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INVITED REVIEW

The role of chemosensitive afferent nerves and TRP ion channels in the pathomechanism of headaches

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Abstract The involvement of trigeminovascular afferent nerves in the pathomechanism of primary headaches is well established, but a pivotal role of a particular class of primary sensory neurons has not been advocated. This review focuses on the evidence that supports the critical involvement of transient receptor potential (TRP) channels in the pathophysiology of primary headaches, in particular, migraine. Transient receptor potential vanilloid 1 and transient receptor potential ankyrin 1 receptors sensitive to vanilloids and other irritants are localized on chemosensitive afferent nerves, and they are involved in meningeal nociceptive and vascular responses involving neurogenic dural vasodilatation and plasma extravasation. The concept of the trigeminal nocisensor complex is put forward which involves the trigeminal chemosensitive afferent fibers/neurons equipped with specific nocisensor molecules, the elements of the meningeal microcirculatory system, and the dural mast cells. It is suggested that the activation level of this complex may explain some of the specific features of migraine headache. Pharmacological modulation of TRP channel function may offer a novel approach to the management of head pain, in particular, migraine.

Keywords TRPV1 · TRPA1 · Meningeal blood flow · Headache · Dura mater

Introduction

Headaches, in particular, migraine, belongs to the most frequent pains for which patients seek medical attention. The mechanisms of migraine headaches are still incompletely understood, but they involve both neurogenic and vascular pathologies of the meninges. Theories focusing either on the vascular or central and peripheral neuronal processes have been evolved which could explain some but not all fundamental aspects of this pain disorder. The functional properties and electrophysiological traits of meningeal primary afferents have also been characterized in great detail, but a pivotal role of a particular class of primary afferent neurons has not been advocated. In recent years, the role of transient receptor potential (TRP) channels in the pathophysiology of different pain disorders has been well established [11, 40, 98]. The existence and functional significance of meningeal chemosensitive primary afferent nerves, which are sensitive to vanilloids and other irritants and express the transient receptor potential vanilloid 1 (TRPV1) and the transient receptor potential ankyrin 1 (TRPA1) receptors, are now well-documented [34, 96, 116]. Since in most organs and tissues of the body TRP ion channels are intimately involved in the mediation of noxious events [16, 26, 67, 73, 95], this review focuses on the evidence that support the critical involvement of TRPV1 and TRPA1 channels in the pathophysiology of primary headaches, in particular, migraine.

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Nerves and neuroreceptors of the dura mater encephali

Classical anatomical and functional studies have revealed some of the most important aspects of headache mechanisms. Investigations into the origin of intracranial pain suggested that the dura mater encephali is the main, and probably the only, pain-sensitive structure within the cranium [44, 106]. Topographical analysis of the localization of "pain receptors" also disclosed that almost exclusively the paravascular regions of the dura mater but not areas remote

from the larger blood vessels are sensitive to painful stimulation [102]. Anatomical studies demonstrated the distribution of sympathetic and trigeminal sensory nerves within the dura mater of several mammalian species, including man [2, 46, 70, 91, 92]. The dura mater is densely innervated by both sympathetic and sensory nerves, which run freely in the dural stroma or are clearly associated with meningeal arteries and veins. Chemical neuroanatomical studies disclosed the various populations of meningeal nerves containing classical transmitters such as noradrenaline and the peptides substance P (SP), neurokinin A (NKA), and calcitonin gene-related peptide (CGRP) [18, 38, 125]. Most of these mediators are contained in unmyelinated axons, but electron microscopy revealed large numbers of myelinated nerve fibers, too [2]. Electrophysiological studies have revealed specific populations of dural sensory nerve fibers, many of which showed response properties characteristic of nociceptive afferents [120]. The majority of these nociceptive afferents responded to noxious mechanical stimuli but also to chemical agents, such as capsaicin [119, 121]. Sensitivity to capsaicin is a fundamental feature of nociceptive afferent fibers, which express the archetypical nociceptive ion channel, the TRPV1 receptor [17, 59, 61]. The existence of unmyelinated capsaicin-sensitive afferent nerves in the rat dura mater has been also demonstrated in electron microscopic studies utilizing an experimental neuroanatomical technique making use of the selective neurotoxic action of capsaicin [34, 72]. Retrograde labelling combined with immunohistochemistry demonstrated many TRPV1-immunoreactive trigeminal ganglion neurons that innervate the dura mater [116]. In addition, immunohistochemical findings furnished direct evidence for a dense innervation of the rat dura mater by TRPV1-immunoreactive paravascular and stromal nerve fibers [36]. Immunohistochemical studies have further characterized the chemical phenotypes of dural afferent fibers and revealed a subpopulation of TRPV1-immunoreactive nerves, which also showed proteinase-activated receptor-2 (PAR-2)-immunoreactivity. Dural mast cells localized, in part, in the close vicinity of blood vessels and also of afferent nerves displayed strong PAR-2-immunoreactivity, too [36, 128]. Recently, another member of the TRP receptor superfamily, the TRPA1, has also been found to be functional on trigeminal dural afferent nerves [76, 96]. The available experimental evidence suggests that TRPA1 receptors are expressed in chemosensitive primary afferent neurons that are peptidergic and also express the TRPV1 receptor [62, 66, 76, 118].

