Extracranial projections of meningeal afferents and their impact on meningeal nociception and headache.

Schueler M, et al. Pain. 2013.

Abstract

Headaches can be evoked by activation of meningeal nociceptors, but an involvement of pericranial tissues is debated. We aimed to examine a possible extracranial innervation by meningeal afferents in the rat. For in vivo neuronal tracing, dextran amines were applied to the periosteum underlying the temporal muscle. Labeling was observed 2 days later in the parietal dura mater, trigeminal ganglion, and spinal trigeminal nucleus with confocal and electron microscopy. In the hemisected rat head, extracellular recordings were made from meningeal nerve fibers. Release of calcitonin gene-related peptide (CGRP) from the cranial dura mater during noxious stimulation of pericranial muscles was quantified. In vivo capsaicin was injected into the temporal muscle while meningeal blood flow was recorded. In the parietal dura mater, labeled C- and Aδ fibers ramified extensively, accompanied the middle meningeal artery, and passed through the spinosus nerve into the maxillary and mandibular, but not the ophthalmic division of the trigeminal ganglion. Some fibers could be traced into the ipsilateral spinal trigeminal nucleus. Electrophysiological recordings revealed afferent fibers with mechanosensitive receptive fields both in the dura mater and in the parietal periosteum. Noxious stimulation of the temporal muscle caused CGRP release from the dura mater and elevated meningeal blood flow. Collaterals of meningeal nerve fibers project through the skull, forming functional connections between extra- and intracranial tissues. This finding offers a new explanation of how noxious stimulation of pericranial tissues can directly influence meningeal nociception associated with headache generation and why manual therapies of pericranial muscles may be useful in headaches.

PMID

23707274 [Indexed for MEDLINE]

Innervation of rat and human dura mater and pericranial tissues in the parieto-temporal region by meningeal afferents.

Schueler M, et al. Headache. 2014.

Abstract

OBJECTIVE: To reinvestigate the innervation pattern of the dura mater of rat and human middle cranial fossa, the morpho-functional substrate of headache generation, and adjacent extracranial tissues with neuronal in vitro tracing.

BACKGROUND: This study was initiated by recent structural and functional findings of meningeal afferent fibers which innervate the cranial dura mater and may project to extracranial tissues.

METHODS: Anterograde and retrograde neuronal in vitro tracing was made in formaldehyde fixed hemisected rat and human skulls. The fluorescent tracer DiI was applied to proximally cut meningeal nerves in rat and to distal branches of the spinosus nerve in human calvaria lined by dura mater. After several weeks, the dura mater and deep extracranial tissues were examined with fluorescence microscopy.

RESULTS: In addition to a network of meningeal nerve fibers, several fiber bundles were observed, leaving the skull through emissary canals and fissures to innervate the pericranial temporal, parietal, and occipital periosteum. Traced fibers were seen spreading into deep layers of the temporal and upper neck muscles. Retrograde neuronal tracing revealed labeled cell bodies exclusively in the mandibular and maxillary division of the rat trigeminal ganglion, and centrally projecting fibers were identified in the spinal trigeminal tract. Electron microscopy of the cross-sected spinosus nerve showed myelinated and unmyelinated axons with similar numbers in human and rat.

CONCLUSIONS: We conclude that a proportion of meningeal afferents innervates extracranial tissues like periosteum and pericranial muscles via collaterals projecting through the skull. These afferents may be nociceptive, some may subserve proprioceptive functions. The finding of extracranial projections of meningeal afferents may be important for our understanding of extracranial impacts on headache generation and therapy.

PMID
24673461 [Indexed for MEDLINE]

Meningeal nociception: electrophysiological studies related to headache and referred pain.

Review article

Messlinger K, et al. Microsc Res Tech. 2001.

