin, left periorbital skin, right periorbital skin and right forearm ventral skin. To document the development of cutaneous allodynia, pain thresholds of all modalities were measured on all four sites at 1, 2 and 4 h from the onset of the headache (i.e. the pain).

Cold, warm and mechanical stimulation

Heat and cold stimuli were delivered through a 30 × 30 mm² thermode (TSA 2001, Medoc, Ramat Yishi, Israel) attached to the skin at a constant pressure. Pain thresholds were determined using the Method of Limits (Fruhstorfer *et al.*, 1976; Yarnitsky *et al.*, 1995; Yarnitsky, 1997). To determine pain thresholds, the skin was allowed to adapt to a temperature of 32°C for 5 min and then cooled down or warmed up linearly at a slow rate (1°C/s) until pain sensation was perceived, at which moment the subject stopped the stimulus by pressing a button on a patient response unit. Cold and heat stimuli were repeated three times each and the mean of peak temperatures was considered threshold. Pain threshold to mechanical stimuli was determined by using a set of 20 calibrated von Frey hairs (VFH) (Stoelting, Wood Dale, Ill., USA). Each VFH monofilament was assigned a number in an ascending order (1, 0.0045 g; 2, 0.023 g; 3, 0.027 g; 4, 0.07 g; 5, 0.16 g; 6, 0.4 g; 7, 0.7 g; 8, 1.2 g; 9, 1.5 g; 10, 2.0 g; 11, 3.6 g; 12, 5.4 g; 13, 8.5 g; 14, 11.7 g; 15, 15.1 g; 16, 28.8 g; 17, 75 g; 18, 125 g; 19, 281 g). Because a linear relationship exists between the log force and the ranked number, mechanical pain thresholds are expressed as VFH numbers (rather than their forces). Each monofilament was applied to the skin three times (for 2 s each) and the smallest VFH number capable of inducing pain at two out of three trials was considered threshold. Skin

sensitivity was also determined by recording the patient's perception of soft skin brushing.

Data analysis and criteria for cutaneous allodynia

Changes in skin sensitivity were determined by comparing corresponding pain thresholds obtained in the absence of migraine (baseline) to pain thresholds obtained during migraine at each time point. In our recent study (Burstein *et al.*, 2000), we defined cutaneous allodynia as a change of 1 SD of the baseline threshold, per modality and site. The data were derived from 44 patients examined in the absence of migraine. On the head, these critical values were $>6.8^{\circ}\text{C}$ for cold pain, less than -3.8°C for heat pain and less than -2 VFH numbers for mechanical pain. On the forearms, these critical values were $>8.6^{\circ}\text{C}$ for cold pain, less than -3.5°C for heat pain and less than -2 VFH numbers for mechanical pain.

Results

The patient: demographic data and general features of the migraine

The patient is a 42-year-old, right-handed, married man with a family history of migraine. Since age 14 years, he has suffered 1–2 migraine attacks each month; but otherwise he is in good health, and is an enthusiastic practising physician. His attacks start at various times of the day and last for 12–24 h without treatment and 2–6 h when treated. During migraine, the pain involves temporal, nasal, orbital, periorbital, ear, teeth and scalp regions within the frontal half of the right side of the head in 60% and the left side of the head in 40% of the attacks, but never the two sides simultaneously. The pain increases gradually in intensity until it reaches a level >7 on a 0–10 scale, at which point it usually begins to throb and the patient is obviously miserable.

This patient has noticed that the attacks are more likely to occur if he skips meals, interrupts his sleep, eats cheese, is overtired or has just experienced tension. His migraine attacks begin with serrated lines of bright lights that appear on the visual field contralateral to the migraine pain, blurred and distorted images, and a gradual disappearance of the same visual field. Consequently, the patient experiences numbness and tingling that begin in the fingers and slowly extend up the arm and neck to the face and mouth, where they settle in the lips and half of the tongue contralateral to the migraine. Next, his movements become clumsy and uncoordinated, he encounters auditory (tinnitus), olfactory (bad smells) and gustatory (bitter taste) hallucinations, and finally he develops expressive (reduction in the ability to understand written and spoken speech symbols, and inability to think of the right word) and motor (difficulties in formulating sentences and speaking fluently) aphasia. Some of these symptoms often extend into the headache phase.

At 30–60 min following the commencement of the visual symptoms, his headache appears. It usually is accompanied by intolerance to light (photophobia), noise (phonophobia) and certain odorants (odour-phobia); bitter and unpleasant tastes; nausea and vomiting; diarrhoea and loss of appetite; fatigue and low energy; and a group of symptoms associated with autonomic functions. These symptoms include red eyes and tearing, rhinorrhoea, increased salivation, yawning, feeling cold and frequent sneezing.

