Proceedings of the Indian National Science Academy (2026) 92:34–51
https://doi.org/10.1007/s43538-025-00408-z

REVIEW ARTICLE

Physiological regulation and the role of calcium transporters

Agatha Ngukuran Jikah[1] · Great Iruoghene Edo[2,3] · Patrick Othuke Akpoghelie[4] · Joseph Oghenewogaga Owheruo[4] · Endurance Fegor Isoje[5] · Ufuoma Augustina Igbuku[2] · Ephraim Evi Alex Oghroro[6] · Emad Yousif[3] · Khalid Zainulabdeen[3] · Arthur Efeoghene Athan Essaghah[7] · Dilber Uzun Ozsahin[8,9,10] · Huzaifa Umar[10] · Ahmed A. Alamiery[11]

Received: 26 November 2023 / Accepted: 26 February 2025 / Published online: 5 March 2025

Abstract
Signalling of calcium ions is vital for the normal physiology and survival of cells. Membrane bound organelles like the mitochondria and many other cell-bound proteins and receptors play significant roles in regulating intracellular calcium levels thus maintaining homeostasis of the external and internal cell environments. The regulation of cellular calcium levels is necessary because more or less readings result in detrimental consequences even as grave as cell death. In this review, we consider several families of calcium transporters, some that allow its entry into the cell and others that regulate its efflux from the cell when intracellular levels are abnormal. The TRPV1, TRPV2, TRPV4, TRPM7, calcitonin receptor, calcium sensitive receptor, G-Protein coupled receptors, mitochondrial calcium transporters, calcium uniporter channels, SERCA and PERCA are discussed in details.

Keywords Calcium · TRPVI · TRPV2 · TRPV4 · TRPM7

Introduction

Organisms through regulation of their own intrinsic dynamics manifest a certain ability to put up with the consequences of a disruption arising from changes in their internal or external environments (Vergara et al. 2019). Physiological regulation may therefore be seen as the body's ability to retain a stable internal environment amid changes in external situations (Billman 2020). Different ions and hormones acting as chemical messengers play a great role in effecting communication between different cells, tissues and organs of the body. Within the body, many important cellular processes are regulated by Ca^{2+} channels so that in any instance of an abnormality in the functioning of these ions, there

✉ Great Iruoghene Edo
greatiruo@gmail.com

1 Department of Pharmacy, Faculty of Pharmacy, Near East University, Nicosia, Cyprus

2 Department of Chemistry, Faculty of Science, Delta State University of Science and Technology, Ozoro, Nigeria

3 Department of Chemistry, College of Sciences, Al-Nahrain University, Baghdad, Iraq

4 Department of Food Science and Technology, Faculty of Science, Delta State University of Science and Technology, Ozoro, Nigeria

5 Department of Biochemistry, Faculty of Science, Delta State University of Science and Technology, Ozoro, Nigeria

6 Department of Petroleum Chemistry, Faculty of Science, Delta State University of Science and Technology, Ozoro, Nigeria

7 Department of Urban and Regional Planning, Faculty of Environmental Sciences, Delta State University of Science and Technology, Ozoro, Nigeria

8 Department of Medical Diagnostic Imaging, College of Health Sciences, University of Sharjah, P.O. Box 27272, Sharjah, United Arab Emirates

9 Research Institute for Medical and Health Sciences, University of Sharjah, P.O. Box 27272, Sharjah, United Arab Emirates

10 Operational Research Centre in Healthcare, Near East University, Nicosia, Cyprus

11 Al-Ayen Scientific Research Center, Al-Ayen Iraqi University, AUIQ, P.O. Box: 64004, An Nasiriyah, Thi Qar, Iraq

may be destructive effects on cells (Newton et al. 2016). Some roles within biological systems which are unique to Ca^{2+} are; the generation of electrical signals and membrane potentials, signalling the central cell molecule and the more implicated role of initiating a multitude of cellular processes (Sinenko et al. 2021). The concentration of calcium ions within a cell may differ based on the location. For instance, calcium channels when at rest, promote the maintenance of a very low concentration (10(− 7) M) of calcium within the cell's cytoplasm. This concentration is 1000 times less than that on the outside of the cell. As earlier stated, grave and deleterious consequences including apoptosis can occur from dysfunctional regulation of calcium concentrations since calcium is responsible for regulating nearly all aspects of the cell's function. To avoid such an occurrence, the concentration and signalling processes of calcium in the cell must be tightly regulated (Matuz-Mares et al. 2022). Channels through which calcium is transported between the intracellular and extracellular space are called calcium channels and as their name suggests, these channels are permeable to calcium ions and thus play essential roles in the normal physiology of all eukaryotic cells (Pistritto et al. 2016). These channels function primarily to regulate the levels of calcium within the cell and its compartments. Generally speaking, ion channels present as pore-forming integral membrane proteins consisting of different blends of subunits. These subunits embedded in cell membranes connect with each other forming a channel in the membrane that allows specific ions to go through. The three major components of ion channels are; an ion-permeable pore to provide a pathway for ions, a selectivity filter to provide ion specificity and a gate that controls ion flow (Öster et al. 2022). Calcium channels are of varying forms and differ in both function and structure. In mammals, four major families of these channels are known, namely: Two-pore channels (TPCs), inositol 1,4,5-trisphosphate receptors (IP_3Rs), transient receptor potential (Trp) channels and ryanodine receptors (RyRs) (Jin et al. 2020). RyRs and IP_3Rs channels release Ca^{2+} from endoplasmic reticulum (ER) following the production of cyclic ADP ribose (cADPR) or intracellular messengers IP_3 and Ca^{2+} (IP_3Rs), TPCs channels which are nicotinic acid adenine dinucleotide phosphate (NAADP)-activated channels are in charge of releasing Ca^{2+} from acidic organelles like lysosomes while Trp channels like TrpM, TrpML and TrpP2 are responsible for the release of Ca^{2+} from intracellular stores (Ernst et al. 2013). The responsibility of maintaining the balance between influx of calcium into the cell and efflux of calcium out of the cell is that of calcium channels. Signalling molecules, membrane depolarization and the activity of physical forces (heat) on the membrane are some ways by which calcium channels can be stimulated (Beghi et al. 2022). It is the aim of this review to give an overview of some of these channels, stating their roles in calcium regulation and consequent regulation of physiology in different parts of the body.