Abstract

Headaches, which are usually referred to characteristic sites of the skull, are believed to involve meningeal nociceptors located in the dura mater encephali. Animal experiments show that these meningeal nociceptors are polymodal and usually highly sensitive to mechanical stimulation. These properties are also characteristic for the second order neurons in the spinal trigeminal nucleus, most of which receive convergent input from facial receptive sites. Sensitization of primary and secondary neurons by chemical irritants to mechanical stimuli may be an important mechanism in the generation of headaches. The convergent input from extracranial structures, which seems to be differentially organized in rodents and man, may explain the typical features of referred headache. Targets for analgesics used in the therapy of headaches (non-steroidal antiinflammatory drugs, 5-HT(1) receptor agonists) are probably meningeal nociceptors and different sites of the central trigeminal nociceptive and antinociceptive pathways.

PMID
11301488 [Indexed for MEDLINE]

ATP-sensitive muscle afferents activate spinal trigeminal neurons with meningeal afferent input in rat - pathophysiological implications for tension-type headache.

Nöbel M, et al. J Headache Pain. 2016.

Abstract

BACKGROUND: Tension-type headache and other primary headaches may be triggered or aggravated by disorders of pericranial muscles, which is possibly due to convergent or collateral afferent input from meningeal and muscular

receptive areas. In rodent models high extracellular concentrations of ATP caused muscle nociception and central sensitization of second order neurons. In a rat model of meningeal nociception we asked if spinal trigeminal activity induced by ATP can be modulated by local anaesthesia of distinct muscles.

METHODS: Ongoing activity was recorded from spinal trigeminal neurons with afferent input from the cranial dura mater, the temporal muscle and neck muscles. The stable ATP analogue α,β-methylene adenosine 5'-triphosphate (α,β-meATP, 10 mM) was injected into the ipsilateral temporal muscle, 30 min later followed by injection of local anaesthetics (lidocaine, 2 %) into the ipsilateral neck muscles and/or the temporal muscle.

RESULTS: Injection of α,β-meATP into the temporal muscle caused progressive increase in ongoing activity of most of the spinal trigeminal neurons within 30 min. Injection of lidocaine into the neck muscles and/or the temporal muscle reduced this activation to previous levels within 10 min.

CONCLUSIONS: Distinct spinal trigeminal neurons processing meningeal nociceptive information are under the control of convergent afferent input from several pericranial muscles. Blockade of at least one of these inputs can normalize central trigeminal activity. This may explain why therapeutic manipulations of head muscles can be beneficial in primary headaches.

PMID
27565510 [Indexed for MEDLINE] PMCID PMC5001961

Meningeal nociception: electrophysiological studies related to headache and referred pain.

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Headaches, which are usually referred to characteristic sites of the skull, are believed to involve meningeal nociceptors located in the dura mater encephali. Animal experiments show that these meningeal nociceptors are polymodal and usually highly sensitive to mechanical stimulation. These properties are also characteristic for the second order neurons in the spinal trigeminal nucleus, most of which receive convergent input from facial receptive sites. Sensitization of primary and secondary neurons by chemical irritants to mechanical stimuli may be an important mechanism in the generation of headaches. The convergent input from extracranial structures, which seems to be differentially organized in rodents and man, may explain the typical features of referred headache. Targets for analgesics used in the therapy of headaches (non-steroidal antiinflammatory drugs, 5-HT(1) receptor agonists) are probably meningeal nociceptors and different sites of the central trigeminal nociceptive and antinociceptive pathways.

PMID
11301488 [Indexed for MEDLINE]

Response properties of dural nociceptors in relation to headache.

Review article

Strassman AM, et al. J Neurophysiol. 2006.

Abstract

Single-unit electrophysiological recording studies have examined the activity of sensory neurons in the trigeminal ganglion that innervate the intracranial meninges to better understand their possible role in headache. A key question is whether the meningeal sensory neurons are similar to nociceptive neurons in other tissues or, alternatively, whether they have unique properties that might be of significance for headache pathogenesis and drug therapy. Such studies have indeed found that the intracranial dura is innervated by neurons that exhibit properties characteristic of nociceptors in other tissues, including chemosensitivity and sensitization. This sensitization, consisting of an enhanced responsiveness to mechanical stimuli, might be relevant to symptoms that are

