# PERIPHERAL AND CENTRAL SENSITIZATION DURING MIGRAINE

*Amy Malick*, Rami Burstein*,***

* Department of Neurobiology and the Program in Neuroscience, Harvard Medical School, ** Department of Anesthesia and Critical Care, Beth Israel Deaconess Medical Center, Boston, MA, USA

Reprint requests to: Amy Malick, Department of Neurobiology, Harvard Institutes of Medicine, Room 830, 77, Avenue Louis Pasteur, Boston, MA 02115, USA.

Current theories propose that the pain of migraine is caused by chemical activation of meningeal perivascular fibers. In an animal model of migraine, we have recently shown that chemical activation of meningeal primary afferent nociceptors that innervate the dura could lead to the following: a) peripheral sensitization of these nociceptors to intracranial mechanical stimulation; b) central sensitization of second-order trigeminovascular neurons that receive convergent input from the dura and skin to extracranial mechanical and thermal stimulation; and c) facilitated cardiovascular pressor responses that are usually indicative of pain. These findings provide the first set of evidence for the induction of peripheral and central sensitization along trigeminovascular pain pathways by visceral input from the intracranial dura. We propose that the throbbing pain of migraine is mediated mainly through peripheral and to a lesser extent through central sensitization, and that the development of scalp tenderness is mediated mainly through central sensitization.

KEY WORDS: Allodynia, headache, hyperalgesia, pain, trigeminal.

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## INTRODUCTION

Current theories on the pathophysiology of migraine propose that the activation of meningeal perivascular sensory afferents is initiated by a chemical signal. According to these theories, ions, protons and inflammatory agents that activate and sensitize peripheral nociceptors (1-4) are released in the vicinity of sensory fibers innervating the dura following an episode of cortical spreading depression (5) or neurogenic inflammation (6,7). Although the cause of the initial release of these chemicals is unknown, a concept has recently been developed which suggests that temporary exposure of perivascular fibers to chemical agents may alter their sensitivity to mechanical stimuli. Theoretically, it is possible that chemically mediated sensitization of dura-sensitive peripheral nociceptors can explain the hypersensitivity of migraineurs to changes in intracranial pressure (e.g., during coughing) and the throbbing nature of their pain.

One characteristic of peripheral sensitization is the development of spontaneous activity manifested by the anomalous bombardment of

second order neurons with impulses originating from peripheral nociceptors. Dorsal horn neurons that receive an increased number of signals from the periphery often become hyperexcitable and begin to respond to mild stimuli that do not normally activate them (8-17). Because second-order nociceptive neurons receive convergent input from cerebral blood vessels, meninges, and from facial skin (18), painful signals that arise intracranially during a migraine attack can theoretically induce changes in extracranial sensation. Such changes in extracranial sensation were described for the first time by Edward Liveing in 1873 (19). Further documentation has been provided by a number of clinical studies on scalp tenderness during migraine (20-26).

In a recent series of experiments, we have documented the development of sensitization in the rat trigeminovascular pain pathway following the induction of intracranial pain (27-29). The present paper will summarize these studies.

## METHODS

The methods used in these studies have been previously described in detail (27-29). Briefly, single-unit extracellular recordings were made in the trigeminal ganglion from peripheral nociceptors that innervate the dura overlying the transverse sinus (27), and in the medullary dorsal horn from central trigeminal neurons that receive convergent input from the dura and skin (Fig. 1), (28, 29). Neuronal and cardiovascular (through an intra-arterial line) responses to quantitative mechanical and thermal stimulation were monitored continuously before, during and after the topical application of potentially sensitizing chemicals to the dura. These chemicals included a combination "soup" of histamine, serotonin, bradykinin - $10^{-3}$M, and prostaglandin E2 - $10^{-4}$M, at pH 5.0 (adapted from Steen et al.; 1-4).