Methodology

The research papers used in this review paper were retrieved from prominent database sources like Academia.edu (https://www.academia.edu), PubMed (https://pubmed.ncbi.nlm.nih.gov/) and Web of science (https://access.clarivate.com). Free text keywords were such as "TRPV1 receptors", "TRPV2 calcium channels", "G-protein coupled receptors", "structure of TRPV4 Protein", "calcium sensitive channel", "Mitochondrial calcium ion transporter", "functions of TRPM7 in the nervous system", "expression of TRPV2 in the nervous system" "calcium sensitive receptor function", CaSR in the cardiovascular system" plasma membrane channels", "expression of TRPV1 in the CNS", "functions of NCLX Protein" and other related information from related journals.

The descriptions of various calcium channels

Plasma membrane calcium channels

Plasma membranes are critical points where calcium channels carry out their functions of regulating the influx into and efflux of calcium ions from the cell (Qu et al. 2022). Voltage-gated calcium channels which function to swiftly transport calcium into the cytoplasm are among the most important types of calcium channels (Senatore et al. 2016). They act in response to an alternation in voltage athwart the cell membrane usually propelled by an electrochemical gradient. These channels are particularly critical for the initiation of various processes within the cell; gene transcription and muscle contraction to mention but a few. Other calcium channels that regulate the efflux of calcium from the cell and thus bring about a low cytosolic level are; the sodium/calcium ion exchanger (NCX) and the plasma membrane calcium ATPase (PMCA) pumps (Brini and Carafoli 2011). These calcium efflux channels are crucial to the cell in that before calcium can be used as a second messenger, a low cytosolic concentration must be attained. Moreover, the channels are also requisite for bringing calcium dependent cellular processes to termination points. Sensory cells and neurons are other examples of cell types that have distinctive varieties of calcium channels on their plasma membranes. Eventually, it can be said that the plasma membrane serve as an essential location for calcium channels both providing a source for calcium and a milieu for egesting it (Brini and Carafoli 2011).

The movement of Ca^{2+} along its concentration gradient athwart the plasma membrane and into cells is supported by some plasma membrane channels; Voltage-gated

Ca^{2+} channels (Ca_v family), store-operated Orai channels and transcient receptor channels. These are among the various calcium channels that are implicated in Ca^{2+} influx. Usually, these channels are activated only upon depolarization of the plasma membrane and are required for refilling of intracellular Ca^{2+} stores after the release of Ca^{2+}. They are also crucial components in a multitude of signalling pathways (Dixon and Trimmer 2023).

The PMCA pump

The pump was discovered by Schatzmann as an ATP-driven system that excluded calcium from erythrocytes. Initially, most of the work concentrated on erythrocytes, but then spread gradually to other cells, including those of excitable tissues, where a larger calcium extrusion system, the sodium/calcium exchanger, predominates quantitatively. The pump was secluded and purified using a calmodulin column (Brini and Carafoli 2011). The pump operates with high calcium ion affinity and low transport capacity with a 1:1 calcium ion/ ATP stoichiometry. It functions as a calcium ion/hydrogen exchanger, but the matter of calcium ion/ hydrogen ion stiochiometry is still controversial. Recently, the activity of the pump in native membranes has been found to be insensitive to the variations of the membrane potential, showing an electroneutral hydrogen ion and calcium ions reaction (Brini and Carafoli 2011). Under optimal conditions the calcium ions affinity of the PMCA pump is lower than that of the SPCA pumps, although high enough to enable it to operate with reasonable efficiency even under the calcium concentration conditions prevailing in most cytoplasms at rest. More recently, however, synthetic peptides of the caloxin family peptides of which several have been tested, bind to the extracellular domains of the pump and could thus in principle be used to repress the PMCA pump in intact cell systems. They have also been asserted to have isoform-specific inhibitory properties (Boutin et al. 2022). Following its cloning, the PMCA pump showed the same essential membrane organization and topology properties of the SERCA Pump, which had already been realised at the time of the cloning. The catalytic phosphorylation site as expected is conserved as are other important consensus domains, but prominent sequence/domain different with respect to the other two calcium ions pumps also exist for instance, in the first cytosolic loop that contains an acidic phopholipid binding domain and especially in the long cytosolic COOH-terminal tail, which is absent in the SERCA and SPCA pumps (Boutin et al. 2022). Comparing it with the sequence of the SERCA pump also reveals important difference in the amino acids that contribute to the formation of the calcium ion binding sites. As already mentioned, one essential acidic residue that contributes coordinating oxygen to site 1 of the SERCA pump is missing in transmembrane domain 5 of the PMCA pump which thus does not have site 1. As in the case for site 2 of the SERCA pump, the residues that coordinate calcium ions in the single PMCA site are part of the transmembraned domains 4 and 6 (Marisa Brini and Carafoli 2009). Intriguingly, the insertion of the missing acidic residue in transmembrane 5 of the PMCA pump by a mutagenesis approach raised its calcium ions/ ATP stoichiometry to 2, suggesting the formation of a second calcium ion binding site which matches to site 1 of the SERCA pump (R). The domains, the major among them being the calmodulin binding domain, has the canonical amphipathic helix secondary structure of calmodulin binding domains (Marisa Brini and Carafoli 2009). Calcium ions binding motifs recognized upstream and downstream of the calmodulin binding domain could exhibit regulatory roles on the pump's activity. Other mechanisms by which the pump is activated are the protein kinase A and protein kinase C, a polymerization process implicating the calmodulin binding sequence in the COOH-terminal tail of the pump, and the cleavage by calpain. The cleavage by calpain happens immediately upstream of the COOH-terminal calmodulin binding domain and irreversibly activates the pump, making it insensitive to calmodulin (Yang and Tsai 2022). This irrevocable mechanism of activation could become important in situations of pathological calcium ions overload that would need increased exporting ability of calcium ions (Bootman and Bultynck 2020).

