Research Submissions

2003 Wolff Award: Possible Parasympathetic Contributions to Peripheral and Central Sensitization During Migraine

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Background.—Neurologic signs of increased parasympathetic outflow to the head often accompany migraine attacks. Because increased parasympathetic outflow to the cranial cavity induces vasodilation of cerebral and meningeal blood vessels, it can enhance plasma protein extravasation and the release of proinflammatory mediators that activate perivascular nociceptors. We recently showed that activation of intracranial perivascular nociceptors induces peripheral and central sensitization along the trigeminovascular pathway and proposed that these sensitizations mediate the intracranial hypersensitivity and the cutaneous allodynia of migraine.

Methods.—The present study investigates possible parasympathetic contributions to the generation of peripheral and central sensitization during migraine by applying intranasal lidocaine to reduce cranial parasympathetic outflow through the sphenopalatine ganglion.

Results.—In the absence of migraine, patients were pain-free, and their skin sensitivity was normal. Their mean baseline pain thresholds were less than 15°C for cold, more than 45°C for heat, and more than 100 g for mechanical pressure. Their mean pain score was 7.5 of 10 (standard deviation, 1.4) during untreated migraine and 3.5 of 10 (standard deviation, 2.4) after the nasal lidocaine-induced sphenopalatine ganglion block ($P < .0001$). Most patients developed cutaneous allodynia during migraine, and their mean pain thresholds changed to more than 25°C for cold, less than 40°C for heat, and less than 10 g for mechanical pressure. Following the nasal lidocaine administration (sphenopalatine ganglion block), this allodynia remained unchanged in spite of the pain relief.

Conclusion.—These findings suggest that cranial parasympathetic outflow contributes to migraine pain by activating or sensitizing (or both) intracranial nociceptors, and that these events induce parasympathetically independent allodynia by sensitizing the central nociceptive neurons in the spinal trigeminal nucleus.

Key words: migraine, allodynia, pain, headache, sphenopalatine ganglion, nociceptors, trigeminal

Abbreviations: SPG sphenopalatine ganglion, QST quantitative sensory testing, VFHs von Frey hairs

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Migraine attacks are often accompanied by increased parasympathetic activity signs such as conjunctival injection, lacrimation, nasal congestion, rhinorrhea, salivation, diarrhea, and frequent urination.[1] These signs encouraged clinicians to treat migraine attacks by reducing the parasympathetic outflow to the cranial cavity by blocking the sphenopalatine ganglion (SPG) through the nose. Historically, this is a time-honored procedure dating back to 1908, when Sluder first described it as an effective way of treating nonspecific head pains.[2] Prior to the introduction of synthetic local anesthetics, the SPG was blocked by local application of cocaine to the nose.[3] In the last 2 decades, intranasal applications of lidocaine and other synthetic local anesthetics (which presume to block the SPG) were found effective in treating vascular headaches such as cluster headache and migraine.[4-10] Although the mechanism by which

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intranasal lidocaine alleviates the pain is not fully understood, it is believed to reverse the parasympathetic contribution to intracranial vasodilation by blocking the SPG.[11] Current theories propose that the result of vasodilation of cranial blood vessels is a plasma extravasation and the consequent release of inflammatory mediators that activate perivascular nociceptors and generate the head pain.[12,13]

We showed recently that activation of these nociceptors could lead to their sensitization and that this sensitization could explain the intracranial hypersensitivity (ie, the throbbing of pain and its aggravation during routine physical activities) during migraine.[14,15] Another consequence of the sensitization of intracranial nociceptors is sensitization of second-order "central" trigeminal neurons in the spinal trigeminal nucleus.[16] Because these central neurons process sensory information from both the periorbital skin and intracranial vasculature, their sensitization could explain the scalp tenderness that so often accompanies migraine attacks.[14,17-22] Detailed investigation of this phenomenon showed that during migraine nearly 80% of the patients develop mechanical and thermal cutaneous allodynia within the referred pain area on the ipsilateral head.[23] In most of these patients, the allodynia extended even beyond the referred pain area to include the contralateral head and the upper limbs.