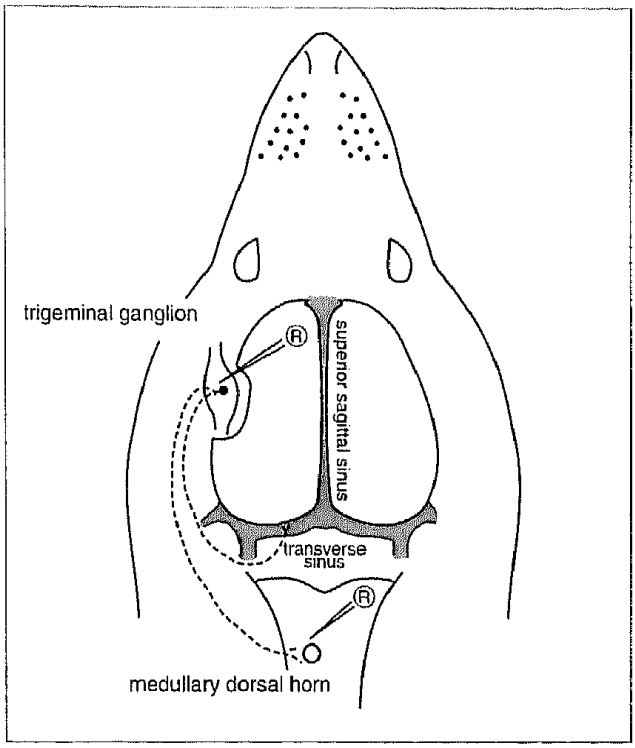


Fig. 1 - Experimental setup.

## RESULTS

### *Peripheral sensitization*

The goal of this study was to test the hypothesis that inflammatory agents such as histamine, bradykinin and prostaglandins can activate and sensitize trigeminal primary afferent neurons that innervate the dura (27). Fifteen mechanosensitive meningeal primary afferent neurons in the trigeminal ganglion were studied (Fig. 2). They were identified by their responses to electrical and mechanical (Fig. 2A) stimulation of the dura overlying the ipsilateral transverse sinus. In each case, neuronal responses to mechanical indentation of the dura (with calibrated von Frey monofilaments) were recorded before and after the application of inflammatory agents (histamine, serotonin, bradykinin, and prostaglandin E2, pH 5.0) to the dural receptive field (Fig. 2B). Prior to chemical irritation of the dura, mechanical thresholds were 0.86±0.98 g (mean ± s.d.). Five