The PMCA pump in cardiovascular disease Hypertension is a major risk factor for cardiovascular disease, affects approximately 30% of the adult population globally (Adhikary et al. 2022). The genome-wide association studies of diastolic and systolic blood pressure has for the past 5 years reported the most important single nucleotide polymorphisms associated with these diseases to occur at multiple loci in and around ATP2B1, the gene which encodes PMCA1(Adhikary et al. 2022). This result is same amongst several ethnicities including those of South Asian, East Asian and Europe; two studies carried out in African-American populations however demonstrated no relations between ATP2B1 and hypertension. Although the effects of ATP2B1 variants on diastolic and systolic blood pressure are small, just about 1 mmHg, Levy (1996) predicted the risk of developing hypertension to increase by 17 and 37% dependent on whether one or two respective alleles are affected. This result of a link between ATP2B1 and hypertension are not limited to adults because a certain investigation found that ATP2B1 single nucleotide polymorphism rs2681472 is linked with an increased risk of hypertension in Chinese children (Levy 1996), and the same single nucleotide polymorphism also predisposes Chinese women to early-onset preelampsia during pregnancy. Cardiovascular diseases other than hypertension are also demonstrated to be associated by genetic association and candidate

gene studies with ATP2B1. Some studies currently show that single nucleotide polymorphism in the ATP2B1 locus is capable of increasing the risk of coronary artery disease and myocardial infarction in Caucasian and Asian populations (Kim et al. 2024). Mutations also link with many cardiovascular disease risk factors such as coronary artery calcification and salt sensitivity in chronic kidney disease (R). These investigations collectively show the significance of PMCA pumps in human health and its possible functions in cardiovascular disease, and collectively suggest that PMCA may have critical functions in calcium clearance and homeostasis in endothelial cells and vascular smooth muscle.

The TRPV1 channel

The Transient Receptor Potential Vanilloid 1 (TRPV1) channel is a polymodal (responds to heat and other chemicals) ion channel with functions widely linked to the generation of pain (Shuba 2021). TRPV1 channels are expressed largely on nociceptive afferent fibres within the entire body (Aleixandre-Carrera et al. 2021). TRPV1 channels have also been described as non-selective cation channels seeing that several agonists of exogenous and endogenous nature like; vanilloid capsaicin, low pH voltage, noxious heat and various lipids (like *N*-arachidonoyl-dopamine NADA, eicosanoids and anandamide) all activate this receptor (Ciardo and Ferrer-Montiel 2017). A functional TRPV 1 receptor will possibly exist as a heteromeric or homomeric complex composed of four subunits that organize to form functional cation-porous apertures. Upon the activation of TRPV1, many signalling pathways are either activated or inhibited (Corradi et al. 2019), for instance, when the cell is at a negative holding potential, this activation leads to an influx of sodium and calcium ions bringing about a depolarization of the cell (Rorsman and Ashcroft 2018). Normally, upon exposure to a noxious stimulus, TRPV1 channels found on the sensory nerve endings unlock and depolarize the membrane thereby initiating action potentials that travel to the central nervous system (CNS), undertaking sensory neurons' afferent functions (Shuba 2021). Electrophysiological recordings and binding assays agree to a great extent that for this channel to be completely activated, at the least, two capsaicin molecules must be bound to it (Liu et al. 2020). Although TRPV1 is mostly expressed in the sensory neurons as a dictator of stimuli from pain and heat, it can also be seen without the sensory nervous system in areas like the adipocytes, skeletal muscle, immune cells and epithelial cells. This means that in addition to afferent functions, the TRPV1 channels also have contributions to efferent functions of sensory neurons (Abdalla et al. 2022). This efferent function is realized through the action of released mediators on adjacent cell types by the target tissue seeing that the peripheral terminals of some of the sensory neurons largely dispersed in the skin and internal organs of the body can upon been stimulated by capsaicin, release their transmitter content (e.g. neuropeptides) (Coles et al. 2017). TRPV1's involvement in pathological and physiological processes in a number of tissues (like the urogenital, respiratory and cardiovascular systems) is linked majorly to the ability of these capsaicin- sensitive nerve endings to release neuropepetides for their efferent functions. In these extra sensory nervous system locations, TRPV1 channels are usually activated by a mixture of pro-inflammatory molecules, endovanilloids and vanilloids to elicit carcinogenesis, muscle constriction and cell division (R). Figure 1 illustrates the TRPV1 channel.