In the present study, we investigated the possible parasympathetic contributions to the generation of peripheral and central sensitization during migraine by determining changes in pain thresholds measured in the absence of migraine and during a migraine attack, prior to and shortly after the application of lidocaine into the nose (which presumably blocks the SPG).

METHODS

Selection of Patients.—Patients were recruited randomly from the clinical caseload of the pain management center and the neurology services at Beth Israel Deaconess Medical Center and Massachusetts General Hospital, Boston. Women and men who were 18 to 70 years old, met the criteria of the International Headache Society Classification Committee for migraine with or without aura,[24] had 1 to 6 migraine attacks each month in the last 3 years, were able to communicate clearly in English, and were able to give an informed consent were included in this study. Exclusion criteria included peripheral nervous system injuries resulting in chronic pain and the use of opiates or other analgesic drugs for reasons other than migraine. 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.

Experimental Protocol.—Thirty patients were initially scheduled for a 2-hour session to classify their migraine type and to document the symptoms that usually accompany their migraine. This was done when they were migraine-free and at least 7 days had elapsed since their last migraine attack. A thorough medical history was taken from each patient, with questions on all details pertaining to migraine. Subsequently, while resting in a quiet room, quantitative sensory testing (QST) was performed to determine pain thresholds to cold, warm, and mechanical stimuli. Thresholds were measured in the following locations at a randomized order: left periorbital skin, right periorbital skin, left forearm-ventral skin, and right forearm-ventral skin. Patients were instructed to return to the pain clinic during a moderate-to-severe (pain intensity 7 or greater on a 0 to 10 scale) migraine attack (3 to 4 hours from its onset) in which they had not taken any antimigraine or analgesic medications. History relevant to the attack was taken, the pain intensity was rated, and QST was repeated. Changes in skin sensitivity were determined by comparing pain thresholds obtained in the absence of migraine (baseline) to pain thresholds obtained during migraine at each skin location. Subsequently, lidocaine was applied intranasally to block the SPG, pain scores were recorded every 5 minutes, and QST was repeated at 30 to 60 minutes after the block. Quantitative sensory testing performed during migraine attacks (before and after treatment) were all done by examiners who were unaware of the results of the baseline (control) QST and the presence or absence of allodynia. By not sharing with patients the results of their QSTs (both in the absence of migraine and during migraine) it was also possible to keep them unapprised of the presence or absence of allodynia. Because of the severity with which migraine headache presents,

we found no satisfactory way to keep patients or examiners unaware of the presence of pain.

Intranasal Lidocaine Application (Sphenopalatine Ganglion Block).—Patients were positioned in a recumbent position with a pillow under the shoulders and the head hyperextended and slightly rotated to the side of the migraine. A Q-tip soaked with 2% viscous lidocaine was used to numb the nostril orifice and a 1- to 2-inch flexible intravenous catheter attached to a 10-mL syringe was inserted toward the nasopharynx through the middle turbinate. Two doses of 2% viscous lidocaine (2 mL each at 10-minute intervals) were administered while patients refrained from swallowing or from changing their head position for 5 to 10 minutes. For those patients who were unable to refrain from swallowing, the lidocaine was applied by inserting lidocaine-soaked Q-tips through the nose to the nasopharynx and leaving them in place for 5 to 10 minutes.

Because of an inability to record the activity of single neurons in the SPG of a patient awake, we have no direct evidence that the ganglion was indeed blocked by the nasal lidocaine procedure described above. Even so, multiple lines of indirect evidence strongly support our impression that the SPG was in fact blocked. For example, during migraine attacks 63% of the patients presented with ipsilateral lacrimation (tearing), 50% with ipsilateral nasal congestion, and 36% with rhinorrhea—symptoms that are usually attributed to increased parasympathetic tone during migraine (especially in the absence of other pathologies). The intranasal lidocaine application described above stopped the tearing, decongested the nose, and ended the rhinorrhea in almost all cases. (These data are not reported in the "Results" section because we had no reliable way to quantify them.) Since the SPG sends postsynaptic parasympathetic fibers to the lacrimal glands and to the blood vessels and glands of the mucous membranes of the nose,[25] it is reasonable to propose that it was blocked by the lidocaine.