In a fully developed headache, his pain is easily aggravated by routine physical activity such as coughing, bending over, walking and climbing stairs. The skin, nasal mucosa and cornea become hypersensitive and hyperaesthetic, and activities such as brushing his hair, shaving, breathing through the nose and wearing contact lenses or glasses become painfully intolerable. This increased sensitivity usually outlasts the pain by 24–48 h.

The development of cutaneous allodynia

The patient was first seen in our clinic during a 10-day migraine-free period. He was relaxed, comfortable, free of any pain and sophisticated in his communication. Pain thresholds to cold, heat and mechanical stimuli of the head and forearms were within the normal range; they revealed no signs of increased skin sensitivity or cutaneous allodynia. They are shown on the left column of each table in Fig. 1 (baseline).

Six months later, the patient was seen again, this time during a migraine attack. He arrived in the clinic 90 min after the beginning of visual disturbances (zigzag of lights and scotoma) and 60 min after the beginning of head pain. He was sensitive to light, noise and smell. He described himself as sleepy and anorexic. The pain intensity of his migraine was 5–6 on a visual analogue scale, and his discomfort was obvious. At that time, measurements of his pain thresholds (Fig. 1) revealed mild signs of cutaneous allodynia within the referred pain area on the ipsilateral head, but not in any other location. The cutaneous allodynia that developed at that time was expressed as changes in cold (pain threshold decreased by 58% of the eventual decrease) and mechanical (pain threshold decreased by 33% of the eventual decrease), but not heat pain thresholds (Fig. 2). The decrease in heat pain threshold on the ipsilateral forearm was considered insignificant because it did not meet the criteria for allodynia and was partially reversed later.

One hour later (2 h from the onset of head pain), the patient's sensitivity to light and noise had increased, and an almost non-stop yawning had developed. He became nauseous, chilled, less communicative and slightly irritable. The pain intensity of his migraine was 7/10 and his misery was apparent. He kept his eyes closed and avoided head movements. At that time, measurements of his pain thresholds (Fig. 1) revealed that as cutaneous allodynia developed further on the ipsilateral head, it appeared for the first time on the contralateral head and ipsilateral forearm (Fig. 2). On