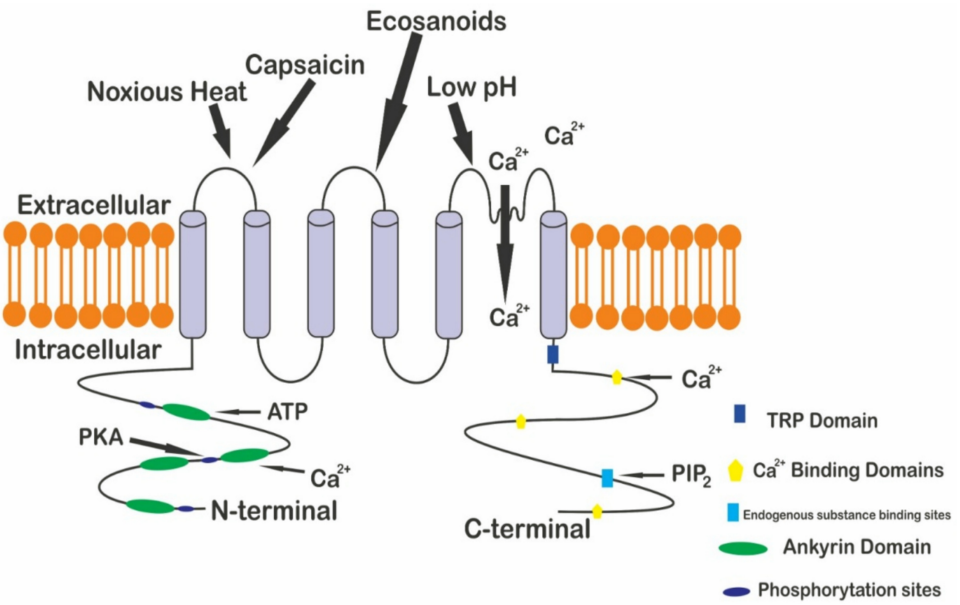


Fig. 1 The TRPVI calcium channel

The presence and functions of TRPV1 in the nervous system

TRPV1 in the CNS modulates both neuronal and glial activity, mediating a range of pathways from synaptic transmission and plasticity to glial reactivity (Meza et al. 2022). Although present in the entire CNS, the TRPV1 channel found at the sensory neurons of the dorsal root ganglion is the most robust of all. Documentations from investigations of TRPV1 expressions in the CNS that were carried out using a combination of immunocynochemistry, radioligand binding and knockout mice exist (Matsushita et al. 2018), the investigations show that TRPV1 is mainly localized in the hippocampus and cortex. Some of the studies state that the olfactory, dentate gyrus, hypothalamus, locus coeruleus, spinal cord and superior colliculus all have expressions of TRPV1 (Zahola et al. 2019). A report (that used a mouse model) however indicated that expressions of TRPV1 in the CNS are limited and contest to the reports of its widespread presence outside of the nociceptors in the sensory ganglia. The report claimed that the channel's expression was constrained to the hippocampus, the posterior caudal hypothalamus, the periaqeductal grey and the rostral midbrain (Koivisto et al. 2022). Despite this incongruence concerning how exactly TRPV1 is expressed in the CNS, its presence there at least indicates that the channel has broad functions that are not limited to sensory transmission (Bennett et al. 2019). Within the cell, TRPV1 is expressed in synapses and cell bodies but mostly on the post-synaptic dendritic spines of synaptic vesicles and neurons. In the neuritis and cell bodies of both neurons differentiated by retinoic acid induction and sensory neurons also, TRPV1 is highly expressed (Gomez et al. 2020). The cells of retinal ganglion also express TRPV1 in discrete pockets in axons and in soma. Furthermore, the microglia and asrocytes have also been found to express the TRPV1 protein (Wang et al. 2022). TRPV1 is found to be up-regulated in both developing neuritis and cell bodies during the retinoic acid- prompted differentiation of neuroblastoma cells into neurons. Moreover, activating TRPV1 can also result in the retraction of growth cones as well as the creation of varicosities along neurites (Kalinovskii et al. 2022). Recent studies have suggested that other than neurites and growth cones, TRPV1 can also regulate synaptic transmission. TRPV1 is further found to colocalize with synaptic proteins at filopodia tips in diagnosis related groups (DRGs) cell lines resulting in vesicle fusion. This is suggestive that TRPV1 is a modulator of neurotransmitter discharge (Andresen 2019). Solitary tract neurons also require TRPV1 for the release of asynchronous glutamate. In addition to this, the release of dopamine is also subject to TRPV1 activation. Upon activation by capsaicin in the ventral tegmental area, the release of the neurotransmitter dopamine is initiated (Zhong et al. 2021). TRPV1 activation by capsaicin in neuroblastoma cells gets intracellular calcium levels to be elevated resulting in the increase of norepinephrine from its vesicles. Activation of TRPV1 in the peripheral nervous system brings about an increase in calcium release that further leads to the release of calcitonin gene- related peptide and neuropeptides substance (Zhai et al. 2020).

The TRPV2 channel

The transient receptor potential vanilloid type 2 (TRPV2) also belongs to the TRPV family. It was identified by two teams working independently and using different procedures (Ribeiro et al. 2022). TRPV2 comprises of a large N-terminal domain that contains about 390 amino acids. The location of the gene encoding TRPV2 is on chromosome 11, a location 10 Mb apart from TRPV1 (Santoni and Amantini 2019). TRPV2 is a non selective cation channel that is also permeable to calcium (Pottosin et al. 2015). It can like TRPV1 also be activated by heat (> 52 °C) but additionally, mechanical stress, cannabidiol, and other synthetic ligands (probenecid, 2-aminoethoxydiphenyl borate (2-APB) also activate this channel. TRPV2 is ubiquitously expressed within the body and its expression level may be high in certain types of cells and tissues. It can be found in the intestinal and gastric neurons, lungs, eye, endoplasmic reticulum, spleen, brain and spinal cord, in red blood cells among other numerous cells (Haustrate et al. 2020). Unlike the TRPV1, TRPV2 is expressed within the central nervous system in different areas like in the neurons of the forebrain, the supraoptic nucleus, arcuate nucleus, paraventricular nucleus, nucleus ambiguous, hypoglossal nucleus and the nucleus of the solitary tract (Santoni and Amantini 2019). When these cells are stimulated by phosphtidylinositol 3-kinase- activating ligands, mechanical stress or cannabidiol, osmoregulation and a regulation of the autonomic nervous and cardiovascular systems occur, stomach and intestinal muscles are relaxed and GI transit is promoted. In addition to been regulated by heat and different ligands, other lines of evidence suggest that the TRPV2 channel can also be regulated by mechanical stress. (Froghi et al. 2021) reported that membrane stretch on the TRPV2 channel also causes its activation and consequent release of calcium ions. The results further showed that applied membrane stretch also brings about the movement of TRPV2 from the intracellular pool to the plasma membrane. TRPV2 can therefore be viewed as a stretch- activatable calcium channel. 2-APB was also confirmed to be an activator of the TRPV2 channel, although a consequent study demonstrated that this occurs not in human but mice species. The plant *Cannabis sativa* finds application in herbal medicines used against pain, the plant is composed of many cannabinoids (cannabinol, cannabidiol, tetrahydrocannabivarin, e.t.c). However, it is unknown if cannabis induces the translocation of TRPV2