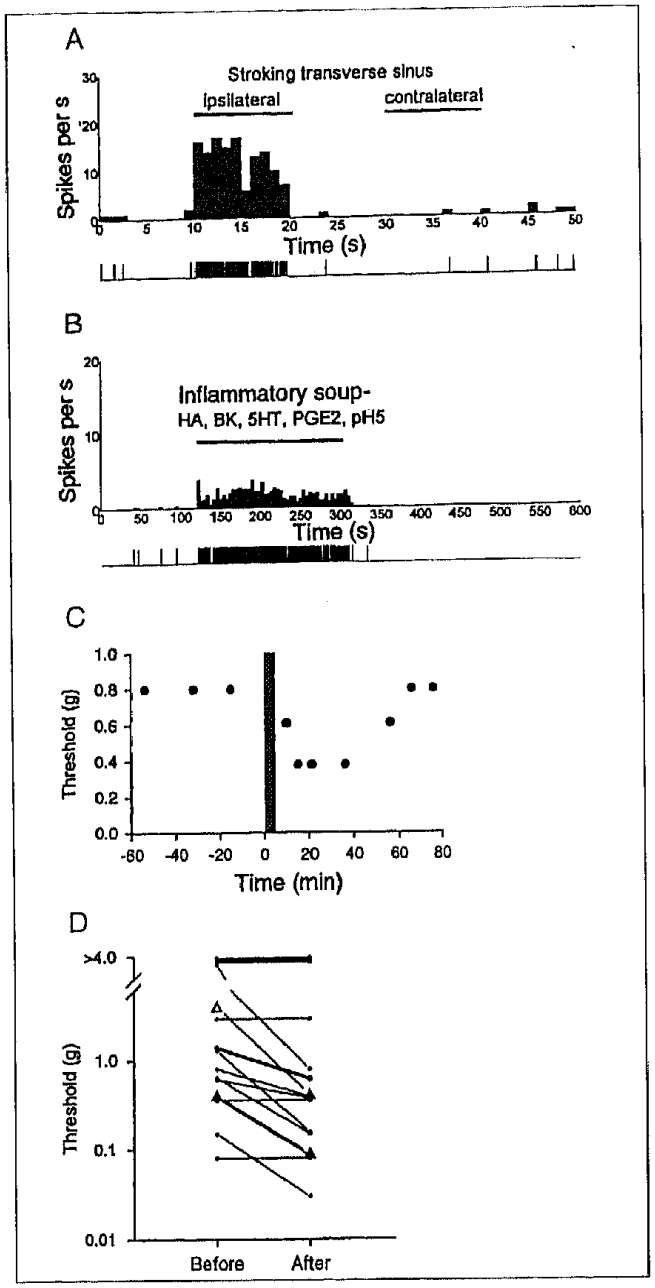


Fig. 2 - The development of peripheral sensitization following chemical irritation of the dura. A. Peristimulus time histogram showing the response of a mechanosensitive meningeal primary afferent neuron to mechanical stroking of the ipsilateral but not contralateral transverse sinus. B. Peristimulus time histogram showing the response of a mechanosensitive meningeal primary afferent neuron to topical application of inflammatory mediators (serotonin, bradykinin, prostaglandin E2, all 10uM, and histamine, 100uM, pH 5.0) to the dura overlying the ipsilateral transverse sinus. C. Time course of the development of mechanical sensitization. In this case, the smallest force required to activate the meningeal primary afferent neuron by dural indentation with von Frey monofilaments was 0.8 g prior to the chemical stimulation (black rectangle) of the dura, and 0.4 g after chemical stimulation. D. Individually plotted response thresholds of 17 neurons both before and after the application of inflammatory or acidic chemicals. (Adapted with permission from ref. 27).

minutes after chemical irritation, 66% of the neurons became hypersensitive and started to respond to dural indentation with mechanical forces that produced minimal or no responses prior to the chemical stimulation (Fig. 2C). Neuronal responses typically showed maximal levels of hypersensitivity at 20 min, and returned to baseline approximately 90 min after the chemical stimulation. Such sensitization to mechanical stimuli was observed both in neurons that discharged in direct response to the sensitizing agent (no. = 6) as well as in neurons that did not (no. = 5).

*Central sensitization*

The goal of this study was to test the hypothesis that chemical activation and sensitization of meningeal sensory neurons can lead to activation and sensitization of central trigeminal neurons that receive convergent input from the dura and skin (28). This hypothesis was investigated by recording changes in the responsiveness of 23 dura-sensitive nucleus caudalis (Vc) neurons to mechanical stimulation of their dural receptive fields and to mechanical and thermal stimulation of their cutaneous receptive fields following local application of inflammatory mediators or acidic agents to the dura. These 23 dura-sensitive neurons responded primarily to nociceptive stimuli (70% were classified as wide dynamic range and 22% as high threshold), and were found to project to a number of hypothalamic, thalamic, and brainstem nuclei). Figure 3 (see over) provides an example of the changes that occurred in an individual neuron. Following chemical stimulation of the dura: a) ninety-five percent of the neurons showed significant increases in sensitivity to mechanical indentation of the dura: their thresholds to dural indentation decreased from 1.57 to 0.49g (means, $p<0.0001$), and their response magnitudes to identical stimuli increased 2-4 fold; b) eighty percent of the neurons showed significant increases in cutaneous mechanosensitivity: their responses to brush and

