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The role of TRPM8 channels in oxidative stress

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Abstract

The human body, with its innate sensitive ability, tries to keep the free radicals formed due to the natural production of the organism in a line known as oxidant-antioxidant balance. Disruption of this balance is called oxidative stress. The mitochondria constantly produce free oxygen radicals during the body's oxygen consumption. The free oxygen radicals released can be both harmful and beneficial. The role of oxidative stress in the pathogenesis of inflammatory, chronic, or degenerative diseases is known. Transient receptor potential (TRP) channels are non-selective cation channels essential in regulating calcium (Ca^{2+}) concentration in various neuronal and non-neuronal cell types and tissues. It has been reported that excessive Ca^{2+} influx and oxidative stress caused by TRPM8 channel activation play a role in apoptosis. Therefore, the TRPM8 channel may help prevent oxidative stress-induced damage. Additionally, TRPM8 channels regulate Ca^{2+} cell homeostasis and function as a cellular sensor and cold temperature transducer. In this review, we examined the role of the TRPM8 cation channel in situations that may be caused by oxidative stress based on recent studies.

Keywords: Oxidative Stress; TRP Channels; TRPM8 Channel; Ca^{2+}

Introduction

Transient Receptor Potential (TRP) channels are found in the plasma membrane in many cell types, including neurons. TRP channels are involved in numerous physiological and pathological events in response to a variety of extracellular and intracellular stimuli, such as changes in temperature, pH, or osmolarity, injury, depletion of Ca^{2+} stores, as well as volatile chemicals and cytokines [1]. TRP Melastatin (TRPM), a subfamily of TRP ion channels, are transient receptor channels. The TRPM family takes its name from the first recognized member, melastatin, which is a potential tumor suppressor protein. TRPM family includes 8 proteins. TRPM8 channels from the TRPM family function as a regulator of Ca^{2+} homeostasis, a cellular sensor and a transducer of cold temperature [2]. TRPM8 can be activated by cold temperatures and peppermint oil, eucalyptus oil. G proteins, lipid messengers, and polyunsaturated fatty acids also modulate TRPM8 activity. Experimental studies show that TRPM8 channels have an important place in cancer cell proliferation, survival, migration and neurosecretion [3]. In addition to these studies, there are studies showing that the TRPM8 channel is activated in oxidative stress [4].

Oxidative Stress

Oxygen is the most basic substance of the life cycle. Adenosine triphosphate (ATP) is produced using oxygen through aerobic respiration in the mitochondria. The mitochondria constantly produce free oxygen radicals during the body's oxygen consumption. These by-products are generally reactive oxygen species (ROS) and reactive nitrogen species (RNS) formed by the cellular redox process. ROS are molecules with high reactivity as they become highly elevated. ROS may also be released due to normal metabolism in cell organelles other than mitochondria or for reasons such as ischemia-reperfusion, radiation, aging, and exposure to chemical agents. One of the most essential effects of ROS is that it plays a vital role in the formation of cancer by causing damage to DNA due to damage to nucleic acids [5].

The free oxygen radicals released can be both beneficial and harmful. Free radicals are molecules with very high reactivity. They are produced as a result of normal metabolism in the cell or as a result of aging, radiation, high oxygen pressure, exposure to chemicals, or inflammation. At low or moderate levels, ROS and RNS can benefit cellular responses and immune function. They create oxidative stress at high levels, which can damage all cell structures due to losing balance with antioxidants [6].

Oxidative stress plays a role in the pathogenesis of inflammatory, chronic, or degenerative diseases. There are different endogenous or exogenous mechanisms to prevent oxidative stress in the human body. Endogenous sources include the mitochondrial electron transport chain, endoplasmic reticulum, redox cycle, arachidonic acid metabolism, enzymes, phagocytic cells and endothelial cells, and autoxidation reactions. Exogenous sources include cigarettes, pesticides, solvents, petrochemical products, drugs, alcohol, sunlight, stress, radiation, and even some compounds found in food. Endogenous and exogenous antioxidants act as 'free radical scavengers' by preventing and repairing damage caused by ROS and RNS. Therefore, they can strengthen immune defenses and reduce the risk of cancer and degenerative diseases [7].

