Chapter 2

Role of TRPV1 channel in migraine: Current Overview

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Abstract

Migraine is a neurological disease that is very common in society and is characterized by symptoms such as severe headaches, nausea, and sensitivity to light and sound. Absence from work, decreased productivity and healthcare costs due to migraine impose a high economic burden on patients and countries. For this reason, research on preventing or treating this disease continues intensively towards understanding migraine pathophysiology and drug discovery. In studies investigating migraine pathophysiology, new specific targets have emerged in drug development, such as the Calcitonin Gene and Peptide (CGRP) pathway. Current studies show that imbalance in neuronal calcium (Ca^{2+}) homeostasis is effective in the pathogenesis of neurodegenerative disorders. Transient receptor potential (TRP) cation channels are non-selective cation channels and integral proteins that are widely expressed in the membranes of cells and organelles, especially in mammalian cells, and are involved in various cellular functions. It is known that transient receptor potential (TRP) channels cause neuronal apoptosis in cases of oxidative stress and Ca^{2+} homeostasis in neurological diseases. Therefore, TRP channels in migraine may be useful in preventing cellular damage due to oxidative stress in neurological disorders. TRPV1 (Transient receptor potential family, transient receptor potential vanilloid receptor1) is a non-selective ion channel protein first expressed in the dorsal root, trigeminal and nodos ganglia. Therefore, it is clear that TRPV1 channels have an important role in migraine treatment. Additionally, it has been shown that by using TRPV1 channel antagonists, Ca^{2+} influx into the intracellular environment can be prevented and thus cell homeostasis can be preserved. In this review, we examined the role of the TRPV1 channel in migraine based on recent studies.

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1. Transient Receptor Potential (TRP) Channels

There are various receptors located at the endings of nociceptive sensory nerves that respond to thermal, mechanical or chemical stimuli with threatening/disturbing potential. Most of these are members of a family of nonselective cation channels called TRP channels (1).

TRP channels containing 28 members in mammals have been classified as a new cation channel family. TRP channels blood pressure and smooth muscle regulation of tone, renal Ca^{+2}/Mg^{+2} conduction, pungent taste and odorous compounds, such as perception of mechanical changes, pain, temperature, taste, smell, sound, light it plays a role in many very important processes (2-4).

The TRP family is divided into 7 subfamilies based on amino acid similarities (5). TRP conancial (TRPC) consists of seven subfamilies, TRP vanilloid (TRPV) consists of six subfamilies, TRP melastatin (TRPM) from eight subfamilies, TRP polysteine (TRPP) from three subfamilies, TRP mucolipin (TRPML) consists of three subfamilies and TRP ankyrin (TRPA) consists of a single member (6, 7) (Figure 1)

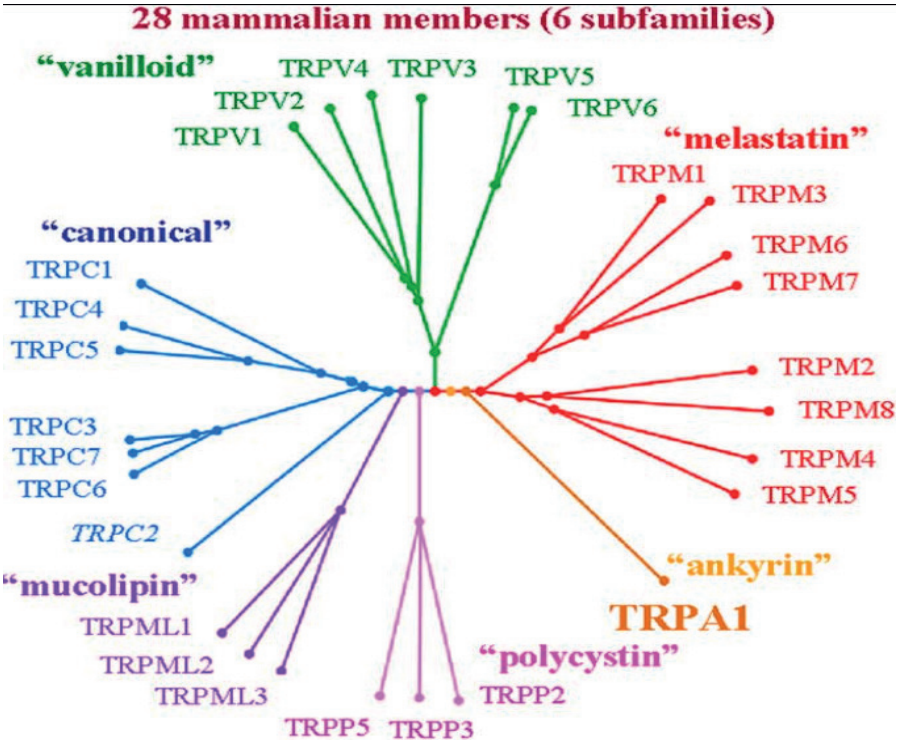

Figure 1. TRP channel superfamily (8).