Quantitative Sensory Testing.—Heat and cold pain thresholds were determined by using the Method of Limits.[23,26-28] Stimuli were delivered through a 30 × 30 mm^2 thermode (TSA 2001, Medoc) attached to the skin at a constant pressure. Adaptation temperature was 32°C. To determine pain thresholds, the skin was cooled down or warmed up linearly at a slow rate (1°C/second) until pain sensation was perceived, at which time the patient stopped the stimulus by pressing a button on a patient response unit. Cold and heat stimuli were repeated 3 times each, and the mean of peak temperatures was considered threshold. Pain thresholds to mechanical stimuli were determined by using a set of 20 calibrated von Frey hairs ([VFHs] Stoelting). 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 an approximate linear relationship exists between the log force and the ranked number, mechanical pain thresholds are expressed as VFH numbers (rather then their forces). Each monofilament was applied to the skin 3 times (for 2 seconds each), and the smallest VFH number capable of inducing pain in 2 of 3 trials was considered threshold. Skin sensitivity was also determined by recording patient's perception of soft skin brushing.

Cutaneous allodynia was determined using the values of the pain thresholds for heat, cold, and pressure measured as described above at the bilateral periorbital and forearm skin areas of patients, both in the absence of and during migraine attacks in the same patients.[23] If, during a migraine attack, the pain threshold of one or more modalities (heat, cold, pressure), measured on the ipsilateral head alone or on the ipsilateral head and one or more of the other 3 skin locations, was reduced by one or more standard deviations of the respective baseline control threshold (implying increased sensitivity to one or more modalities in the respective skin areas), the presence of cutaneous allodynia was inferred. All baseline control standard deviations were calculated as follows: (1) 3 repeated measurements of each modality in each site were taken from each patient in the absence of migraine and their values were averaged, (2) the average values from all patients were then pooled and their means and standard deviation calculated. Standard deviation values on the head were +6.8°C for cold pain, −3.8°C for heat pain, and −2 VFH numbers for mechanical pain. On the forearms, standard deviation values were +8.6°C

for cold pain, −3.5°C for heat pain, and −2 VFH numbers for mechanical pain.

Statistical Analysis.—The database consisted of pain threshold measurements in 30 patients, taken before and during migraine attacks. The resulting distributions were tested for normality, and their descriptive statistics computed. The differences between during and before attack (during-before) were computed on a pairwise basis, and the criteria for allodynia applied yielding 2 groups of patients with migraine: those without cutaneous allodynia (group A) and those with cutaneous allodynia (group B). To increase the sensitivity of detecting cutaneous allodynia, patients in this study were compared to themselves (before versus during untreated versus during treated migraine) rather than to control subjects because the large normative range of pain thresholds reduces the sensitivity of detecting allodynia in regard to the reference range.[28] Differences between during untreated migraine versus during treated migraine versus before migraine were computed on a multiple-sample pairwise basis. Differences in mean pain threshold between the respective skin sites were judged (significant or not significant) by using appropriate pairwise multiple-sample comparison (Newman-Keuls, Kruskal-Wallis) tests.