Transient Receptor Potential (TRP) Channels

Ion channels are responsible for cellular electrogenesis and electrical conduction and are vital for cells. TRP channels were first identified in the photoreceptor cells of the genus Drosophila fruit flies in the 1960s. They are expressed on the plasma membrane in many cell types, including neurons. TRP channels are sensitive to various external factors such as heat, pressure, light, and chemical stimuli and play a role in nerve conduction, pain perception, taste sensation, and thermoregulation processes. TRP channels represent the large family of cation channels [8]. Members of the TRP cation channel superfamily were identified for the first time in photoreceptor cells of the Drosophila genus of vinegar flies. TRP channels are permeable to sodium (Na^{+}), calcium (Ca^{2+}), and magnesium (Mg^{2+}) and are nonselective cation channels. Since the extracellular Ca^{2+} concentration is almost 20,000 times higher than the intracellular one, it is thought that the ions passing through the TRP channels, which open and close depending on the increase or decrease in the Ca^{2+} concentration in the cytosol, are of great importance in maintaining the vital activities of the cell. Cationic flow through these channels, which show activation or inactivation depending on the Ca^{2+} concentration in the cytosol, is essential in fulfilling the cell's vital functions. It is also known that TRP channels are located not only in the plasma membrane but also in cellular organelle membranes. It is suggested that the basic structure of TRP channels consists of regions that cross the membrane six times. It is thought that the hydrophobic ring between the 5th and 6th segments is the ion channel-forming pore and that the NH_2 and COOH ends are located in the cytoplasm [9]. (Figure 1).

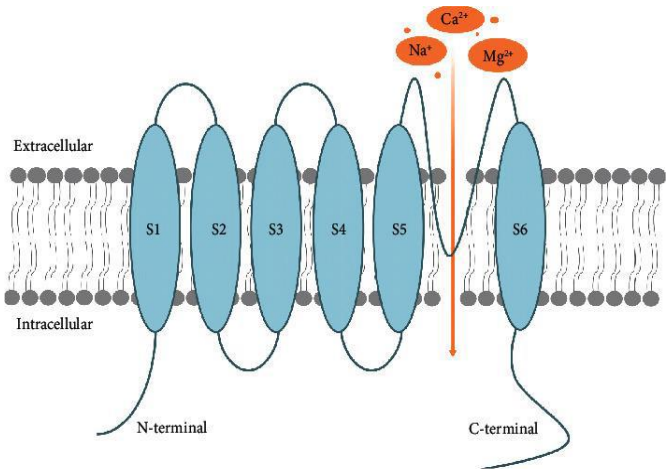

Figure 1. *Schematic representation of TRP channels [10].*

TRP channels in mammals are classified into 28 different types according to their amino acid sequences. These types are further divided into six sub-main families: Ankyrin (TRPA), Canonical (TRPC), Melastatin (TRPM), Polycystin (TRPP), Mucolipin (TRPML), Vanilloid (TRPV) [11]. (Figure 2).