to the plasma membrane (Odieka et al. 2022). Probenecid is another activator of the TRPV2 channel and it is shown to do so directly. Inhibitors of TRPV2 may be recognized including tranilast, ruthenium red and etc. Figure 2 gives an illustration of the TRPV2 calcium transporter.

The role of TRPV2 in cancer cells

The TRPV2 channel finds expression as revealed by numerous studies in some kinds of tumour cells such as bladder and prostate tumours. Its presence is also recorded in hepatocellular carcinoma (Bernardini et al. 2019). In some cancer types, it is thought to be involved in migration, growth and cell death. A considerable expression of the channel is also seen in bladder cancer. When (Siveen et al. 2020) investigated the expression of TRPV2 channel in bladder cancer cell lines and discovered that a larger amount of TRPV2 are expressed by poorly differentiated cell lines as compared to cell lines that were well differentiated. The team also demonstrated that administering CBD which activates TRPV2 brought about cell death but only in the cell lines with poor differentiation. They thus projected that TRPV2 is a possible therapeutic target. Additionally, the expression of TRPV2 is also observed in prostate cancer and especially in metastatic cancer patients. Lysophosphatidylinositol and lsophosphatidylcholine instigate the migration of TRPV2 to the plasma membrane.

The functions of TRPV2 in the immune system

In the immune system, TRPV2 is concerned with both adaptive and innate immune responses although the roles in innate immune response appear more prominent. In macrophages and monocytes too, an abundant expression of TRPV2 is observed (Wu et al. 2023). Upon activation by the chemotactic peptide fMet-Leu-Phe, sustained elevation of calcium ions are evoked and TRPV2 is translocated from the endoplasmic reticulum to the plasma membrane. In the phagocytosis of macrophages, TRPV2 is implicated in the signalling pathway triggered by Toll-like receptor 4

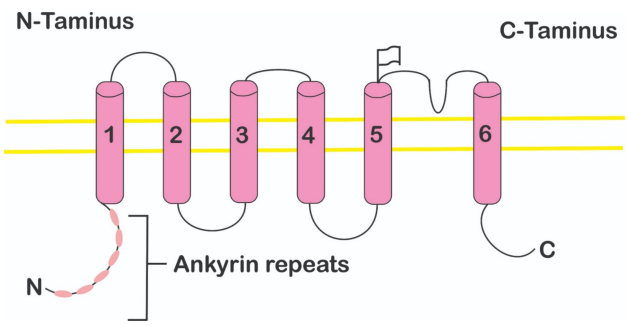


Fig. 2 The TRPV2 calcium transporter

(Entin-Meer and Keren 2020). In granulocytes, TRPV2 is also expressed and thought to be likely involved in regulating the migration of granulocytes. In mast cells also, oligomerization and cell surface expression of TRPV2 is observed. For instance, the pro-inflammatory degranulation of mast cells is a function of a TRPV2-Kinase A signalling module couple. Adding to the innate immune response, TRPV2 is also concerned with adaptive immunity, in the T lymphocytes for example, TRPV2 are expressed both in $CD4^+$ and $CD8^+$ T cells.

The functions of TRPV2 in the nervous system

Been initially characterized as a channel that is activated by heat, its function in nociception was also investigated by numerous studies which discovered that mutant mice that lacked TRPV2 did not exhibit abnormalities in thermal sensing and hence, no information as to the role of TRPV2 in thermal sensing (Mickle et al. 2016). However, its presence in trigeminal ganglia and DRG neurons makes reasonable the thought that it functions in nociception. During the development of neurons of the brain and spinal cord also, expression of TRPV2 is observed (Salzer et al. 2019). In the paraventricular and supraoptic nucleus parts of the hypothalamus also, the expression of TRPV2 is considered critical for osmoregulation. TRPV2 also finds expression in the myenteric plexus which indicates that the channel is also expressed in afferent neurons (Mecawi et al. 2022). Even though some details about the TRPV2 channel have been outlined, various uncertainties yet remain, for instance, the vesicles that carry TRPV2 and the medium for endocytosis and exocytosis all need identification.