Temporal and spatial development of cutaneous allodynia during migraine

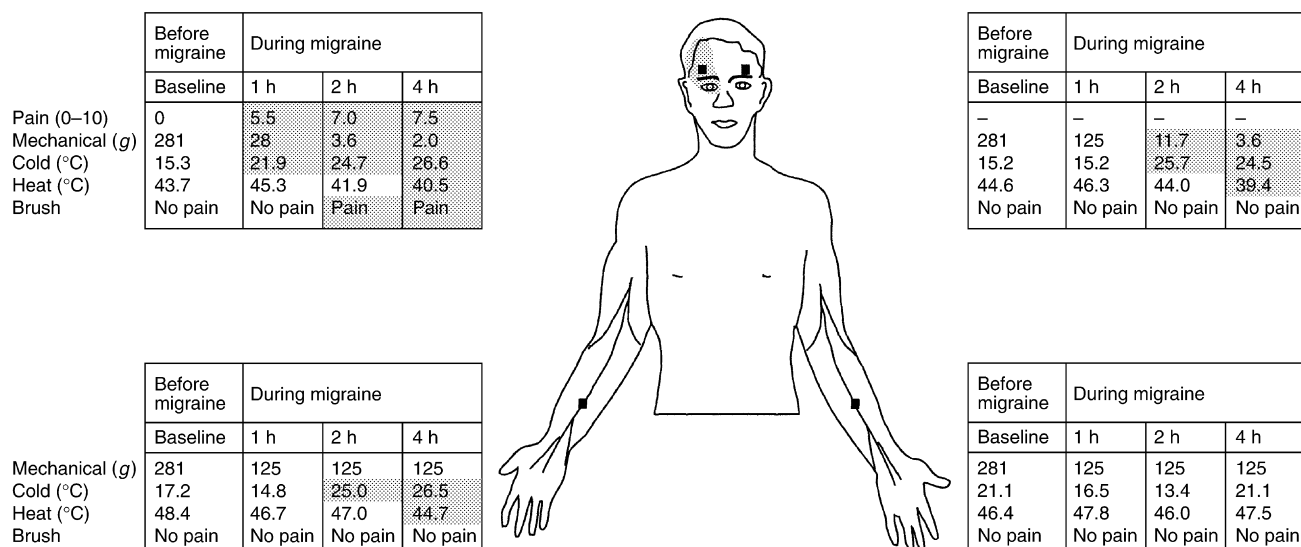


Fig. 1 Mechanical, cold and heat pain threshold changes in the ipsi- (patient's right side) and contralateral head and the two forearms during a single migraine attack. The referred pain area is marked on the face. In the absence of migraine, this patient was pain-free and his skin sensitivity was normal. One hour into the migraine, he developed cold and mechanical cutaneous allodynia on the ipsilateral head (indicated by shaded areas in the tables) but not in any other site. Two hours into the attack, the allodynia increased on the ipsilateral head and appeared on the contralateral head and ipsilateral forearm. At 4 h, heat allodynia was also detected while mechanical and cold allodynia continued to increase. Black squares indicate sites of sensory testing.

the ipsilateral head, cold and mechanical pain thresholds decreased by >80% and the heat pain threshold by 56%. The appearance of brush-induced pain at that time indicated the development of a dynamic component in the mechanical allodynia. The cutaneous allodynia that developed on the contralateral head was again expressed by changes in cold (pain threshold decreased by 100% of the eventual decrease) and mechanical (pain threshold decreased by 63% of the eventual decrease), but not heat pain thresholds (Fig. 2). On the ipsilateral forearm, cutaneous allodynia was expressed by changes in pain threshold to cold stimuli only (it decreased by 84% of the eventual decrease).

Two hours later (4 h from the onset of head pain), the patient's extremities were cold, he began to shiver and the nausea gave way to vomiting. His concentration diminished, he grew impatient and more irritable, and his suffering became evident as the pain became intolerable (7–8/10). At that time, measurements of his pain thresholds (Figs 1 and 2) revealed even further decreases on both sides of the head and the ipsilateral forearm. Only at 4 h from the onset of the attack did heat allodynia eventually develop at the three allodynic sites. Noticeably, no cutaneous allodynia of any kind developed on the contralateral forearm even at that time point.

Discussion

This report describes the gradual development of cutaneous allodynia during a migraine attack in a reliable patient who was willing to endure the pain and remain untreated for the duration of the study. It shows that intracranial

hypersensitivity (when the pain is aggravated by head movements and starts to throb) develops shortly (within 20 min) after the onset of pain, and that cutaneous allodynia starts to develop later, 60 min after the pain onset. This cutaneous allodynia develops gradually along spatial and temporal domains and across the different modalities. Spatially, it affects the referred pain area on the ipsilateral head before it affects the contralateral head and ipsilateral forearm. Temporally, it starts mildly and in the following 3 h it becomes more severe as pain thresholds continue to decrease. For this patient, we interpret these findings as follows.

(i) Sensitization of peripheral nociceptors that innervate intracranial blood vessels and the meninges (Strassman *et al.*, 1996) may explain how mild mechanical stimuli such as small increases in intracranial pressure during coughing or bending over could aggravate the pain. Current understanding of various pain models suggests that the initial activation of peripheral nociceptors following tissue damage, if not stopped within minutes, could increase the excitability of these nociceptors for hours and even days (Meyer and Campbell, 1981; LaMotte *et al.*, 1982). The expression of this excitability is usually an increase in the ongoing firing rate and a decrease in the minimal stimulus intensity required to activate them (Bessou and Perl, 1969; Beitel and Dubner, 1976). The clinical correlation of this sensitization is spontaneous pain (resulting from the ongoing activity) and induction of pain by usually non-noxious stimuli (resulting from the threshold decrease).

(ii) Sensitization of second-order nucleus caudalis neurons that receive convergent input from cerebral blood vessels