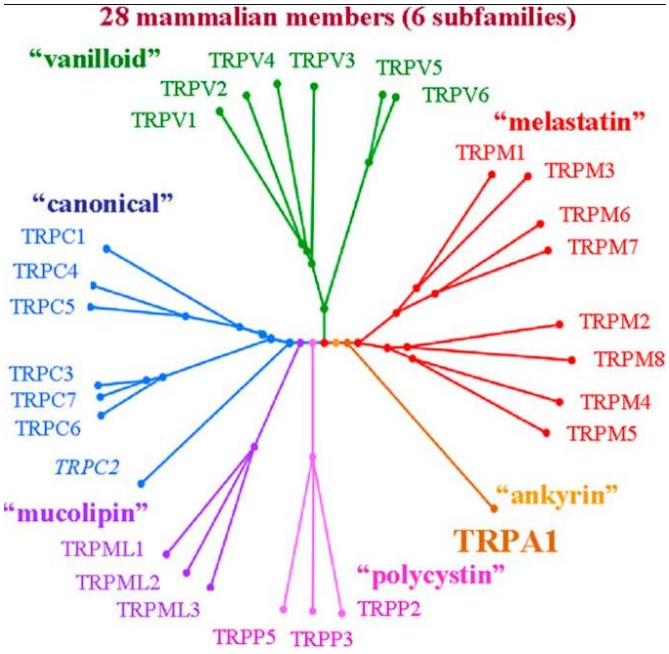

Figure 2. *TRP channel superfamily [12].*

Transient Receptor Potential Melastatin (TRPM) Channels

The TRPM family is the largest subfamily of the TRP family. The family has eight members, from TRPM1 to TRPM8. Members of this family have received increasing attention in recent years as drug targets for the treatment of type II diabetes, cardiovascular diseases, neurodegenerative disorders, inflammation, and inflammatory pain. TRPM subfamily was first identified in mammals as four homologous pairs by being found in tumor suppressor genes. These are TRPM1/TRPM3, TRPM2/TRPM8, TRPM4/TRPM5, TRPM6/TRPM7 [13]. Most TRPM channels are non-selective Ca^{2+} permeable cation channels. Only TRPM4 and TRPM5 channels are impermeable to Ca^{2+}, whereas TRPM6 and TRPM7 channels are highly permeable to Ca^{2+} and Mg^{2+} [14].

Structure and Functions of TRPM8 Ion Channels

The TRPM8 gene has many genetic variations with potential functional and phenotypic consequences. In recent genome-wide association studies (GWAS), the TRPM8 gene was identified as one of the migraine susceptibility genes. TRPM8 is expressed in subpopulations of sensory neurons [15]. TRPM8 is known to play a role in inflammation and neuropathic pain and is classified as a cold and menthol receptor [16]. These are expressed in various tissues, including trigeminal sensory neurons [17, 18]. TRPM8 ion channels regulate Ca^{2+} homeostasis and function as a cellular sensor and cold temperature transducer. TRPM8 has also been shown to be abnormally expressed in various malignant and solid tumors [19] (Figure 3).

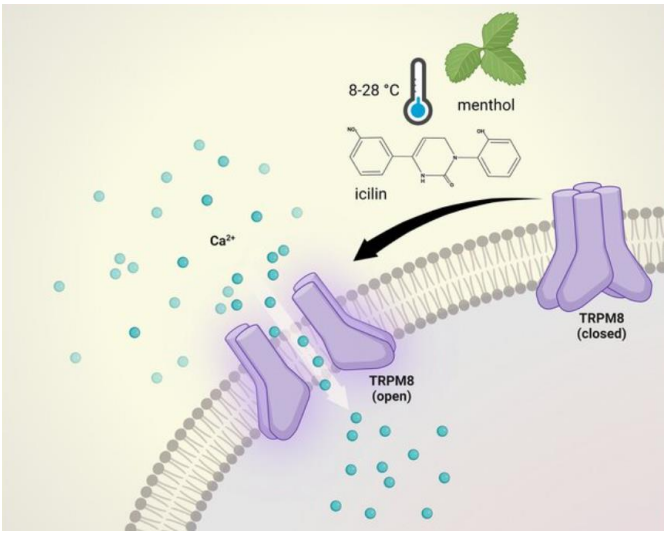

Figure 3. *TRPM8 receptor activation [20].*

In humans, the TRPM8 gene is located in the 2q37.1 region of chromosome 2. The gene spans 102124 bases and contains 25 exons. In humans and rodents, the TRPM8 gene encodes a protein of 1.104 amino acids [21]. The TRPM8 gene encodes the TRPM8 channel, is activated at low temperatures (8 ^{0}C - 28 ^{0}C), and is a non-selective cation channel [22]. TRPM8 is located in A-delta and C fiber afferents. Additionally, it is activated by cold and by several chemical agonists known to produce cold stimuli, such as menthol, icilin, and eucalyptol

[23] (Figure 4).