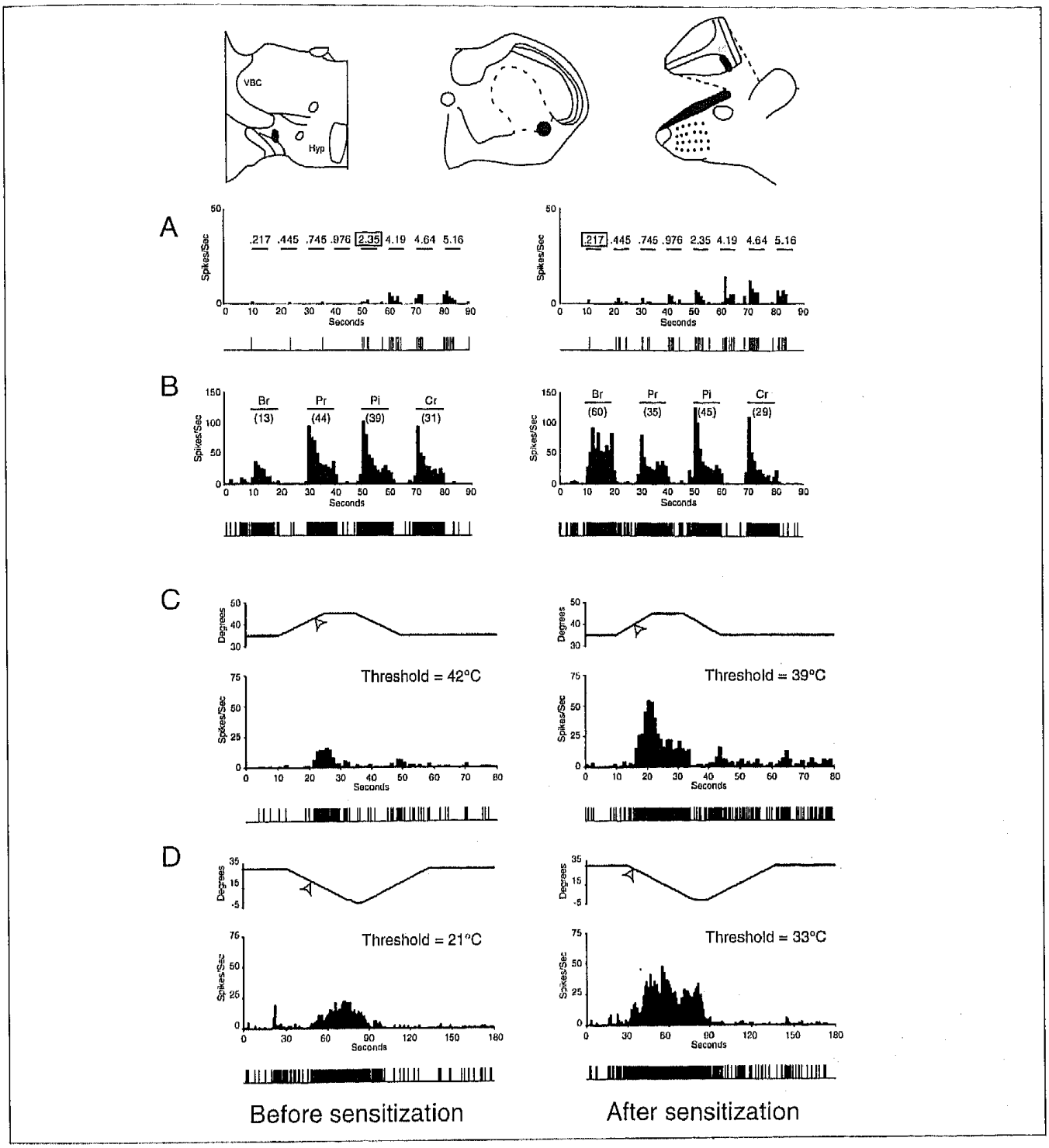


Fig. 3 - The development of intracranial and extracranial hypersensitivity following chemical irritation of the dura. Comparisons of physiological responses of a dura-sensitive neuron in lamina V of Vc that projects to the hypothalamus (top row). The responses of the neuron to a graded increase in the intensity of mechanical indentation of the dura (A), mechanical stimulation of the skin (B), and slowly heating (C) and cooling (D) the skin are shown before (left column) and after (right column) the irritation of the dura with the low pH buffer. Black area in the hypothalamus depicts low-threshold point for antidromic activation, black dot in the brainstem depicts recording site, black areas on the skin and dura depict sizes and locations of receptive fields prior to the chemical irritation of the dura, and gray area on the dura depicts the expanded receptive field following the chemical irritation. Numbers above lines in A indicate forces of von Frey hairs, boxes in A depict the mechanical threshold, and numbers under lines in B indicate mean number of spikes per second in response to each stimulus. Arrowheads in C and D show the temperature at which a response occurred. Note the drop in the mechanical threshold of the dural receptive field, the exaggerated response to brushing the skin, and the drop in the thresholds for heating and cooling the skin. VBC = ventrobasal complex; Hyp = hypothalamus; Br = brush; Pr = pressure; Pi = pinch; Cr = crush. (Adapted with permission from ref. 28).

pressure increased 2.5-fold ($p<0.05$) and 1.6-fold ($p<0.05$), respectively; c) seventy-five percent of the neurons showed a significant increase in cutaneous thermosensitivity: their thresholds to slow heating of the skin changed from 43.7±0.7 to 40.3±0.7°C (mean ± s.d., $p<0.005$), and to slow cooling from 23.7±3.3 to 29.2±1.8°C ($p<0.05$); d) dural receptive fields expanded within 30 min and cutaneous receptive fields within 2-4 hours; and e) ongoing activity developed in wide-dynamic range and high-threshold, but not in low-threshold neurons. These changes represent a state of hyperexcitability in these second-order central trigeminal neurons.