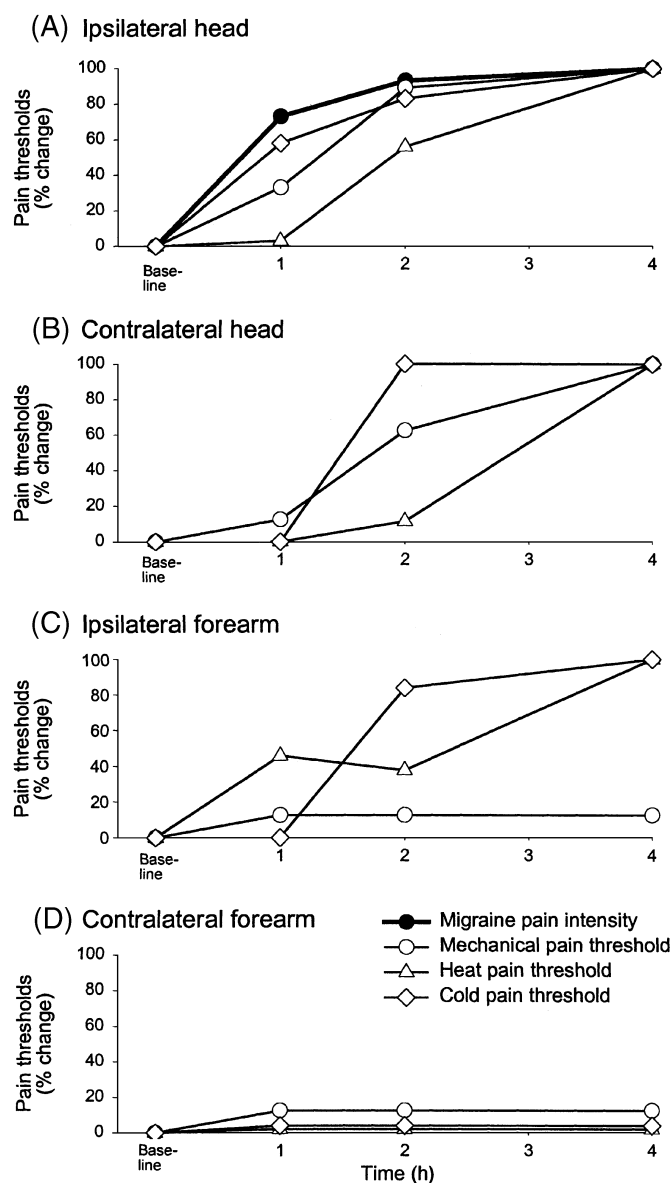


Fig. 2 Site-specific development profile of pain (bold line in A) and the three modalities of cutaneous allodynia (A–D). The values of pain intensity and pain thresholds at each time point and each site are presented as a percentage of the respective maximal change. Note that the allodynia is not fully developed in the first 2 h of the attack.

and the meninges, intracranially, and from the ophthalmic skin, extracranially, can explain how pain signals that arise from meningeal nociceptors during a migraine attack can induce cutaneous allodynia within the referred pain area in the periorbital region. This interpretation is based on the parallel time table for the development of mechanical, cold and heat allodynia in this human psychophysical study (Fig. 3A) and central sensitization of a nucleus caudalis dura-sensitive lamina V neuron (Fig. 3B) in animal electrophysiological studies (Burstein *et al.*, 1998; Yamamura *et al.*, 1999). Current understanding of central sensitization suggests that when hyperexcitable peripheral nociceptors are

spontaneously active, even in the absence of peripheral stimuli, the impulses they generate propagate centrally and reach second-order nociceptive neurons in the dorsal horn. The unusual bombardment of second-order neurons by impulses that come from peripheral nociceptors can induce long-lasting hyperexcitability in these second-order neurons, and as a result they also become spontaneously active and begin to respond to mild stimuli that normally do not activate them (Woolf, 1983; Cook *et al.*, 1986; Simone *et al.*, 1991; Torebjork *et al.*, 1992; McMahon *et al.*, 1993; Ren and Dubner, 1993; Woolf and Doubell, 1994; Koltzenburg *et al.*, 1995; Woolf *et al.*, 1995; Magerl *et al.*, 1998). The clinical manifestation of this sensitization is also spontaneous pain and induction of pain by usually non-noxious stimuli (Dubner, 1991). However, because second-order neurons receive direct input from peripheral nerves that supply different cutaneous and visceral structures, their sensitization by peripheral nociceptors that innervate one organ can change the way in which they process sensory signals that arise in another organ.

(iii) Sensitization of third-order trigeminovascular neurons that receive convergent input from second-order dorsal horn neurons located in nucleus caudalis (i.e. process sensory information from the head) and in the cervical enlargement (i.e. process sensory information from the upper limbs) can explain how pain signals that arise from meningeal nociceptors during a migraine attack can induce cutaneous allodynia outside the referred pain area. This hypothesis is based on the finding that cutaneous allodynia was first detected in the ipsilateral head at the 1-h test and in the contralateral head and ipsilateral forearm at the 2-h test. Neuronal recording in animals provided two lines of evidence to support this hypothesis. The first shows that receptive fields of second-order neurons in nucleus caudalis that receive intracranial input do not extend beyond the innervation territory of the trigeminal nerve (Davis and Dostrovsky, 1988; Dostrovsky *et al.*, 1991; Strassman *et al.*, 1994; Ebersberger *et al.*, 1997; Burstein *et al.*, 1998; Yamamura *et al.*, 1999), and the second shows that third-order neurons require more time than second-order neurons to become sensitized (Guilbaud *et al.*, 1986).