RESULTS

Demographic Data.—Thirty patients (25 women and 5 men) participated in this study. They were classified according to whether they developed cutaneous allodynia during migraine or not.[23] Those exhibiting no cutaneous allodynia during migraine (5 of 30 patients) were classified as group A, and those exhibiting cutaneous allodynia at least within the referred pain area on the ipsilateral head (25 of 30 patients) were classified as group B. Of the 25 patients in group B, 4 developed additional allodynia in one site outside the referred pain area, 6 in 2 additional sites, and 13 in all 4 tested sites. Patients in group A were younger (mean age, 35.2 years; range, 26 to 40 years) than the patients in group B (mean age, 41.2 years; range, 28 to 67 years), but the differences did not reach statistical significance ($P = .19$) with this sample size. They also experienced migraine fewer years. (The number of years each patient experienced migraine was calculated by subtracting age of onset from patient's age.) Patients in group A experienced migraine 13.6 years, and patients in group B experienced migraine 23.0 years. This difference, however, was also not significant with our sample size ($P = .1$). Of the 30 patients, 83% reported at least one of the following parasympathetic-related symptoms: lacrimation, nasal congestion, or rhinorrhea, and 17% reported none.

Effects of Intranasal Lidocaine (Sphenopalatine Ganglion Block) on Pain Intensity.—Patients were asked to score their pain intensity in the absence of migraine, while experiencing a 4-hour migraine, and every 5 minutes after the nasal lidocaine was administered to block the SPG. In those cases in which the nasal lidocaine application reduced the pain intensity, it reached maximal effect within 10 to 30 minutes. Patients in group A were generally less likely than patients in group B to experience significant pain relief by the nasal lidocaine. This tendency was also reflected in the magnitude of the pain relief; it was reduced by 24% when applied to the patients in group A (mean pain scores were 0 [standard error (SE), 0] in the absence of migraine, 7.8 [SE, 0.6] during migraine, and 5.9 [SE, 0.9] after the lidocaine application; $P < .05$) and by 53% when applied to the patients in group B (mean pain scores were 0 [SE, 0] in the absence of migraine, 7.4 [SE, 0.3] during migraine, and 3.5 [SE, 0.5] after the block; $P < .0001$).

Patients who presented with none of the parasympathetic-related symptoms (ie, lacrimation, nasal congestion, rhinorrhea) were less likely than those who presented with at least one of these symptoms to experience significant pain relief by the nasal lidocaine. The pain relief magnitude of the patients who were parasympathetic asymptomatic was reduced by only 15% (pain threshold score was 0 in the absence of migraine, 6.5 [SE, 0.4] during migraine, and 5.5 [SE, 0.7] after the lidocaine application; $P = .2$). In contrast, it was reduced by 53% when applied to the patients who were parasympathetic symptomatic (pain threshold score was 0 in the absence of migraine, 7.5 [SE, 0.3] during migraine, and 3.5 [SE, 0.5] after the lidocaine application; $P < .0001$).

Of the 30 patients, 15 experienced the pain only within the frontal region of the cranium and 15 experienced it both in the frontal and occipital regions. Within group A, nasal lidocaine reduced the pain

(ie, by more than 50%) in 8 patients. Within group B, nasal lidocaine was effective in reducing only the frontal pain in 7 patients and both the frontal and occipital pain in 1 patient. In 2 patients, the pain was relieved but we did not document changes in the frontal and occipital regions separately because we were unaware of the need to do so at the early stage of the study. Thus, in 7 (54%) of the 13 cases in which we documented the changes in pain intensity over both the frontal and occipital regions, the application of nasal lidocaine reduced the frontal pain selectively.

Effects of Intranasal Lidocaine (Sphenopalatine Ganglion Block) on Cutaneous Allodynia.—Cutaneous allodynia developed in 25 patients during their migraine attack. Of these, 23 patients were willing to repeat the QST after the intranasal lidocaine administration. A representative case of a patient experiencing cutaneous allodynia during a moderate (pain intensity, 7 of 10) migraine attack and the effects of nasal lidocaine are illustrated in Figure 1. This patient had normal pain thresholds in the absence of migraine. Five hours after the onset of a unilateral (right side) attack, when the pain intensity was 7 of 10, he developed cold and heat allodynia on both sides of the head and cold allodynia on the forearms (shaded numbers in B, Figure 1). Thirty minutes after the lidocaine administration, his pain intensity dropped by 57% (from 7 of 10 to 3 of 10) while the cutaneous allodynia continued to worsen. His pain thresholds revealed the presence of cold, heat, and mechanical allodynia at all tested sites.