It has been determined that TRP cation channels have important roles in the physiopathology of many diseases. Although these channels have many structural similarities, the activators of the subtypes of these channels differ. It is suggested that the basic structure of TRP channels consists of regions that cross the membrane 6 times, except for some TRPPs. It is known that the hydrophobic ring between segments 5 and 6 is the ion channel-forming pore and that the NH2 and COOH ends are located in the cytoplasm (Figure 2). TRP subtypes function by forming homo or heterotetrameric structures (10).

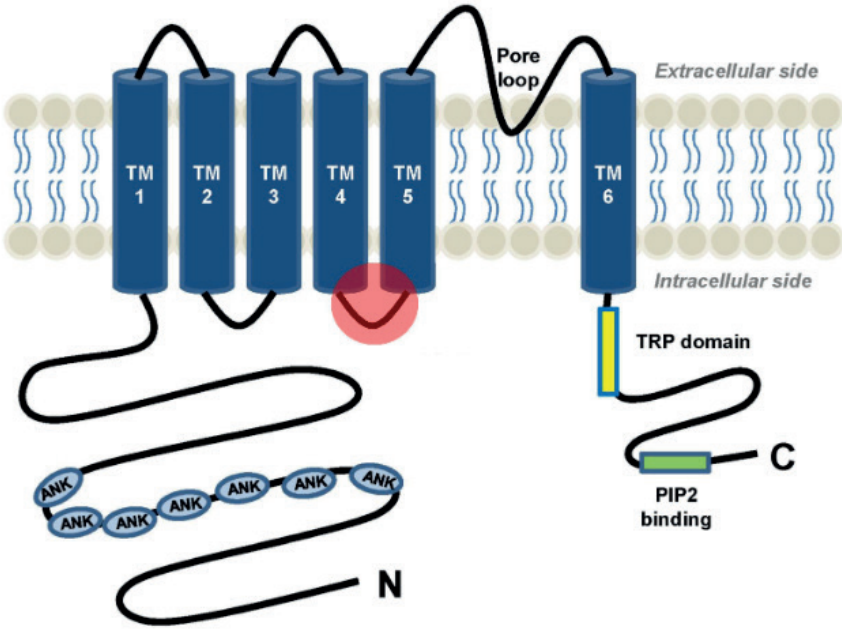

Figure 2. A topological structure of sensory TRP channels is illustrated (9).

In vivo, functional TRP assembly of channel complexes, homo/hetero multimerization and structural it is managed by complex formations with proteins (11). The differences between the physiological functions proposed in different tissues and the functions and properties of TRP channels observed in heterologous expression systems can be explained by these formations.

1.1. TRPV Cation Channels

The TRPV (vanilloid) family, which has six members in mammals, is divided into 4 subgroups are divided into: TRPV1/TRPV2, TRPV3, TRPV4 and TRPV5/6 (12, 13). TRPV Members of the family function

as tetrameric complexes. TRPV channels all have 3-5 NH_2-terminal ankyrin repeats (14).

TRPV2 is a voltage-activated channel and functions as a mechanosensor in vascular smooth muscle (15) and it probably plays a role in the pain pathway through degeneration of skeletal muscle and cardiac muscle (16). Physiological functions of the TRPV4 channel include central and peripheral thermosensitivity, mechanosensitivity, osmosensitivity and basal Ca^{2+} homeostasis (17). The highest Ca^{2+} selective channels of the TRP family are TRPV5 and TRPV6 channels, and these channels are regulated by Ca^{2+}. (18). While these two channels conduct calcium under physiological conditions, transports monovalent cations in the absence of extracellular calcium. TRPV5 in the kidney TRPV6 is important in the intestine while it is important for Ca^{2+} reabsorption (19). Among these channels, TRPV1 has attracted the most attention regarding pain modulation.

1.1.1. TRPV1 Cation Channel

TRPV1 is an ion channel activated by high temperature (43) and acid (pH5), which can produce effects similar to Capsaicin and CAP. TRPV1 is widely found in sensory neurons and ganglia. It is also found in other neurons and in various cells that do not contain neurons (20). When these receptors are activated by various stimuli, the flow of Ca+2 ions into the cell is stimulated (21, 22). Vanilloids are divided into two groups: exogenous and endogenous (23). Examples of endogenous vanilloids are pH changes and high temperature changes due to inflammation, and exogenous vanilloids include resinferatoxin, anandamide, found in cathus, and CAP, the active ingredient of hot pepper (24). CAP is the most commonly used exogenous vanilloid in the study of these channels (25).

TRPV1, pain transmission and inflammation-induced thermal hyperalgesia has been held responsible for the activation (26). By modulating TRPV1, which is located on the peripheral endings of nocireceptors that provide pain perception, perception of pain messages in the somatosensory system and the development of inflammatory thermal hyperalgesia can be achieved. By understanding the mechanisms underlying the modulation of TRPV1 by various agents, new treatment opportunities may be offered to reduce pain (27).