As in any other case report, caution must be exercised in reaching conclusions based on a single case. Nevertheless, the sequence in which peripheral and central components of the trigeminovascular pain pathway sensitized in this case report correlates with the common clinical experience that migraineurs are most responsive to anti-migraine medications when treated in the initial 30–60 min of the attack. Currently, drugs such as 5-HT_{1B/1D} agonists, NSAIDs (non-steroidal anti-inflammatory drugs) and anti-histaminergics are used most commonly to abort migraine attacks (Olesen *et al.*, 1993). Because these drugs target peripheral nociceptors and have no known direct effects on the activity of second- and third-order neurons, they are expected to be most effective prior to the development of central sensitization, within the first hour of the attack. Our belief that the initiation of central sensitization depends on the incoming impulses in

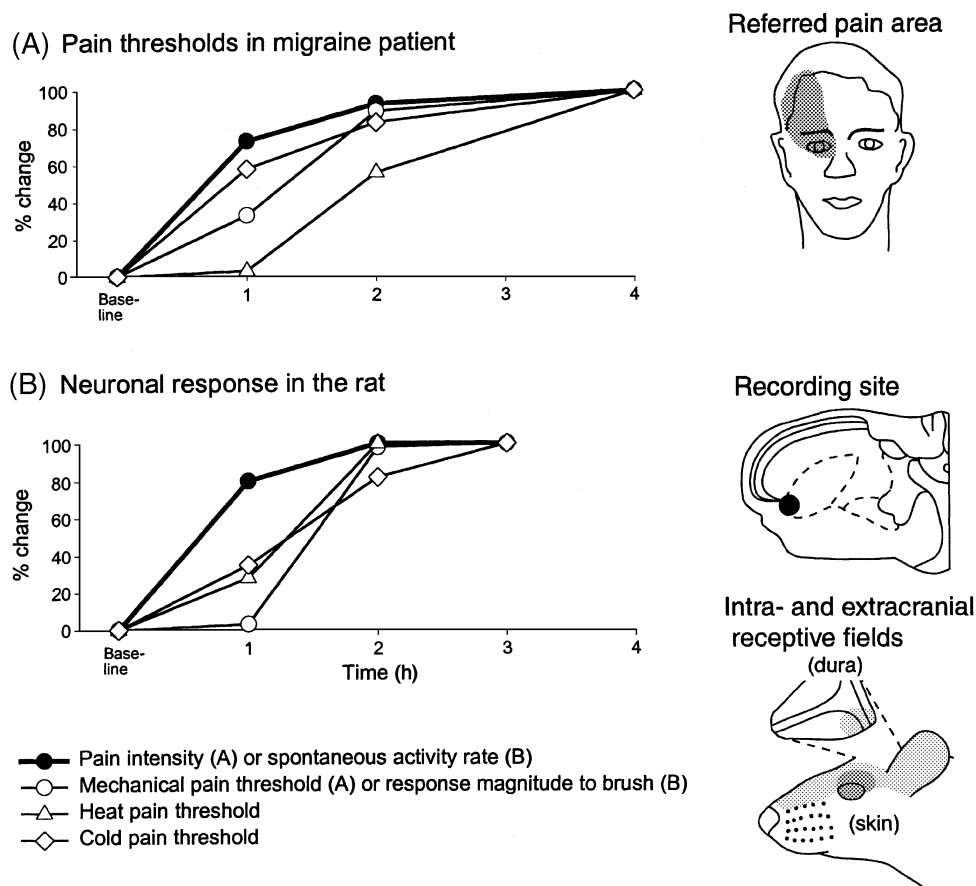


Fig. 3 The development of pain and allodynia during the patient migraine (A) parallels the development of central sensitization in the animal model (B) (adapted from Burstein *et al.*, 1998). The line drawings in A illustrate spontaneous pain and pain threshold changes in response to mechanical, cold and heat stimulation of the human periorbital skin ipsilateral to the migraine. The line drawings in B illustrate changes in the response properties of a wide dynamic range neuron in lamina V of the spinal trigeminal nucleus that receives convergent input from the dura and the skin. The neuron sensitized following a brief chemical stimulation of its dural receptive field. First, it developed spontaneous activity and then it began to respond to mechanical, cold and heat skin stimulation that prior to the sensitization induced minimal or no responses.

the peripheral nociceptors and that the maintenance of central sensitization is independent justifies the common clinical wisdom of recommending that patients use these medications immediately at the onset of the migraine attack.

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