The means (n = 23) of cold, heat, and mechanical pain thresholds that were measured in the absence of migraine (baseline), during untreated migraine, and after the nasal lidocaine (SPG block) at each of the 4 tested sites (ipsilateral head, contralateral head, ipsilateral forearm, contralateral forearm) are illustrated in Figure 2. In the absence of migraine, this patient population exhibited normal skin sensitivity to cold (pain threshold, less than 15°C), heat (pain threshold, more than 45°C), and mechanical (pain threshold, more than 17 VFH) stimulation. During migraine (mean pain score, 7.5), however, their cold pain thresholds changed by nearly 10°C (to about 25°C), heat pain thresholds by 6°C (to about 39°C), and mechanical pain thresholds by 5 VFH numbers (to about 12 VFH) as the skin became significantly more sensitive. Following the administration of nasal lidocaine to block the SPG, their altered pain thresholds remained unchanged in spite of the more than 50% pain relief they experienced. As indicated in the Table, both during migraine and post-SPG block, pain thresholds differed ($P < .01$) from baseline pain thresholds, but not from each other.

COMMENTS

We used nasal lidocaine application to block the SPG and to investigate the parasympathetic effects on pain intensity and cutaneous allodynia during migraine. We found that most patients who develop moderate to severe pain 4 to 8 hours after the onset of an attack also exhibit increased intracranial sensitivity and cutaneous allodynia on the head and forearms. The lidocaine-induced SPG blocks relieved the pain intensity (and the throbbing) by over 50%, but did not reduce the cutaneous allodynia. These findings suggest that increased parasympathetic tone contributes to the activation of perivascular nociceptors, that the activation of these nociceptors contributes significantly to the pain intensity and to the initiation of central sensitization, and that the maintenance of this central sensitization is for most part independent of the incoming impulses from the activated nociceptors.

Parasympathetic fibers that innervate cerebral and dural blood vessels originate in the sphenopalatine and otic ganglions and contain acetylcholine (Ach), vasoactive intestinal polypeptide (VIP), and nitric oxide (NO).[29-35] Because the same cerebral and dural blood vessels are also supplied by unmyelinated sensory fibers that contain substance P and calcitonin gene-related peptide (CGRP),[29,31,32,36] it has been proposed that the activation of parasympathetic fibers can alter the environment of the perivascular sensory pain fibers and by doing so, activate them.[37] Theoretically, sensory pain fibers can be activated directly or indirectly (or both) by the release of Ach, VIP, and NO in their vicinity. Regarding the direct route, it is known that Ach can activate unmyelinated C fibers and induce the release of CGRP and substance P,[38-42] an action thought to be mediated through muscarinic (M3) or nicotinic (or both) receptors located on this class of peripheral nociceptors.[40,41,43,44] As for the indirect route, several