TRPV1 channels contain cysteine groups in their structure (28). Cysteines have an antioxidant role in many nerve cells. The amino acid cysteine is a source of many antioxidants such as glutathione (GSH) , lipoic acid and glutathione peroxidase. Studies have shown the regulatory role of GSH and N

acetyl cysteine (NAC) antioxidants in TRPV1 channel activation (29). When the cysteine groups in this TRPV1 structure are activated by oxidative stress and nitric oxide, TRPV1 channels open and NA^{+} and Ca^{+2} flows ocur (30).

2. Migraine

Migraine is a disease that is frequently encountered among neurological diseases, includes gastrointestinal and autonomic symptoms as well as neurological symptoms, has a high economic burden on society, and is characterized by recurrent headaches. While migraine negatively affects individuals' quality of life and business life, it also causes economic losses by increasing drug use (31).

The term 'migraine' means 'hemicrania' in Greek, 'half of the head', and it is known that in most migraine cases, the headache occurs on one side of the head. However, in some cases, it may be observed as bilateral pain in the back or front of the head (32). Patients also reported that they experienced neck pain before or during a migraine attack (33). It has been reported that some migraine patients may have stiffness in the neck area, head tilting forward, and trigger points in the neck muscles (34, 35).

The neurobiological mechanisms and changes in multisensory information processing related to the causes that lead to the onset of a migraine attack have not yet been fully explained. Although significant changes have occurred in recent years in the field of drug development for migraine treatment and various candidate molecules that are relatively selective to pain pathways have been discovered, the expected results have not yet been achieved (36). Thanks to triptans developed especially for migraine, better results have begun to be obtained in the treatment of primary headache disorders. However, despite the success of triptans, excessive drug use is associated with headaches and has significant side effects, although it is not seen in all migraine patients (37). To overcome these problems, monoclonal antibodies targeting calcitonin gene-related peptide (CGRP) and its receptor have recently been developed, but safety problems have been reported as a drawback (38).

3. The role of TRPV1 Cation Channel in Migraine

The role of TRPV1 in stimulating sensory neurons involved in the transmission and determination of pain sensation has been addressed in many studies, and these channels have been shown to be important regulators of nociceptive and inflammatory pain.TRPV1 was the first TRP channel to be extensively studied in migraine and headache. Factors such as capsaicin

(CAP) or resinoferatoxin (RTX), heat, acid, oxidative stress products and endocannabinoids (Anandamide, etc.) that can produce CAP-like effects are called vanilloids. These activate TRPV1 channels. These channels are also activated by prostaglandins and bradykinin. TRPV1 is expressed trigeminal origin in humans which co-express and release CGRP. In recent studies, in the trigeminal ganglion, TRP channels co-localize with CGRP (39), and the number of CGRP and TRPV1 immune reaction cells increase in the trigeminal ganglion of migraine rats.

Migraine-related factors in the trigeminal nerve were evaluated as a result of the application of Xiongmatang extract to mice suffering from experimental migraine. At the end of the study, although the TRPV1 gene increased in the migraine model, it was found to be regulatory in mice given xiongmatang extract. Moreover, according to western blot results, although the CGRP gene was overexpressed in the migraine model, it was decreased in the treatment group (40). In the study conducted by Liao et al., an increase in TRPV1 levels was observed in the trigeminal ganglion cells of rats created as a migraine model with nitroglycerin compared to the control group (41).

Evans et al. suggested that the possible mechanism of action of sumatriptan, an antimigraine drug, is that it blocks TRPV1-mediated calcitonin gene related peptide (CGRP) release and that the TRPV1 channel should be targeted in treatment (42). Another study shows that Zhengtian (ZTP) can significantly improve headache migraine symptoms in drug-administered rats, and TRPV1 may be one of the important molecular mechanisms. It also highlighted the effect of ZTP on TRPV1 protein expression level in both cortex and hippocampus of mice (43).

Martins et al. showed in his study that transient receptor potential TRPV1 stimulation, which is a non-selective cation channel in sensory neurons, can trigger a severe headache attack and the trigeminovascular system can be activated. This results in a nociceptive response and calcium-dependent release of CGRP from the trigeminal nerve terminals in the dura. As a result, TRPV1 activation activates dural nociceptors, causing central sensitization and cutaneous allodynia (44).

To investigate the possible role of TRPV1 levels in migraine progression, a study evaluated the change in TRPV1 levels in plasma, hippocampus and somatosensory cortex in Epidosic Migraine (EM) and Chronic Migraine (CM) groups using a rat migraine model; Somatosensory cortex showed a significantly higher increase in TRPV1 in the CM group than in the EM group. This showed that headache severity and frequency may increase with increasing somatosensory cortex TRPV1 expression level (45).

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