*Cardiovascular correlation*

The goal of this study was to determine whether non-painful stimuli such as mild dural indentation or skin brush are perceived as painful when trigeminal brainstem dura-sensitive neurons become sensitized (29). To address this issue, we correlated sensory stimuli with the cardiovascular and neuronal responses they induce. The rationale for measuring cardiovascular changes such as the pressor response is based on the concept that such responses are correlated with visceral and cutaneous stimuli which cause tissue damage and pain (Woodworth and Sherrington 1904).

In 24 experiments, neuronal and cardiovascular responses to mechanical and chemical stimulation of the dura (Fig. 4A), and to mechanical (Fig. 4B) and thermal (Fig.4C) stimulation of the skin were recorded simultaneously (see over). Prior to chemical stimulation, mechanical indentation of the dura with von Frey monofilaments induced neuronal and blood pressure (BP) responses when the applied forces were 2.35 g (median). Twenty minutes following chemical stimulation with inflammatory soup (IS), a significant increase in the mechanical sensitivity of the dural receptive field was manifested as a drop in the minimum force (threshold) required to activate neuronal (2.35 to 0.445 g) and BP (2.35 to 0.976 g) responses (median ± s.d., unpaired Wilcoxon signed rank test, $p<0.0001$). This intracranial hypersensitivity lasted for at least 1-7 hours.

Sixty minutes after chemical stimulation of the dura with the IS, a significant increase in the mechanical sensitivity of the skin was manifested as increased neuronal and BP response magnitudes to brush and pressure ($p<0.05$). Neuronal responses to brush and pressure increased 2-fold and 1.6-fold, respectively, while BP responses to brush and pressure increased 3-fold and 1.5-fold, respectively.