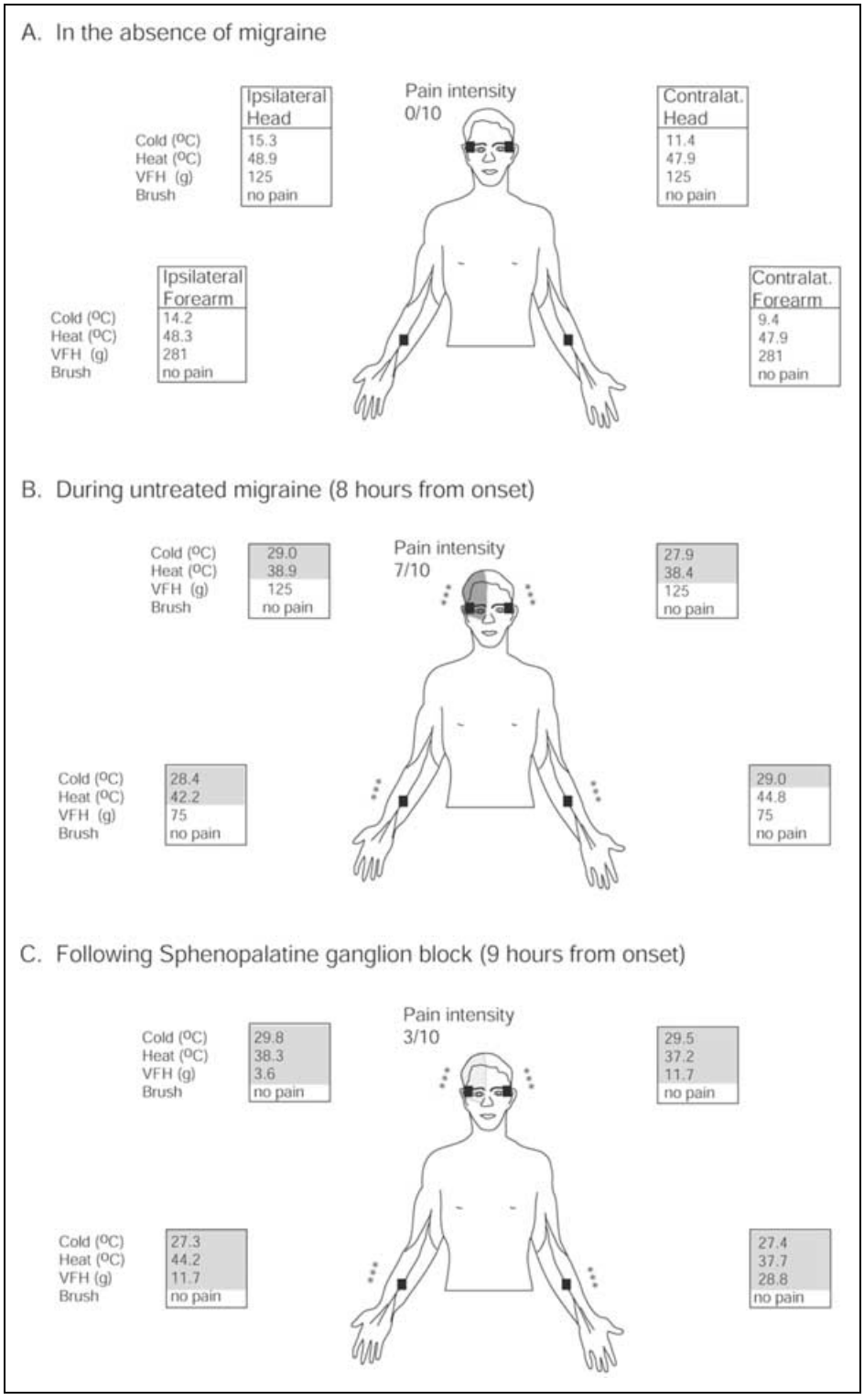

Fig 1.—Development of pain and cutaneous allodynia during migraine and their responses to sphenopalatine ganglion (SPG) block. Pain scores and pain thresholds to cold, heat, and mechanical (von Frey hair [VFH] pressure and skin brush) stimulation of the 4 skin sites at baseline (A), during migraine (B), and following SPG block (C) are shown in the tables. Dark and light gray regions of the face depict relative pain intensity and the referred pain area. Triple asterisks along the different body sites indicate the presence of cutaneous allodynia in the tested regions. Shaded areas inside the tables identify changes in pain thresholds that fulfill the criteria for allodynia.