Although most studies dealing with headache mechanisms in the context of neurogenic inflammation considered the involvement of peptidergic primary afferent neurons which express the TRPV1 receptor, it should be emphasized that a large population of TRPV1-expressing neurons are not peptidergic [19, 105]. Non-peptidergic nociceptive primary sensory neurons may be identified through their binding of the plant lectin, *Griffonia simplicifolia* isolectin B4 (IB4). The possible significance of non-peptidergic nociceptive afferents as regards the pathomechanism of headaches has been rarely addressed. It is conceivable that these non-peptidergic TRPV1-expressing nerves do not contribute to local neurogenic vascular reactions, but they provide a parallel afferent pathway for the transmission of nociceptive signals. Although available evidence indicates that the IB4-positive and the IB4-negative subpopulations of TRPV1-expressing sensory ganglion neurons also show distinct functional characteristics [82, 113], especially under inflammatory conditions [12, 49], the significance of a possible parallel processing of dural nociceptive information remains to be elucidated.

The concept of the trigeminovascular nocisensor complex

The exact mechanisms of the generation of primary headaches like migraine are still unclear, but apparently, they involve both neurogenic and vascular events. Whereas cortical spreading depression is believed to play an important role in the development of migraine aura [78, 115, 129], the pathophysiological changes in the trigeminovascular system are considered to be of fundamental importance in the generation and maintenance of headache pain. Dysfunctions of the peripheral and/or the central components of the trigeminal nociceptive pathway may be responsible for the generation of intracranial pain and changes in blood flow in headache patients [5, 10, 13, 20, 90]. Many, but not all, trigeminovascular afferents contain vasoactive peptides, such as SP and CGRP. These peptides contained in primary sensory neurons serve not only as transmitters at the central synapses of nociceptive afferents [32, 56, 79], but they also play a pivotal role in the mechanisms of the neurogenic inflammatory response originally described in exteroceptive innervation territories (for reviews, see [23, 64, 87]). This unique neurovascular reaction has two components, neurogenic vasodilatation mediated through CGRP and neurogenic plasma extravasation mediated by SP. Neurogenic inflammation is a sterile inflammatory reaction brought about by the release of CGRP, SP, and probably NKA from sensory nerve endings as a consequence of antidromic or orthodromic stimulation of nociceptive afferent nerves [42, 48, 60, 61, 103, 112]. The biological significance of neurogenic inflammation is somewhat obscure and may differ in different organ systems and tissues, but a protective role of sensory neurogenic vasodilatation seems obvious [6]. An increase of blood flow in tissues flooded with microbial products and/or inflammatory mediators may promote the removal of noxious agents and help to restore tissue

homeostasis. Tissue reactions related to neurogenic inflammation have been shown to aggravate or attenuate tissue injury [31, 41, 50, 63, 64, 68]. In the dura mater, induction of a neurogenic inflammatory response through electrical stimulation of chemosensitive trigeminal afferents has been shown to produce an increase in vascular permeability that could be prevented by depletion of chemosensitive afferents and/or sensory neuropeptides by prior capsaicin desensitization [14]. The significance of neurogenic plasma extravasation as regards migraine pathogenesis in humans is controversial [127]. Clinical studies suggested that a migraine attack can neither be alleviated nor prevented by neurokinin antagonists. Hence, neurogenic plasma extravasation was suggested to be of minor significance as a pathogenetic factor of migraine [29], although more recent studies have demonstrated an increase in meningeal blood vessel permeability during migraine aura in humans [57]. In contrast, neurogenic sensory vasodilatation mediated also by peptide, in particular CGRP, release from chemosensitive afferents appears to play an important role in the pathomechanism of migraine. Its release into the jugular blood has been demonstrated during migraine attacks in humans [52], and, importantly, non-peptide CGRP antagonists have been shown to alleviate migraine headache [39, 101, 110].