characteristic of certain headaches that indicate the presence of an exaggerated intracranial mechanosensitivity. Studies that examined whether the anti-migraine agent sumatriptan might inhibit this sensitization (in addition to its well-known inhibition of neurotransmitter release) found that it had no inhibitory effect but rather produced a calcium-dependent discharge, which might account for the initial worsening of headache that can follow sumatriptan administration. In studies that examined the effects of vasodilator agents, nitroprusside produced mixed effects on mechanosensitivity, whereas calciton gene-related peptide (CGRP) had no effect on either spontaneous or mechanically evoked discharge. These results call into question the role of vasodilation in headache and suggest that the role of CGRP in headache may be through its action as a central neurotransmitter rather than through vasodilation and activation of meningeal nociceptors. In general, studies of meningeal sensory neurons have not found evidence of unique properties that distinguish them from nociceptive neurons in other tissues. Ultimately the distinctive clinical characteristics of headache may prove to be related not so much to any differences in the intrinsic molecular or cellular properties of the meningeal sensory neurons but rather to the distinctive properties of the tissue that they innervate.

PMID
16492942 [Indexed for MEDLINE]

The mechanism of peripheral and central sensitization in migraine. A literature review.

Review article

Tajti J, et al. Neuropsychopharmacol Hung. 2009.

Abstract

Migraine attacks are characterized by unilateral throbbing, pulsating headache associated with nausea, vomiting, photophobia, phonophobia and allodynia. Peripheral sensitization is an acute, chemical-induced form of functional plasticity, which converts high-threshold nociceptors into low-threshold sensory neurons. This form of sensitization occurs when the nerve terminals (meningeal nociceptors) of the neurons of the trigeminal ganglion are soaked with the "inflammatory" soup (prostaglandin E2, bradykinin, serotonin and cytokines) along the vasculature of the cerebral dura mater. Peripheral sensitization in migraine attacks is explained clinically by intracranial hypersensitivity (the headache worsens during coughing or physical activity) and by a throbbing element in the pain of migraine (sensitized nociceptors become hyperresponsive to the otherwise innocuous and unperceived rhythmic fluctuation in intracranial pressure produced by normal arterial pulsation). The essence of central sensitization is that the second-order neurons in the trigeminocervical complex become hyperexcitable. The altered behavior of the second-order neurons is based on the increased glutamate sensistivity of the NMDA receptors and the neuronal nitric oxide synthase activity stimulated by nitric oxide. This process is explained clinically by face and scalp allodynia and by neck stiffness (extracranial tenderness).

PMID
19731814 [Indexed for MEDLINE]

The development of cutaneous allodynia during a migraine attack – clinical evidence for the sequential recruitment of spinal and supraspinal nociceptive neurons in migraine.

Burstein R, et al. Brain. 2000.

Abstract

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.

PMID
10908199 [Indexed for MEDLINE]

An association between migraine and cutaneous allodynia.

Burstein R, et al. Ann Neurol. 2000.

Abstract

Recent animal studies on the mechanism of migraine show that intracranial pain is accompanied by increased periorbital skin sensitivity. These findings suggest that the pathophysiology of migraine involves not only irritation of meningeal perivascular pain fibers but also a transient increase in the responsiveness (ie, sensitization) of central pain neurons that process information arising from intracranial structures and skin. The purpose of this study was to determine whether the increased skin sensitivity observed in animal also develops in humans during migraine attacks. Repeated measurements of mechanical and thermal pain thresholds of periorbital and forearm skin areas in the absence of, and during, migraine attacks enabled us to determine the occurrence of cutaneous allodynia during migraine. Cutaneous allodynia is pain resulting from a non-noxious stimulus to normal skin. In 79% of the patients, migraine was associated with cutaneous allodynia as defined, and in 21% of the patients it was not. The cutaneous allodynia occurred either solely within the referred pain area on the ipsilateral head, or within and outside the ipsilateral head. Cutaneous allodynia in certain well-defined regions of the skin during migraine is an as yet unreported neurological finding that points to hyperexcitability of a specific central pain pathway that subserves intracranial sensation.