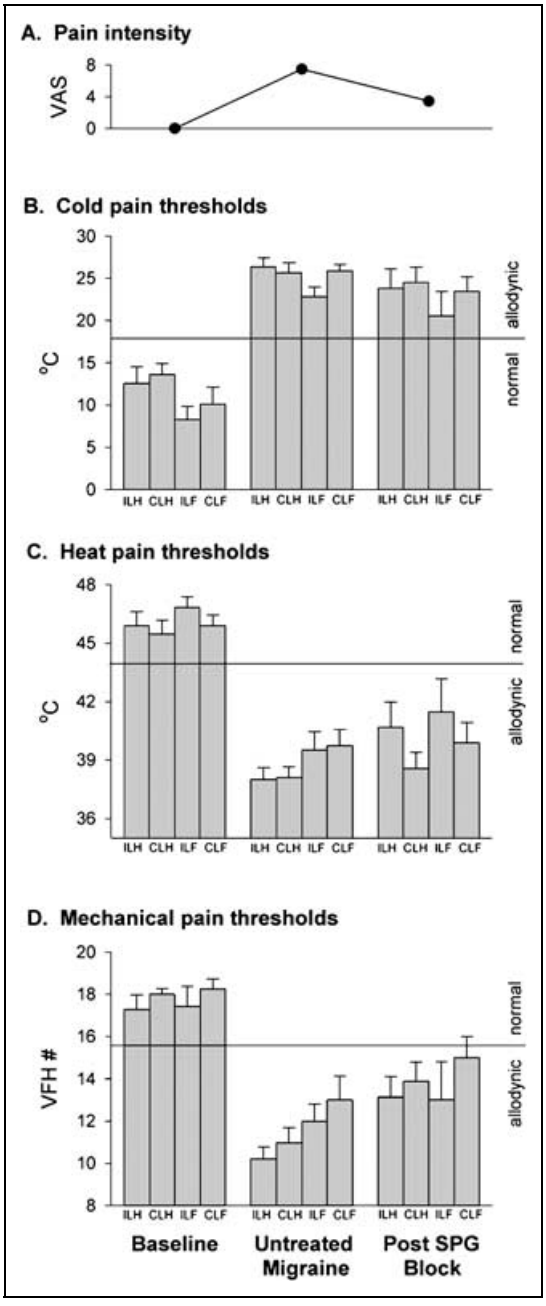

Fig 2.—Histograms showing mean (±95% confidence interval) cold (B), heat (C), and mechanical (D) pain thresholds in the absence of migraine (left cluster), during untreated migraine (middle cluster), and after sphenopalatine ganglion (SPG) block (right cluster) at each of the 4 tested sites: ipsilateral head (ILH), contralateral head (CLH), ipsilateral forearm (ILF), and contralateral forearm (CLF). Horizontal lines (B-D) mark one SD below mean pain thresholds at baseline, which is the criterion for allodynia. The line plot on top (A) illustrates the pain intensity during migraine and the significant (more than 50%) pain relief following the SPG block (VAS indicates visual analog scale). Note that cutaneous allodynia did not change significantly after the treatment. VFH indicates von Frey hairs.

theories recently have been proposed. According to these theories, parasympathetic stimulation causes the release of Ach, VIP, and NO around meningeal vasculature. These substances can induce mast cells degranulation and plasma protein extravasation,[41,45-48] events that release inflammatory mediators (such as histamine, serotonin, bradykinin, and prostaglandins) and are shown to directly activate and sensitize somatic and visceral nociceptors including those innervating the dura. Histamine, for example, is a headache-inducing monoamine that stimulates endothelial H_1 receptors to activate nitric oxide synthase (NOS), the enzyme that catalyzes the formation of NO.[49-51] Because NO mediates endothelium-dependent and neurogenic-dependent vasodilation and regulates (in part) platelet aggregation and inflammatory response, it is thought to play a causative role in migraine pain.[52-56]