The TRPV4 channel

The TRPV4 is the last member of the TRPV family and it has close homology to TRPV1. It was initially related as an osmosensor that opened in reaction to hypotonic swelling of the cell (Saldías et al. 2021). The TRPV4 ion channel protein which was originally known as “vanilloid-receptor related osmotically activated channel” is encoded by the TRPV4 gene (Rosenbaum et al. 2020). This protein channel consists of 871 amino acids and is located mainly in the transmembrane region but with some part situated in the cytoplasm (the human TRPV4 gene is located on chromosome 12q23-q24). This non-selective cation channel is characterized with a moderately high permeability for calcium ions. TRPV4 is extensively expressed in the immune, nervous, cardiovascular, urinary, and digestive and respiratory systems. It is also expressed as a plasma membrane channel in almost all ocular structures and in cilia and intracellular stores also, it performs some possible auxiliary functions (Zhang et al. 2023). Some earlier reports dictated that the

TRPV4 channel could not solely be activated by heat but this was latter made void as osmotic stress was seen to be significantly increased as did body temperature (Toft-Bertelsen et al. 2019). Mechanical force, physical and chemical (endocannabiboids, arachidonic acid, epoxyeicosatrienoic acid) stimuli, protein kinase C and the derivates of phorbol ester are others besides temperature that activates this channel and upon this activation, calcium based cations rush into the cyptoplam to sustain signal transmission, osmotic pressure stability and signal transmission. The permeability of TRPV4 for calcium greatly becomes reduced when two amino acids D672 and D682 are neutralized. While this action reduces the permeability of calcium, it on the other hand, increases the passage of monovalent ions (K^+, Na^+, Li^+) (Kemény and Ducza 2022). In skin cells, activation of TRPV4 leads to the promotion of mechanical responses of endothelial cells and subcutaneous fibroblasts manifested as skeletal muscle relaxation and vasodilation. During the onset of neural and vascular development also, activating the TRPV4 channel of neurons and capillary endothelial cells further activates downstream phosphatidylinositol 3-kinase thus inducing the activation of α-integrin protein, which facilitates the remodelling and localization of the endothelial cells and neurons (Yu et al. 2019). When TPRV4 is activated in adipocytes, the synthesis of fatty acid is increased and fatty acid oxidation is attenuated to reduce heat production. Wound healing, cell proliferation, cell and tissue regulation, production and secretion of aqueous humour, lens contractility and accommodation, neural excitability, regulation of epithelial and endothelial barriers and cell death are some other likely functions carried out upon TRPV4 activation. The Prolonged exposure of TRPV4 to heat stress leads to a reduction in the expression of the channel. Figure 3 is an illustration of the TRPV4 transporter.

The presence and function of TRPV4 in the CNS

TRPV4 are widely distributed in CNS been found in the endothelial cells or in neurons. Numerous authors have shown that the activation of the TRPV4 channel by physiological temperature leads to a slim depolarization of the resting membrane potential in hippocampal neurons (Marini et al. 2023). Furthermore, disease states like hyperthermia can also enhance the activation of the TRPV4 channel and lead to brain edema (Nazıroğlu et al. 2020). Contrariwise however, activating TRPV4 after an ischemic stroke reduces the size of the brain infraction and further brings about stronger neurogenesis. Moreover, the modulation of the microglia cells by lipopolysaccharide (LPS) is seen to be repressed upon the activation of TRPV4. TRPV4 also works jointly with TRPV1 in the feeding of related neuroendocrine cells mediated by glucocorticoid regulation (Xie et al. 2021). TRPV4 is also expressed in the astrocytes which are a heterogeneous group of glial cells. Astrocytes are known to perform functions of maintaining cerebral blood flow and controlling systemic circulation, modulating synaptic transmission and the release of neurotransmitter, enhancing brain development. These cells are thus vital for providing the functional and structural integrity of the CNS. The position of astrocytes within the CNS is also such that they can easily make several contacts with brain capillaries from one end and neuronal synapses on the other end. In this way, the regulate communication between the vascular system and the neuronal cells while also sensing changes in the neuronal synaptic activity. Astrocytic TRPV4 particularly have been shown to be involved in cell volume control, neuronal excitability, regulation of brain blood flow and neurovascular coupling (Tureckova et al. 2023).

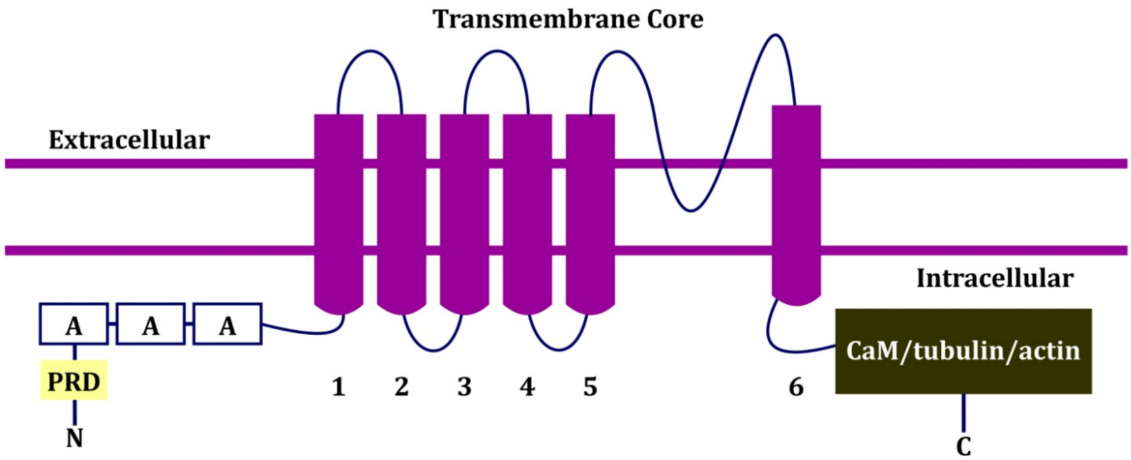


Fig. 3 The TRPV4 calcium transporter

The function of TRPV4 in cell migration and motility

Reports from some studies have stated that the activation of TRPV4 reduces migration of neuroendocrine cells while mediating the migrations of both pulmonary artery smooth muscle and AA-induced migration of endothelial cells (Lee et al. 2017).