Animal models of intracranial pain and headaches have also provided valuable data on the mechanisms of meningeal sensory neurogenic vasodilatation. Electrical stimulation of meningeal nerves produces vasodilatation in dural blood vessels, which is mediated by the release of CGRP from sensory nerves [77]. This was supported by the findings that both peptide and non-peptide CGRP antagonists inhibited meningeal neurogenic vasodilatation [94, 122]. Prior treatment of the animals with capsaicin greatly reduced or even completely abolished dural neurogenic vasodilatation due to the depletion of sensory neuropeptides and/or afferent nerves [34, 35]. Importantly, capsaicin, the archetypical TRPV1 agonist also evoked an increase in meningeal blood flow after local application in a rat open cranial window model of migraine headache. This vasodilatory response was abolished through prior capsaicin desensitization and by capsazepine, a TRPV1 antagonist [34]. These findings indicated that meningeal neurogenic vasodilatation is mediated through the activation of chemosensitive afferent nerves, which are sensitive to capsaicin and express the TRPV1 ion channel. The involvement of this particular class of sensory nerves in meningeal neurogenic plasma extravasation and activation of trigeminovascular nociceptive afferents is also well established [89]. Hence, activation of second-order neurons of the trigeminal nucleus caudalis by meningeal application of capsaicin or other chemical agents was inhibited after neonatal or systemic administration of capsaicin as assessed with the c-fos technique [99]. Electron microscopic and immunohistochemical data furnished direct evidence for the existence and distribution of unmyelinated capsaicin-sensitive TRPV1 immunoreactive sensory nerve fibers in the rat dura mater [34–36, 116]. Investigations into the significance of chemosensitive afferent nerves in meningeal vascular reactions have also revealed that at least a subpopulation of these particular afferents express the PAR-2 receptor, the activation of which elicits vasodilatation [36]. PAR-2 activation-induced vasodilatation is mediated by CGRP and a pathway involving nitric oxide [36, 37]. The activation of PAR-2 receptors localized on meningeal chemosensitive afferent nerves may be brought about by proteolytic enzymes, e.g., by tryptase released from activated mast cells. Activation of mast cells has been shown after electrical or chemical stimulation of dural afferent nerves, and it is believed to modulate the neurogenic inflammatory response [30]. This assumption is supported by the findings, which demonstrated that activation of PAR-2 induced sensitization of the TRPV1 receptor [36]. These observations suggest that PAR-2-mediated activation and sensitization of meningeal chemosensitive C-fiber nociceptors may significantly contribute to the pathophysiology of headaches.

Considering the possible mechanisms that may operate to maintain headache pain, a complex interplay among the different pain-producing agents implicated in meningeal nociception should be taken into account. Stimulation of chemosensitive afferent nerves, e.g., through activation of the TRPV1 receptors by inflammatory mediators, such as bradykinin, prostanoids, endovanilloids, and low pH, characteristic of inflammatory exudates, induces a CGRP-mediated marked increase in meningeal blood flow locally and activation of second order neurons in the caudal trigeminal nucleus centrally [80]. Similarly, activation of the TRPA1 receptors by, e.g., environmental irritants results in the release of CGRP from the dura mater and may also produce head pain [76, 96]. The activation of meningeal chemosensitive afferents also leads to the release of vasoactive tachykinins, SP, and NKA, which may elicit an increase in vascular permeability and moderate vasodilatation, too. Tachykinins and CGRP may affect meningeal mast cells resulting in the release of mast cell constituents and mediators, such as histamine and the proteolytic enzyme, tryptase [65, 81]. These, in turn, may further activate meningeal chemosensitive nociceptors resulting in additional neuropeptide release and central activation. Moreover, activation of neuronal PAR-2 receptors produces sensitization of the TRPV1 receptor [36], resulting in a further increase in dural blood flow. At present, it is unclear whether axon reflex mechanisms are involved in meningeal nociceptive functions, but previous findings have suggested the participation of sensory axon collaterals in neurogenic inflammatory responses in other somatic and visceral organs [3, 33, 84, 108] (Fig. 1).