PMID
10805332 [Indexed for MEDLINE]

Repeated noxious stimulation of the skin enhances cutaneous pain perception of migraine patients in-between attacks: clinical evidence for continuous sub-threshold increase in membrane excitability of central trigeminovascular neurons.

Weissman-Fogel I, et al. Pain. 2003.

Abstract

Recent clinical studies showed that acute migraine attacks are accompanied by increased periorbital and bodily skin sensitivity to touch, heat and cold. Parallel pre-clinical studies showed that the underlying mechanism is sensitization of primary nociceptors and central trigeminovascular neurons. The present study investigates the sensory state of neuronal pathways that mediate skin pain sensation in migraine patients in between attacks. The assessments of sensory perception included (a) mechanical and thermal pain thresholds of the periorbital area, electrical pain threshold of forearm skin, (b) pain scores to phasic supra-threshold stimuli in the same modalities and areas as above, and (c) temporal summation of pain induced by applying noxious tonic heat pain and brief trains of noxious mechanical and electrical pulses to the above skin areas. Thirty-four pain-free migraine patients and 28 age- and gender-matched controls were studied. Patients did not differ from controls in their pain thresholds for heat (44+/-2.6 vs. 44.6+/-1.9 degrees C), and electrical (4.8+/-1.6 vs. 4.3+/-1.6 mA) stimulation, and in their pain scores for supra-threshold phasic stimuli for all modalities. They did, however, differ in their pain threshold for mechanical stimulation, just by one von Frey filament (P=0.01) and in their pain scores of the temporal summation tests. Increased summation of pain was found in migraineurs for repeated mechanical stimuli (delta visual analog scale (VAS) +2.32+/-0.73 in patients vs. +0.16+/-0.83 in controls, P=0.05) and repeated electrical stimuli (delta VAS +3.83+/-1.91 vs -3.79+/-2.31, P=0.01). Increased summation corresponded with more severe clinical parameters of migraine and tended to depend on interval since last migraine attack. The absence of clinically or overt laboratory expressed allodynia suggests that pain pathways are not sensitized in the pain-free migraine patients. Nevertheless, the increased temporal summation, and the slight decrease in mechanical pain thresholds, suggest that central nociceptive neurons do express activation-dependent plasticity. These findings may point to an important pathophysiological change in membrane properties of nociceptive neurons of migraine patients; a change that may hold a key to more effective prophylactic treatment.

PMID

12927642 [Indexed for MEDLINE]

The sensory innervation of the calvarial periosteum is nociceptive and contributes to headache-like behavior.

Zhao J, et al. Pain. 2014.

Show full citation

Abstract

Headaches are thought to result from the activation and sensitization of nociceptors that innervate deep cephalic tissues. A large body of evidence supports the view that some types of headaches originate intracranially, from activation of sensory neurons that innervate the cranial meninges. However, the notion of an extracranial origin of headaches continues to be entertained, although the identity of deep extracranial cephalic tissues that might contribute to headaches remains elusive. Here we employed anatomical, electrophysiological, and behavioral approaches in rats to test the hypothesis that the sensory innervation of the calvarial periosteum is nociceptive. Neural tracing indicated that the calvarial periosteum overlying the frontal and parietal bones is innervated primarily by small and medium-sized neurons in the trigeminal ganglion's ophthalmic division. In vivo single-unit recording in the trigeminal ganglion revealed that calvarial periosteal afferents have slowly conducting axons, are mechanosensitive, and respond to inflammatory mediators, consistent with a nociceptive function. Two distinct neuronal populations were distinguished based on their peripheral axonal trajectory: one that reached the periosteum through extracranial branches of the trigeminal nerve, and another that took an intracranial trajectory, innervating the cranial dura and apparently reaching the periosteum via the calvarial sutures. In behavioral studies, inflammatory stimulation of these afferents promoted periorbital tactile hypersensitivity, a sensory change linked to primary headaches. Activation and sensitization of calvarial periosteal afferents could play a role in mediating primary headaches of extracranial and perhaps also intracranial origin, as well as secondary headaches such as postcraniotomy and posttraumatic headaches. Targeting calvarial periosteal afferents may be effective in ameliorating these headaches.