The TRPM7 channel

TRPM7 is an outwardly-rectifying divalent cation channel that is permeable to a number of metals, especially Ca^{2+} and Mg^{2+}. TRPM7 uniquely contains a protein kinase domain that is fused to the C-terminus of an ion channel. The channel belongs to the melastatin- related subfamily of transient receptor potentials. Given its widespread cell and tissue localization, it has also been suggested that TRPM7 provides a general means of cell entry for a variety of trace metals including Zn^{2+}, Ni^{2+}, Ba^{2+}, Co^{2+}, Mn^{2+}, Sr^{2+}, and Cd^{2+}. According to recent studies, TRPM7 plays a vital role in homeostasis, mg^{2+} absorption and also carries out a variety of other functions in the mammalian cell. TRPM7 was found located in melanocytes and in increased levels, it was present in metastatic melanoma cells (Cordier et al. 2021). In these cells, TRPM7 was seen to guard the melanocytes from death. Been able to detoxify the intermediates of melanin, it is thought that the ion channel will serve a significant factor in the homeostasis of melanocytes (Yee et al. 2014). TRPM7 according to other reports, is implicated both in pathological and physiological processes, counting; organogenesis, embryonic development and organism survival TRPM7's kinase domain is thought to be vital for cell growth and proliferation either through chromatin remodelling or eEF2-kinase activation and likewise has TRPM7's ion channel region been believed to important for cell survival through regulation of Mg^{2+} homeostasis in cells (Jiang et al. 2021). From non-neural cells also, a significant function of TRPM7 in membrane trafficking has been described, in this effect; TRPM7 is implicated in presynaptic vesicle recycling in both PNS neurons and neuroendocrine cells. It is reported also that TRPM7 may regulate the release of positively charged acetylcholine in PNS sympathetic neurons during vesicle fusion (Zhang et al. 2023). In Fig. 4, we pictorially represent the TRPM7 transporter.

Functions of TRPM7 in the nervous system

TRPM7 exist ubiquitously in the nervous system where it regulates some animal behaviour like memory and learning in rat models (Held and Tóth 2021). Moreover, investigations carried out in neural cells indicated that TRPM7 plays a vital role in anoxic cell death (Sun et al. 2020). During

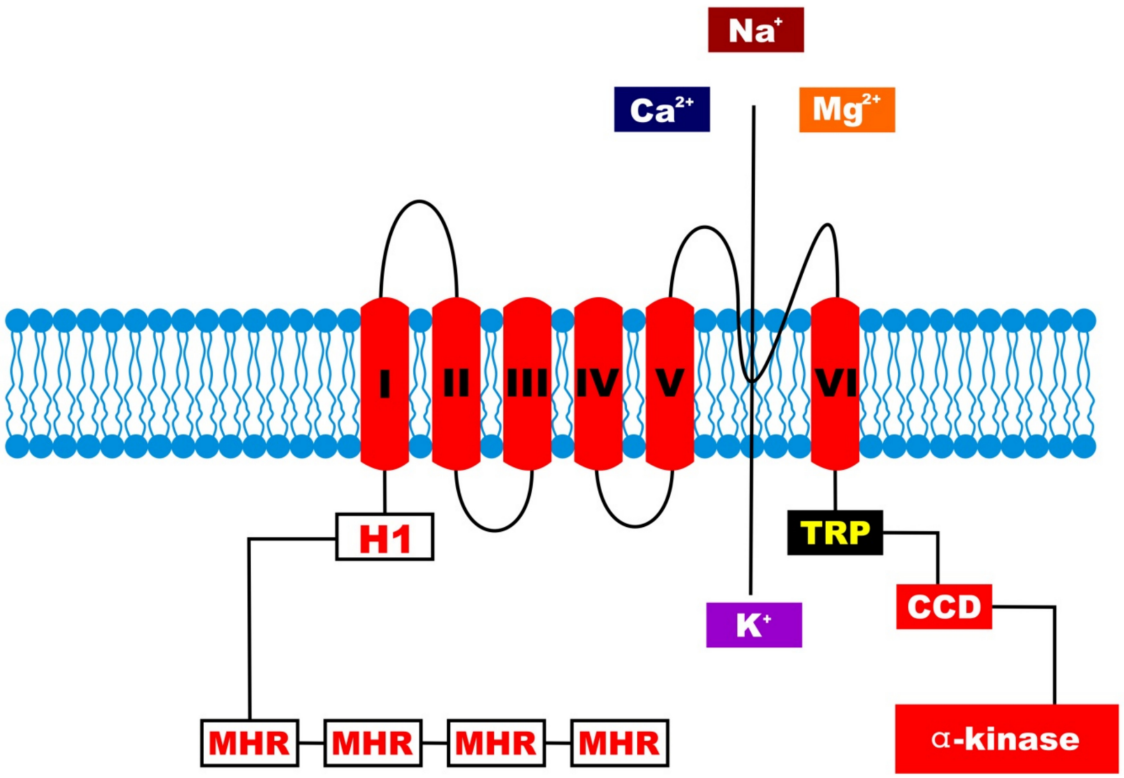


Fig. 4 The TRPM7 calcium transporter

the development of neuronal cell death which followed oxygen and glucose depletion, a TRPM7-like Ca^{2+} current was observed. Additionally, a siRNA-induced knockdown of TRPM7 blocked Ca^{2+} uptake, manufacture of free radicals and apoptosis. Other investigations also indicated that following brain ischemia, the reduction in levels of Mg^{2+} and Ca^{2+}, observed were implicated by TRPM7. In the membranes of synaptic vesicles in noradrenergic neurons also, TRPM7 was found localized. This resulted in the channel forming complexes with proteins of other synaptic vesicles like synaptotagmin I and synapsin I. Furthermore, the release of acetylcholine and the fusion of small synaptic vesicles required TRPM7 ion channel activity (Jiang et al. 2021).