The events, which follow the activation of dural chemosensitive nocisensors, may be regarded as components of a positive feedback regulation, which may generate an

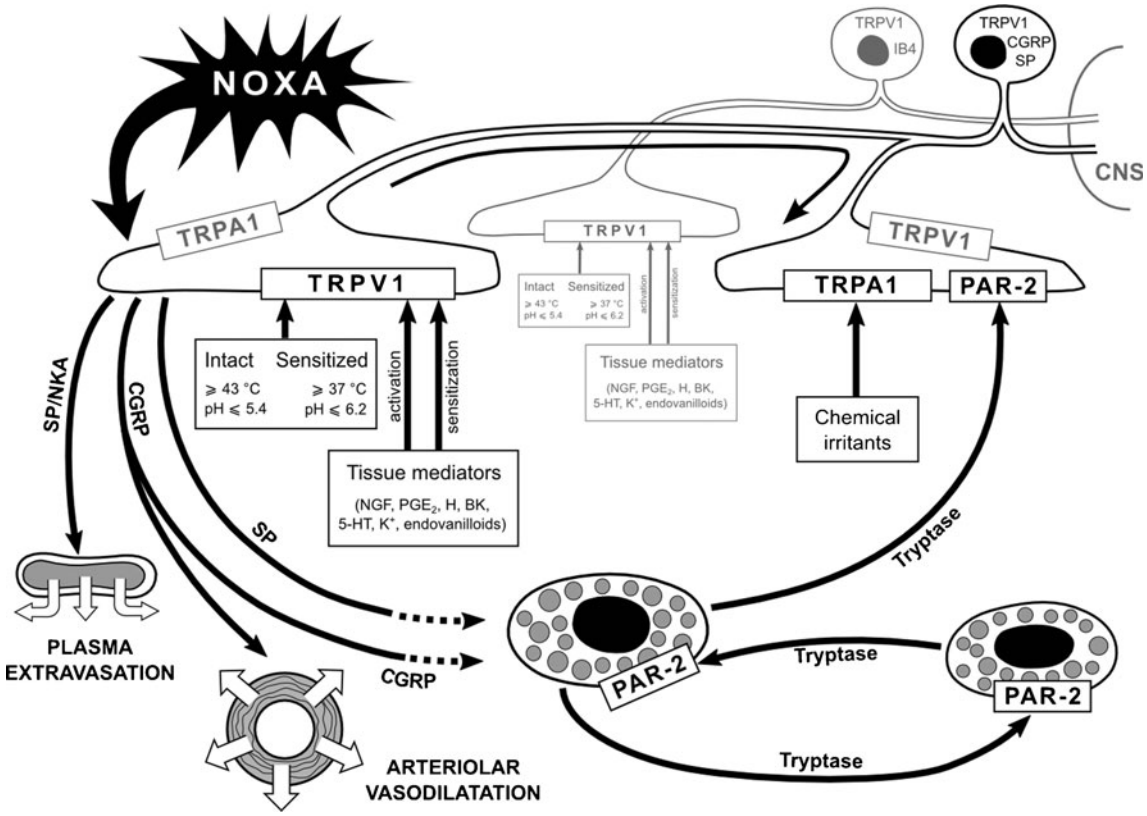

Fig. 1 Functions of the trigeminovascular nocisensor complex. The dural chemosensitive afferent nerves equipped with specific nocisensor molecules, in particular, TRP channels, the elements of the meningeal microcirculatory system, and the dural mast cells comprise the components of the trigeminovascular nocisensor complex. Stimulation of dural nociceptors by noxious agents results in the parallel transmission of nociceptive signals toward the central nervous system through peptidergic and non-peptidergic (IB4-positive) primary sensory neurons. Importantly, peptidergic nerves also release the vasoactive peptides CGRP and SP if stimulated, which produce vasodilatation and plasma extravasation, respectively. Stimulated nociceptors may also activate other nociceptive endings through an axon reflex mechanism (*curved arrow*). A variety of tissue mediators may excite or sensitize the TRP channels, which may also be sensitized through the activation of PAR-2 receptors by mast cell tryptase. Mast cells may be activated by CGRP and SP released from the nociceptor terminals and also by mast cell tryptase. Available evidence suggests a mutual activation of mast cells through the PAR-2 receptor, which provides a possibility for a self-triggering mechanism of mast cells resulting in an augmentation of the primary response. For further details, see text. *BK* bradykinin, *CGRP* calcitonin gene-related peptide, *5-HT* serotonin, *IB4 G. simplicifolia* isolectin B4, *NKA* neurokinin A, *PAR-2* proteinase-activated receptor-2, *PGE2* prostaglandin E2, *SP* substance P, *TRPA1* transient receptor potential ankyrin 1, *TRPV1* transient receptor potential vanilloid 1, *NGF* nerve growth factor, *H* histamine, *CNS* central nervous system

exaggeration of the initial nociceptive and vascular responses. This assumption is in line with clinical observations showing a significant worsening of the initial symptoms in the course of a migraine attack. The mechanisms leading to the initiation of the migraine attack are, at present, as enigmatic as the mechanisms operating at the cessation of the headache pain.

Considering the available experimental evidence, a concept of a trigeminovascular nocisensor complex is proposed. It is further suggested that the peripheral mechanisms participating in the initiation, maintenance, and cessation of head pain may be explained in the frame of this concept.

The elements of this complex include the trigeminovascular chemosensitive primary afferent neuron with its peripheral and central processes, the meningeal vascular bed, and the dural mast cells. It is suggested that the elements of this complex are both anatomically and functionally intimately interconnected and may be regarded as an important physiological and pathophysiological entity. Morphological studies furnished evidence for the close association of meningeal sensory nerves with blood vessels and also with mast cells [46]. Activation and sensitization of meningeal nociceptors by a variety of blood- and tissue-born inflammatory agents is the most important peripheral mechanism in the initiation of a migraine attack [51]. Some of these agents may act on their specific receptors expressed on nociceptors, whereas others may activate the TRPV1 and TRPA1 ion channels. The biochemical pathways for the activation of these specific nociceptive channels are now well established [93].

