



Review

The role of TRPM8 in the pathophysiology of migraine

Eduardo de Almeida Guimarães Nogueira Yara Dadalti Fragoso

MS & Headache Research, ¹Clinical Medicine and ²Neuroimmunology, Headache, Santos, São Paulo, Brazil



Eduardo de Almeida Guimarães Nogueira
eduagn@hotmail.com
Guaiabó 66 cj 2013, Santos, SP,
Brazil CEP 11035-260
Phone/Fax: +55 13 3273-6828.

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Mario Fernando Prieto Peres

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Abstract

The transient receptor potential melastatin 8 (TRPM8) is a member of the mammal TRPM subfamily. TRPM8 is involved in menthol-induced cold allodynia, a condition that activates the left lateral thalamus and the primary and secondary somatosensory cortices, which are related to pain processing. Cold is a well-known trigger of migraine. Thirty-nine articles were identified, 27 of which were selected for review after reading the abstracts. Fourteen papers were further excluded. TRPM8 seems to be involved in the pain mechanism of migraine and therefore should be considered as a target for the development of therapies against this type of primary headache.

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Introduction

The transient receptor potential melastatin 8 (TRPM8) is a member of the mammal TRPM subfamily.¹ TRPMs are part of the transient receptor potential (TRP) family, a group of 28 positively charged permeable ion channels expressed in cell membranes and organelles.² TRPM8 acts as a sensor in the cutaneous tissue for low temperatures leading to pain and even allodynia when nervous injury occurs.³ TRPM8 is involved in menthol-induced cold allodynia, a condition that activates the left lateral thalamus and the primary and secondary somatosensory cortices, which are related to pain processing.⁴

TRPM8 induces cold allodynia and, at the same time, it is necessary for cooling/menthol-based analgesia.² Regarding migraine, it is equally curious that cold temperatures can trigger a migraine attack, while menthol can cause pain relief. If TRPM8 is involved in the pathophysiology of migraine, it might be by eliciting two different mechanisms or by involve two different pathways.

According to Weyer and Letho⁵ there are TRPM8 receptors in humans' dura mater that are stimulated when someone is exposed to low temperatures causing activation of the trigeminal pathway, releasing inflammatory mediators such as Calcitonin Gene Related Peptide (CGRP) and thus culminating in the migraine crisis. The same authors also cite an experiment carried out in rodents, in which the researchers administered icilin to the animals' dura mater, causing migraine-mimicking behaviors and when administering a channel antagonist, the crisis disappeared. Another observation was the fact that the administration of sumatriptan together with the TRPM8 agonist did not cause the painful crisis. Very similar experiments were made with CGRP decades ago. The complex formed between TRPM8 channel and 5-HT1B receptor in primary afferent neurons, may be responsible for the amplification of the analgesic effect of TRPM8 activators and serotonergic agonists in tissue- and nerve-injury rat model.⁶

Table 1. A summary of the main findings of the 15 selected papers

Authors	Year	Conclusion
Bennemei S, Dussor G	2019	The repeated identification of TRPM8 variants in GWAS supports continued interest in this channel for the disorder, but it remains unknown whether therapeutics should be agonists or antagonists
Chasman DI, Schürks M, Anttila V et al.	2012	The association of rs10166942 may be stronger among women, which may be related to but would not explain the higher prevalence of migraine in women
Chasman DI, Anttila V, Buring JE, et al.	2014	TRPM8, the candidate gene for this SNP, is thought to mediate the sensation of pain rather than specific neurological or vascular functions that might more directly differentiate the pathophysiology of the migraine sub-classes
Dussor G, Cao YQ	2016	TRPM8 agonists and antagonists may be potential therapeutics, depending on how migraine is triggered in individual patients. TRPM8 may be a novel target for personalized medicine in migraine treatment
Forstenpointner J, Binder A, Maag R, et al.	2019	Experimental cold allodynia is mediated in different cerebral areas depending on the underlying pathophysiology. The cold-induced inhibition of cold pain
Gonzalez-Muniz R, Bonache MA, Martín-Escura C, Gomez-Monterrey I.	2019	The location, expression or morphological changes of the TRPM8 channels in different tissues, such as, eyes, salivary glands, the brain, or the oropharyngeal system, among others, open new opportunities for the treatment of diseases related to these systems
Kayama Y, Shibata M, Takizawa T et al.	2017	TRPM8 activation can relieve migraine by suppressing TRPV1 activity. Facial TRPM8 appears to be a promising therapeutic target for migraine
Ren L, Dhaka A, Cao YQ	2015	Activation of dural TRPM8 channels effectively inhibits meningeal irritation-evoked nocifensive behavior in adult mice. This provides a foundation to further investigate the contribution of postnatal changes of TRPM8-expressing dural afferents to the pathophysiology of pediatric and adult migraine
Samantá A, Hughes TET, Moiseenkova-Bell VY	2018	TRP channels are crucial players in various other physiological and pathological conditions like cancer, renal physiology, cardiac health and neuronal development. Therefore, most TRP channels are important therapeutic targets
Viana F	2010	The identification of specific ion channels, especially TRP channels, involved in different pathophysiological mechanisms including pain, pruritus, headache, chronic cough, and asthma, opens new opportunities for their treatment
Viana F	2018	In healthy human subjects, menthol can change the perception of a previously innocuous temperature into painful, suggesting a role of TRPM8 in cold pain. However, menthol does not aggravate responses in areas with a pre-existing cold allodynia, and can even result in an amelioration of symptoms
Weyer A, Letho SG	2017	Since chemotherapy is associated with changes in TRPM8 expression, perhaps TRPM8 antagonists could be beneficial in the prevention and/or reversal of this chemotherapy-induced cold allodynia. Or, perhaps TRPM8 antagonists could still be useful therapeutics for any other cold-related painful allodynia or hyperalgesia associated with other neuropathic or inflammatory conditions or even migraine or bladder pain