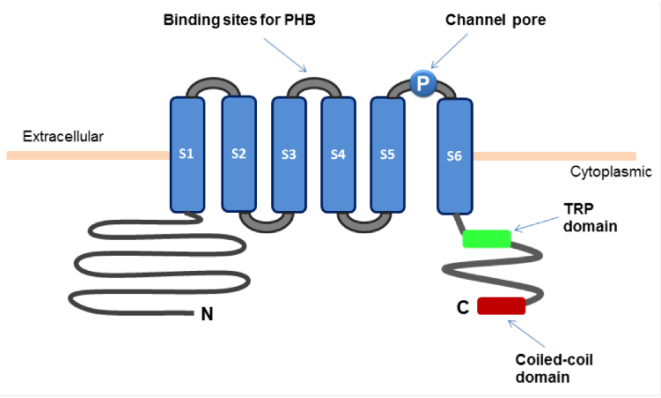

Figure 4. *Schematic diagram for the structure of TRPM8 ion channel [24].*

This channel is generally expressed in peripheral sensory neurons dorsal root (DRG) and trigeminal ganglia (TG) and has been identified as a cold temperature sensor in cutaneous tissue, but is also expressed in deep visceral afferents where cold is unlikely to be a stimulus [25]. In addition, they are expressed at high rates in deep visceral afferents in the prostate, bronchopulmer tissue, bladder, and urogenital system. In the cell, this channel exposes a plasma membrane and has a membrane localization. However, in prostate cancer cells, TRPM8 has also been reported to be detected in the endoplasmic reticulum membrane [26].

TRPM8 oxidative stress relationship

Especially in the last 10 years, TRP cation channels have aroused great interest in understanding the etiology of many inherited and acquired diseases, thanks to the crucial roles of the members of this family in cell functions. A study on the TRPM8 channel observed that Ca^{2+} and oxidative stress parameters increased due to menthol application to breast and prostate cancer cells [27]. A study conducted by Baş et al. found that oxidative stress and ADPR treatments could induce TRPM8 activation and result in excessive Ca^{2+} entry, apoptosis, and mitochondrial oxidative stress [28]. Another study indicated that activation of TRPM8, using a pharmacological agonist, partially reversed the Ang II-induced oxidative stress and JAK2 signaling activation [29]. Oxidative stress increased in mice due to H_2O_2 administration, and it was observed that the increased oxidative stress decreased with the application of the TRPM8 antagonist. This study shows that oxidative stress affects urothelial function, including the TRPM8 channel-mediated mechanism, and that these effects may have critical aging-related effects. [30].

Conclusions and Future Perspectives

This review discusses the relationship of the TRPM8 cation channel with oxidative stress. Since the TRPM8 cation channel is permeable to ions such as Na^+ and Mg^{2+}, especially Ca^{2+}, intracellular ion balance and tissue damage occur due to increased ROS. These activities lead to inflammasome release, mitochondrial production, and apoptosis. Continuing research on TRPM8 is open to promising new developments for diagnosing and treating many diseases. We hope that an important step will be made in discovering TRPM8-specific inhibitors. There is a great need for more research on this subject.

Ethical Declarations

The current study has no study with human and human participants. The study is not subject to ethics committee approval.

Conflict of Interest Statement

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financial Disclosure

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Author Contributions

All of the authors declare that they have all participated in the design, and execution of the paper and that they have approved the final version.

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