The activated nociceptor nerves transmit nociceptive impulses toward the central nervous system, and they also release vasoactive peptides, which exert their effect on neighboring blood vessels. CGRP causes vasodilatation whereas SP/

NKA may cause an increase in vascular (mainly postcapillary venular) permeability, i.e., a neurogenic inflammatory response [24, 114]. In addition, these vasoactive peptides also induce mast cell activation resulting in the release of mast cell mediators, such as histamine and mast cell tryptase [30]. These, in turn, may activate receptors of the nociceptive nerve terminals resulting in further neuropeptide release that strongly amplifies the initial vascular reaction and possibly also the central transmission of the nociceptive signal. The primary reaction is further augmented through the sensitization of nociceptors by inflammatory mediators, including nerve growth factor, and also by the activation of PAR-2 receptors. Sensitization of meningeal nociceptors through the activation of PAR-2 receptors co-expressed with the TRPV1 receptors in chemosensitive afferents has been revealed recently [36]. This observation is particularly interesting in the light of a self-amplification mechanism of mast cell degranulation through which mast cells may amplify their own activation–degranulation signals in an autocrine or paracrine manner [55]. The available data of human studies and animal experiments suggest that many facets of the peripheral pathomechanisms of head pain may be explained in the frame of the proposed concept of the trigeminovascular nocisensor complex. The elements of this system function in a concerted manner to initiate and to maintain and augment the vascular and nociceptive responses associated with migraine headaches, e.g., through blood, tissue, and nociceptor-born inflammatory mediators, and through nocisensor sensitization and mast cell (auto)activation, respectively. TRPV1 and TRPA1 receptors expressed by chemosensitive afferent neurons play a pivotal role in the functioning of the trigeminovascular nocisensor complex through both the central transmission of nociceptive signals and the peripheral release of vasoactive neuropeptides synthesized and transported in a peripherally regulated manner to their endings in the dura mater. Considering the changes in the levels of CGRP in the jugular blood of humans during migraine headache [52] and the decreased dural CGRP levels after prolonged electrical stimulation of trigeminal afferents [74, 111], it is tempting to suggest that depletion of the peptide from dural afferent nerves and the consequent decreased activation level of the trigeminovascular nocisensor complex may be related to the cessation of head pain. In addition, neurogenic sensory vasodilatation may have also beneficial effects by removing tissue metabolites inducing or aggravating headache attacks [34, 35, 37].