Prior to chemical stimulation, slow increases in skin temperature (1°C/sec) induced neuronal responses at 44.8±0.7°C (mean + s.e.) and BP responses about 2 sec later, at 46.5±0.7°C. The magnitude of these responses was 30.0±6.4 spikes/sec for neuronal activation and 12.1±1.4 mmHg for BP changes. Sixty minutes following chemical stimulation of the dura with IS, increased skin sensitivity to heat was apparent as the lowest temperature capable of initiating neuronal and BP responses dropped significantly by 3.7 and 3.4°C (means, $p<0.0005$), respectively.

These findings demonstrate a close spatial and temporal correlation between the enhanced neuronal and cardiovascular responses.

## DISCUSSION

Based on the three studies presented above, we propose the following:

a) When inflammatory chemicals such as histamine, serotonin, bradykinin and prostaglandin E2 activate meningeal nociceptors for several minutes, the excitability of these nociceptors can increase for hours and even days; resulting in an increase in the ongoing firing rate and a decrease in the minimal stimulus intensity required to activate them.

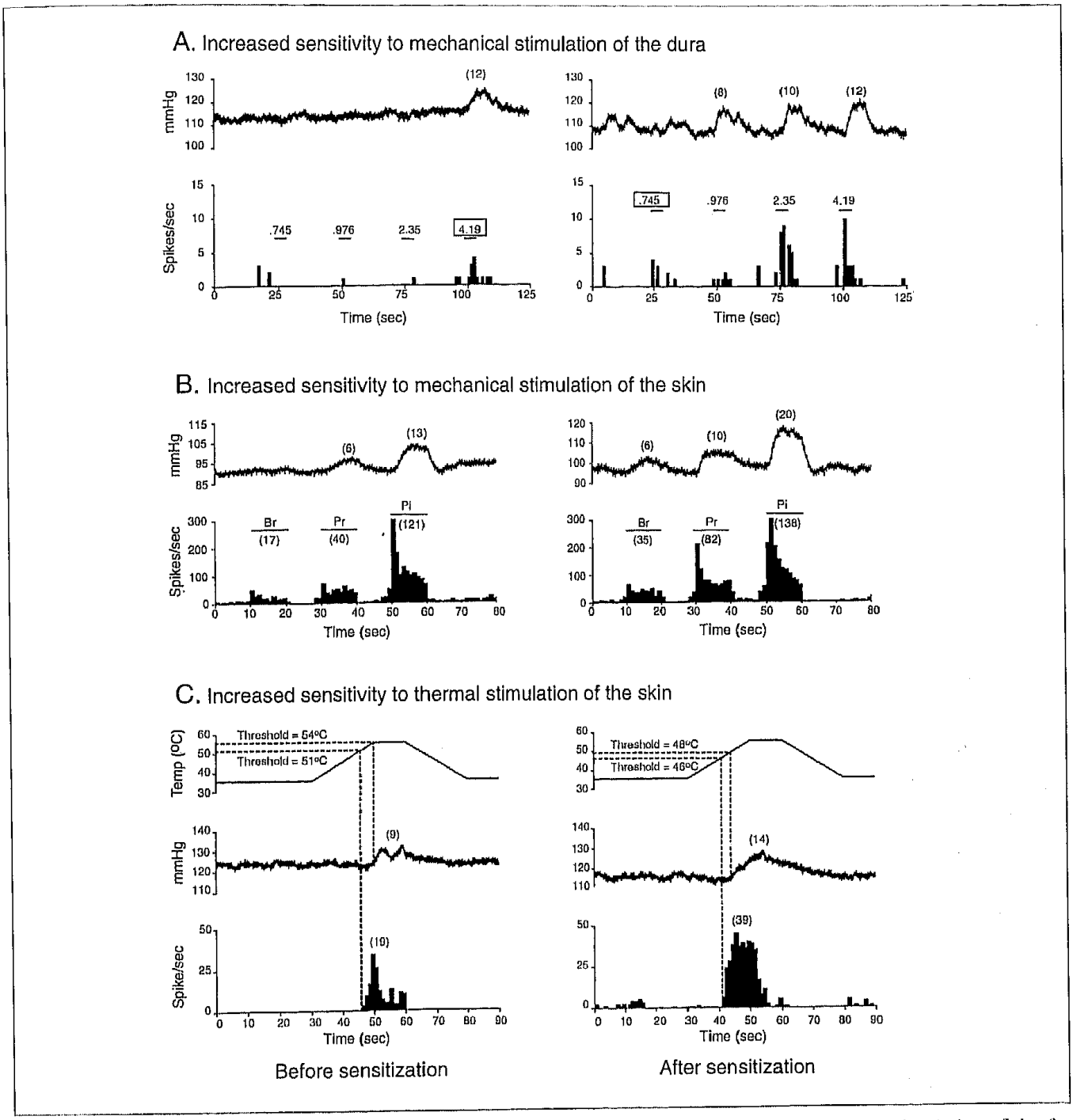


Fig. 4 - Increased sensitivity to mechanical stimulation of the dura, and to mechanical and thermal stimulation of the facial skin following chemical stimulation of the dura. A. Example of the changes in the minimum force required to induce blood pressure and neuronal responses before and after the chemical stimulation of the dura. Note that before chemical stimulation of the dura, neuronal and blood pressure responses were induced only by indenting the dura with a force >4g and that 20 min after chemical stimulation, similar neuronal and blood pressure responses were induced by smaller (<1g) forces as well. B. Example of simultaneous recording of neuronal and blood pressure responses to mechanical skin stimulation showing that prior to chemical stimulation of the dura only pinch and pressure induced neuronal and blood pressure responses and that 60 min after the chemical stimulation similar responses were induced by brushing the skin. C. Example of simultaneous recording of neuronal and blood pressure responses to thermal skin stimulation showing that prior to chemical stimulation of the dura neuronal and blood pressure responses were induced at 51 and 54°C, and that afterwards they