PMID

24769138 [Indexed for MEDLINE]

PMCID
PMC4058402

Sensitization of meningeal sensory neurons and the origin of headaches.

Strassman AM, et al. Nature. 1996.

Abstract

The headaches that accompany certain intracranial pathologies (such as meningitis, subarachnoid haemorrhage and tumour) have been considered to result from mechanical or chemical stimulation of pain-sensitive structures of the intracranial meninges. Although the recurrent headache of migraine is of unknown origin and is not accompanied by an identifiable pathology, it shares with intracranial headaches features that suggest an exaggerated intracranial mechanosensitivity (worsening of the pain by coughing, breath-holding or sudden head movement). One possible basis for such symptoms would be a sensitization of meningeal afferents to mechanical stimuli. Previous studies of neuronal responses to meningeal stimulation have focused primarily on cells in the central portion of the trigeminal pathway, and have not investigated the possible occurrence of sensitization. We have recorded the activity of primary afferent neurons in the rat trigeminal ganglion that innervate the dural venous sinuses. Chemical stimulation of their dural receptive fields with inflammatory mediators both directly excited the neurons and enhanced their mechanical sensitivity, such that they were strongly activated by mechanical stimuli that initially had evoked little or no response. These properties of meningeal afferents (chemosensitivity and sensitization) may contribute to the intracranial mechanical hypersensitivity that is characteristic of some types of clinically occurring headaches, and may also contribute to the throbbing pain of migraine.

PMID
8955268 [Indexed for MEDLINE]

Mechanical response properties of A and C primary afferent neurons innervating the rat intracranial dura.

Levy D, et al. J Neurophysiol. 2002.

Abstract

The intracranial dura receives a small-fiber sensory innervation from the trigeminal ganglion that is thought to be involved in some types of headaches, including migraine. Mechanical response properties of dural afferent neurons were examined to investigate variation across the population in the properties of threshold, slope, adaptation, and incidence of mechanosensitivity. Dural afferent neurons were recorded in the trigeminal ganglion of urethan-anesthetized rats and were identified by their constant-latency response to dural shock. Neurons were classified as fast A (>5 m/s), slow A (5 >or= conduction velocity (CV) >or= 1.5 m/s), or C (<1.5 m/s), based on response latency to dural shock. Mechanical receptive fields were identified by stroking or indenting the outer surface of the dura. Stimulus-response curves were obtained from responses to 2-s constant-force indenting stimuli of graded intensities delivered to the dural receptive field with a servo force-controlled mechanical stimulator. The slow A population had the highest percentage of mechanosensitive units (97%) as well as the highest slopes and the lowest thresholds. Thus by all three criteria, the slow As had the highest mechanosensitivity. Conversely, the fast A population had the lowest mechanosensitivity in that it had the lowest percentage of mechanosensitive units (66%), the lowest slopes, and the highest thresholds. The C population was intermediate with respect to all three properties but was much more similar to the slow As than to the fast As. All three fiber classes showed a negative correlation between slope and threshold. The majority of neurons showed a slowly adapting response to a maintained 2-s stimulus. Adapting neurons could be subdivided based on whether the fitted exponential curve decayed to zero or to a nonzero plateau; the latter group contained the most sensitive neurons in that they had the lowest thresholds and highest slopes. Nonadapting neurons generally had lower initial firing rates than adapting neurons. Fast A neurons exhibited greater and more rapid adaptation than slow A and C neurons. Neurons with the lowest slopes, regardless of CV, had relatively rapid adaptation. The more slowly conducting portion of the C population was distinguished from the other C neurons by a number of properties: more mechanically insensitive neurons, higher thresholds, and more nonadapting neurons. These differences in mechanical response properties may

be related in part to differences in membrane currents involved in impulse generation that have been described in subpopulations of dorsal root ganglion cells.

PMID
12466427 [Indexed for MEDLINE]