Inhaled environmental irritants induce headache through the activation of TRPA1

The TRPA1 ion channel, another member of the TRP receptor superfamily, has emerged recently as possibly the most important receptor activated by noxious chemical agents including environmental irritants [7]. The expression of TRPA1 has been also demonstrated in a population of trigeminal nociceptive neurons [71]. TRPA1 receptors can be activated by noxious cold, different environmental electrophyl irritants like acrolein and formaldehyde and also by pungent ingredients of plant origin, like cinnamaldehyde and allyl isothiocyanate [4, 66, 85, 123]. Hydrogen peroxide, 4-hydroxylnonenal, and a prostaglandin metabolite produced endogenously in sensory ganglion cells excite the TRPA1 receptor [15, 25]. Both exogenous and endogenous activators of the TRPA1 modify cysteine residues of the receptor by the formation of either covalent or not covalent bonds [86, 126]. In susceptible persons asthma, allergic rhinitis, and headache attacks are well-known consequences of exposure to environmental irritants. Recent findings furnished direct evidence for the involvement of TRPA1 receptors in headache mechanisms in humans by showing that umbellulone, the major volatile constituent of the "headache tree", *Umbellularia californica*, provokes headaches through the activation of the TRPA1 receptor [96]. Similarly to TRPV1, activation of trigeminovascular afferents through TRPA1 receptors causes nociceptive responses and the release of CGRP in rodents. Both nociceptive responses and CGRP release were absent in TRPA1-deficient mice [100]. It has been suggested that a number of irritant agents such as chlorine, cigarette smoke, and formaldehyde triggers head pain through the activation of the TRPA1 channel [1, 8, 47, 88]. This suggestion is supported by immunohistochemical and in situ hybridization findings which revealed that 36% of the trigeminal sensory ganglion neurons express TRPA1 in rodents. TRPA1 was present almost exclusively in small- and medium-sized neurons. The overwhelming majority (97 %) of TRPA1-expressing cells contained also the vasoactive neuropeptides CGRP and SP [118]. Double immunostaining of rat sensory ganglion cells revealed that 80% of TRPA1 imunoreactive neurons also expressed the PAR-2 receptor [27]. This high percentage of coexpression provides a firm morphological basis for the functional cooperation between these receptors. Mast cell tryptase activating the PAR-2 receptor may sensitize not only the TRPV1 but also the TRPA1 receptors of trigeminal afferents. PAR-2-mediated TRPA1 sensitization seems to activate an intracellular mechanism that is independent of the protein kinase C pathway. Cleavage of PAR-2 may activate phopholipase C which releases the inhibition of TRPA1 from membrane phosphatidylinositol-4,5-bisphosphate [27].

Interactions of TRPV1 and TRPA1 receptors in trigeminal sensory ganglion cells

Histological and functional observations have revealed the co-localization of TRPV1 and TRPA1 receptors in both the

dorsal root [66, 118] and the trigeminal [66, 109] sensory ganglion neurons. Although the mechanisms of activation of these channels differ significantly, experimental evidence indicates a functional interaction between TRPV1 and TRPA1 receptors which may modify the responses of nociceptive neurons toward the selective chemical activators of these ion channels. By recording mustard-oil-induced ionic currents from Chinese hamster ovary cells co-transfected with TRPA1/TRPV1 mRNAs or trigeminal ganglion neurons isolated from TRPV1 knock-out animals, Salas and coworkers [109] demonstrated that the amplitude, calcium sensitivity, and voltage-dependency of the mustard-oil-induced currents were strongly affected by the presence or absence of the TRPV1 channel. A non-significant difference in the amplitude of the mustard-oil-induced membrane currents between the capsaicin-sensitive and capsaicin-insensitive subpopulations of vagal afferent neurons was also reported [21]. Since mustard oil does not produce a direct activation of TRPV1 receptor at the concentration used in these experiments [43], it was hypothesized that TRPV1 either stabilizes the membrane localization of functional TRPA1 channels or (positively) regulates their sensitivity toward the TRPA1-specific chemical irritants [109]. Conversely, TRPA1 channel activation has been shown to restore the capsaicin sensitivity of TRPV1 following desensitization of the channel with repeated brief exposures to capsaicin [130]. Similar synergisms between the TRPV1 and TRPA1 channels might also occur centrally at the medullary termination sites of chemosensitive dural afferents which co-express these TRP channels [54, 69, 123]. Crosstalk between TRP channels might bear of special importance under conditions of receptor sensitization through inflammatory mediators brought about, in part, by post-translational modifications of the TRP channels [22, 58, 83, 124]. It has been demonstrated that, following sensitization of the TRPV1 channel, the activation threshold for both thermal and chemical stimuli decreases significantly, resulting in the opening of the channel at physiological temperatures [45, 104]. Similarly, endogenous agonists which possess low potency and/or are present at very low tissue concentrations may also activate the sensitized channel [28, 117].