We found in this study that intranasal administration of lidocaine lessens the pain intensity and intracranial hypersensitivity and propose that it is mediated by an SPG block, a block that reduces the parasympathetic outflow to the cranium and the resultant activation of the perivascular nociceptors. Because SPG blocks lessened the pain intensity by over 50% in the patients in group B but by less than 25% in the patients in group A, it is possible that ongoing parasympathetic-sensory interactions contributed more to the pathophysiology of migraine pain in the patients in group B. A further support to the concept that the parasympathetic outflow contributes to migraine pain stems from the observation that SPG block reduced the pain within the innervation territory of the sphenopalatine nerve in the frontal part of the cranium, but not in the occipital region of the cranium. An anatomical explanation for this finding could be that the frontal portion of the cranium is innervated mainly by parasympathetic fibers that originate in the SPG and that the occipital portion of the cranium is innervated mainly by parasympathetic fibers that originate in the otic ganglion. In support of this, Suzuki et al reported that following a bilateral removal of the SPG, VIP positive fibers disappeared completely from the anterior part of the circle of Willis, partially from the middle and posterior cerebral arteries, and were unaffected in the caudal part of the basilar and the vertebral arteries.[57]

P* Values of Changes in Mean Pain Thresholds Presented in Figure 2

Modality	Site	Baseline Versus Untreated Migraine	Baseline Versus Post-SPG Block	Untreated Migraine Versus Post-SPG Block	Test
Cold	ILH	<.01	<.01	NS	Parametric (Newman-Keuls)
	CLH	<.01	<.01	NS	
	ILF	<.01	<.01	NS	
	CLF	<.01	<.01	NS	
Heat	ILH	<.01	<.01	NS	Parametric (Newman-Keuls)
	CLH	<.01	<.01	NS	
	ILF	<.01	<.01	NS	
	CLF	<.01	<.01	NS	
Mechanical	ILH	.007	.13	NS	Nonparametric (Kruskal-Wallis)
	CLH	.033	NS	NS	
	ILF	.26	NS	NS	
	CLF	NS	NS	–	

*SPG indicates sphenopalatine ganglion; ILH, ipsilateral forearm; NS, not significant; CLH, contralateral head; ILF, ipsilateral forearm; CLF, contralateral forearm.

As in all human psychophysical studies, we must consider the possibility that the 53% reduction in the pain level following the administration of nasal lidocaine was a placebo response. Because patients were always aware of their pain but unapprised of the presence or absence of cutaneous allodynia and because nasal lidocaine reduced the pain but not the allodynia, it is possible that the pain reduction was, in part, a placebo response. The placebo phenomenon occurs mainly when patients are aware of the symptom under investigation. Even so, we have 2 reasons to believe that the 53% pain relief was not a placebo response: (1) A recent double-blind, randomized, placebo-controlled study on the ability of intranasal lidocaine to reduce migraine pain showed similar results after taking into consideration the placebo effect.[10] (2) The specificity of the nasal lidocaine-induced pain relief: in spite of being unaware of the possibility that the pain could be relieved in some parts of the head but in others, patients consistently reported pain reduction in the frontal but not occipital portion of the head.

We also found that while the lidocaine-induced SPG block reduced the pain intensity, it did not significantly reverse the cutaneous allodynia within the referred pain area or the other tested sites. Current understanding suggests that cutaneous allodynia is a result of sensitization that develops in either peripheral nociceptors or central nociceptive neurons (or both) following skin injury and that when cutaneous allodynia involves undamaged skin it is mediated by the sensitization of central neurons.[58-63] In a recent series of basic studies on an animal model, we found that a noxious stimulus to the dura induces sensitization in central trigeminal neurons that process information from both the dura and the skin.[16,64] The expression of this sensitization was the development of spontaneous activity in central neurons and enhanced responses to stimulation of their cutaneous receptive fields. In a parallel clinical study of patients with migraine, we reported the development of cutaneous allodynia during attacks, and proposed that this allodynia reflects sensitization of the central trigeminal neurons.[23] Therefore, the failure of lidocaine-induced SPG block to reverse the cutaneous allodynia suggests that increased parasympathetic tone does not contribute to the maintenance of central sensitization.

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