Methods

The authors performed a comprehensive review of the literature in the PubMed database, with the following terms: "TRPM8" AND "Migraine". The references of the selected articles were explored for further potential papers. Inclusion and exclusion of identified articles occurred after discussion and agreement between both authors.

Results

Thirty-nine articles were identified, 27 of which were selected for review after reading the abstracts. Eleven papers were further excluded, as they were not related to the subject of this review. One article in Chinese was excluded. A summary of the main findings of the 15 selected papers is presented in Table 1.

Discussion

The pathophysiology of migraine is still permeated with mysteries, however genetic studies, increasingly shed some light on this very interesting subject. The potential receptor transient melastatin⁸ is expressed at various sites in the human body such as the eyes, brain, salivary glands, urinary system and intestines. And for that reason it is believed that this ion channel is involved in many different diseases, with migraine being one of the most prevalent in the world.⁷

It is known that in humans, TRPM8 is activated when exposed to temperatures below 26°C, being a transducer of physical stimuli in the peripheral sensitive fibers of the skin and mucous membranes. Cold is a well-known trigger of migraine.⁸

The activation of the primary afferent neurons (PANs) that innervate the dura mater and cerebral blood vessels is the cornerstone of the pathogenesis of headaches. Regarding that PANs of the dorsal root ganglia and trigeminal ganglion (TG) also express, TRPM8 channels and CRGP, the stimulation of TRPM8 channels by lower temperatures or cold induced allodynia would activate primary afferent neurons of the trigeminal pathway innervating the dura and cerebral vessels triggering migraine attack.⁹

Genome-wide association studies (GWAS) in humans showed the association between migraine and TRPM8 activation has mostly been observed in individuals from northern Europe. There are three possible combinations of the TRPM8 Single Nucleotide Polymorphism (SNP) rs10166942 in our genetic code. They are: C;C or C;T or T;T alleles. Most of these

individuals from northern Europe carry the T; T allele of the SNP rs10166942 which is the most associated with migraine attacks.¹⁰ Those who carry the C; C or C; T alleles are at lower risk for migraine.

Natural selection would be an explanation for this phenomenon. People who expressed the T; T allele of SNP rs10166942 of TRPM8 in the meninges might be better adapted to the environment in relations to those who do not express them. Therefore, migraine may be interpreted as a price to pay for this "evolutionary advantage".² In addition, the prevalence of rs10166942 seems to occur more often among women, which may be linked to the higher frequency of migraine in women.^{11, 12}

Interestingly, cooling agents such as menthol, icilin and eucalyptol act as agonists of TRPM8 but cause the effect of analgesia and not pain. Dussor and Cao² proposed that the best explanation for this would be the fact that these substances also stimulate the activation of Transient Receptor Potential Vanilloid 1 (TRPV1), concluding, therefore, that the activation of TRPM8 alone is associated with the pain sensation, however when the activation occurs in concomitance with other TRP channels, the body's response is analgesia.

According to Kayama et al.⁹, meningeal inflammation activates TRPV1 trigeminal neurons. After meningeal inflammation, TRPM8 expression is gradually upregulated through transcriptional activation, which leads to increased concomitant expression of TRPM8 and TRPV1. Some of these TRPM8/TRPV1-positive neurons innervate the dura mater and face. In this state, facial TRPM8 stimulation can reverse TRPV1-mediated thermal allodynia in a cell-autonomous manner. The same authors⁹ carried an experience where TRPM8 agonists attenuated the pain mediated by TRPV1 in the trigeminal pathway suggesting that suggest that facial TRPM8 activation can exert an analgesic action by down regulating TRPV1 function at the level of trigeminal ganglia.

The development of new therapies for migraine targeting TRPM8 requires further studies. It is not clear whether these drugs should be agonists or antagonists of the ion channel in question since, depending on the stimulus, both seem to be able to alleviate the migraine attack.²

It should be noted that TRPM8 and TRPV1 are also involved in the pathophysiology of other craniofacial disorders, such as meningitis. Therefore, the applicability of the present review may extend beyond headaches.



Conclusion

TRPM8 seems to be involved in the pain mechanism of migraine and therefore should be considered as a target for the development of therapies against this type of primary headache.

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Eduardo de Almeida Guimarães Nogueira

<https://orcid.org/0000-0002-6035-560X>

Yara Dadalti Fragoso

<https://orcid.org/0000-0001-8726-089X>

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