TRPV1 and TRPA1 receptors localized in trigeminal afferents innervating extracranial tissues may contribute to meningeal sensory neurogenic vascular reactions and head pain

Under experimental conditions, capsaicin, mustard oil, and acrolein through the activation of TRPV1 and/or TRPA1 receptors of the nasal mucosa induce meningeal vasodilatation in the rat which is mediated by the release of CGRP from trigeminal perivascular nerves. Although the contribution of a trigemino-parasympathetic reflex increasing meningeal blood flow after noxious chemical stimulation of the facial mucosa cannot be excluded [53], it is very likely that trigeminal afferents that innervate the nasal mucosa project collaterals to meningeal blood vessels. Nociceptive stimulation of extracranial tissues may activate intracranial collaterals by an axon reflex mechanism and release vasoactive neuropeptides in the meningeal tissue. In humans, inhaled irritants may stimulate such extracranial trigeminal afferents that innervate the nasal mucosa and project collaterals also to the meningeal blood vessels [76, 96]. In mice, immunohistochemistry has revealed CGRP-immunoreactive sensory nerve fibres in the emissary canals and sutures of cranial bones that were branches of dural nerves [75]. Activation of such extracranial collaterals of meningeal sensory vasomotor nerve fibers may explain the induction of headache attacks by extracranial triggers, such as tenderness of scalp muscles. The pathophysiological role of the excitation of TRPV1 and TRPA1 receptors that are localized on extracranial collaterals of meningeal trigeminal afferents is further supported by the beneficial effect of botulinum toxin injection into the pericranial muscles for migraine prevention. Botulinum toxin inhibits the release of CGRP, SP, and glutamate from the primary nociceptive neurons, reducing the neurogenic inflammation in the dura mater and the peripheral sensitization of the nociceptors [9, 97]. This may reduce the inflow of nociceptive information to the central nervous system that may inhibit also the central sensitization of neurons in the trigeminal nucleus caudalis [107]. Clinical studies proved that injection of botulinum toxin into pericranial muscles is an effective treatment in the prophylaxis of migraine.

Concluding remarks

Clinical observations and animal studies provided evidence for a central role of chemosensitive trigeminal afferents, which express the nociceptor ion channels TRPV1 and TRPA1, in the mechanisms of meningeal nociception and headache. Trigeminal chemosensitive primary sensory neurons are comprised of peptidergic and non-peptidergic populations of different functional traits which may serve parallel transmission of the nociceptive information towards the central nervous system. It is suggested that many facets of the peripheral mechanisms of head pain may be explained in the frame of the proposed concept of the trigeminovascular nocisensor complex. The elements of this system function in a concerted manner to initiate and to maintain and augment the vascular, inflammatory, and nociceptive responses associated with migraine headaches, e.g., through blood, tissue, and nociceptor-born inflammatory mediators, and through nocisensor sensitization and mast cell (auto)activation, respectively. TRPV1 and TRPA1 receptors

expressed by chemosensitive afferent neurons play a pivotal role in the functioning of the trigeminovascular nocisensor complex through both the central transmission of nociceptive signals and peripheral release of vasoactive neuropeptides synthesized and transported in a peripherally regulated manner to their endings in the dura mater. Pharmacological and/or genetic manipulations which selectively eliminate chemosensitive nociceptor afferent nerves and/or interfere with the function of the TRP channels, TRPV1 and TRPA1, may offer new approaches to the further understanding of the pathophysiology of headaches and also for the management of primary headaches, in particular, migraine.

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