were induced at 46 and 48°C, respectively. In A, lines above histograms indicate stimulus duration and numbers above these lines depict the force used to indent the dura. Boxes depict the mechanical threshold for eliciting the neuronal response. Numbers in parentheses indicate the magnitude of blood pressure change. In B, lines above histograms indicate stimulus duration and numbers below these lines depict mean spikes/sec. In C, Dotted lines illustrate the initiation times (vertical) and the thresholds (horizontal) of the responses. (Adapted with permission from ref. 29).

b) 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 abnormal bombardment of second order neurons by impulses originating spontaneously from peripheral nociceptors can induce a long lasting hyperexcitability resulting in spontaneously active secondary neurons that respond to mild stimuli which normally cannot activate them.

c) When hyperexcitable second-order neurons that project to the hypothalamus, thalamus and multiple brainstem nuclei become spontaneously active, the impulses they generate reach sensory-discriminative, autonomic, and motivational nuclei that can mediate nociceptive responses in the animal, and altered pain perception, autonomic function and emotional state in humans during the migraine attack.

In the context of migraine, sensitization of peripheral nociceptors that innervate intracranial blood vessels and the meninges might explain how mild mechanical stimuli such as the small increase in intracranial pressure during coughing or bending over aggravates the head pain (7,30). Sensitization of second-order nociceptive neurons in the medullary dorsal horn that receive convergent viscero-somatic input from both intra- and extracranial structures might explain how painful signals that arise from meningeal nociceptors during a migraine attack can induce changes in skin sensitivity during migraine: their sensitization by meningeal primary nociceptors can change the way they process sensory signals arriving from the skin. Such changes in extracranial sensation during migraine have been described by Edward Liveing in 1873, by a number of clinical studies on scalp tenderness (20-26), and most recently by our description of mechanical and thermal cutaneous allodynia (submitted manuscript).

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