The calcium sensitive receptor (CaSR)

The Ca^{2+}-sensing receptor (CaSR) is a cell surface protein which belongs to the family of G-protein coupled otherwise known as seven transmembrane domain receptors (Hannan et al. 2019). CaSR was discovered in 1993 as the first membrane receptor that had ion sensing abilities (Sundararaman and van der Vorst 2021). As implied by its name, this receptor senses fluctuations in calcium levels (even to the smallest miniscule) in the extracellular matrix of cells, thus having principal impact on mineral homeostasis in human beings (Gorvin 2021). The human CASR gene is comprised of 8 axons and is located on chromosome 3. CaSR is expressed in calcitropic tissues like kidneys and parathyroid glands. CaSR can be found in different organs of the body and its function on those parts is determined by their location (Tennakoon et al. 2016). Little wonder then that the secretion of parathyroid hormone, skeletal development, urinary Ca^{2+} excretion and lactation are all essential roles regulated by CaSR. Other ions other than calcium (di- and tri-valent ions like Ba^{2+}, Sr^{2+}, Mg^{2+}, Mn^{2+}, Ni^{2+}, La^{3+} Gd^{3+} and Al^{3+}) and other legends like polypeptides (polysine, polyarginine) calcilytrics, polyamines, calcimimetics and antibiotics also activate the CaSR receptor thus, CaSR undertakes even noncalcitropic roles; in vascular tone, wound healing, neuronal development, insulin secretion, chemotaxis, hormonal secretion etcetera. Abnormal functioning of CaSR receptor results in asthma, neurological and cardiovascular diseases. In order that the structural integrity of the CaSR receptor in its inactive state be maintained, binding of serum phosphate to the receptor is considered a necessity (Vahe et al. 2017). The structure of the CaSR consists of three domains; a seven transmembrane domain, a large N-terminal extracellular domain (ECD) and the intracellular C-terminal domain (Chen et al. 2021). The ECD being the biggest (sometimes called the Venus flytrap because of its size) domain, is vital for the binding of ligands. The intracellular domain on the other hand is made up of different amino acids that assist with intracellular signalling and with positioning the receptor on the cell surface (Geng et al. 2016). Once activated, the CaSR initiates intracellular signalling in diverse stages; in the initial stage, CaSR gets coupled to $G_{i/o}$ and $G_{q/11}$ groups of heterotrimeric G proteins and as a result, signalling pathways are activated (Predescu et al. 2019). Activating CaSR receptor also brings phospholipases to be activated which further activates diacylglcerol (DAG) and inositol triphosphate (IP3) pathways. In this stage, the activated inositol phosphate runs the control of intracellular levels of calcium particularly in the endoplasmic reticulum. In the second stage, activated DAG further activates c-Jun n-terminal kinase and mitogen-activated protein kinase pathways. This results in ample processes within the cell (R). CaSR is pictorially represented in Fig. 5**.**

The presence and functions OF CaSR in the CNS

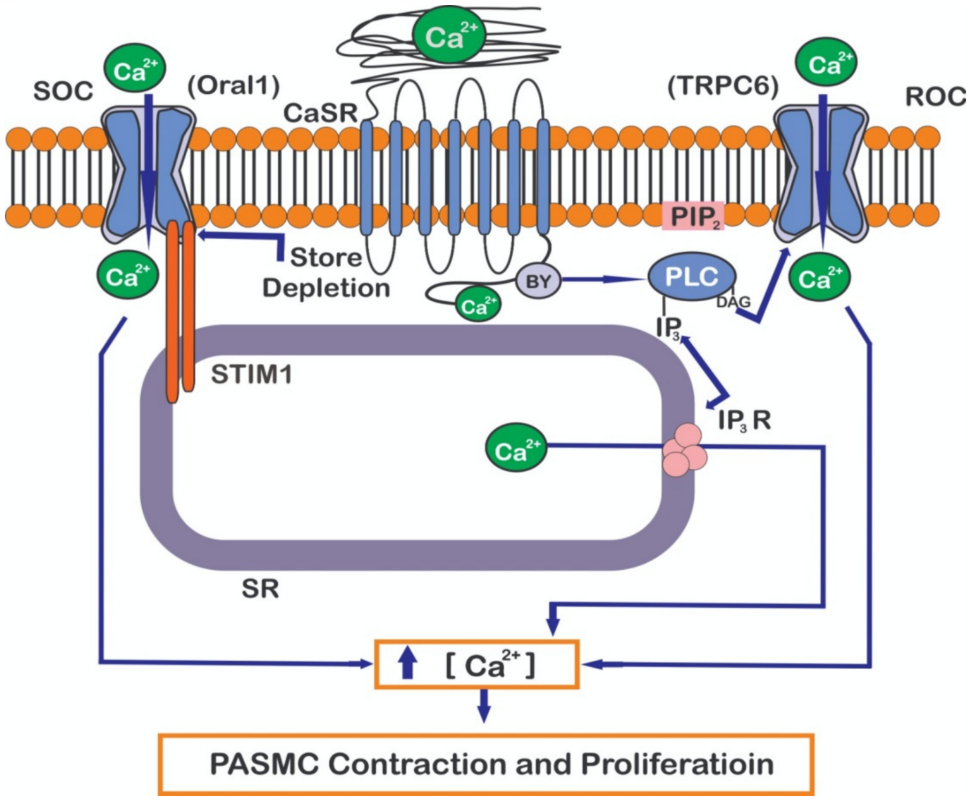
The distribution of the CaSR protein in the brain has been investigated and two transcripts located in the striatum and in the hypothalamus that highly expressed the protein were reported (Giudice et al. 2019). Some lesser expressions were seen in the pituitary. CaSR functions in neurons to sense levels of Ca^{2+}. Not only does it sense the calcium ions implicated in growth and migration but also those involved in neurotransmission and synaptic plasticity (Arjun McKinney et al. 2022). CaSR may participate in the regulation of ionic microenvironment in the CNS and also in myelinogenesis regulation (see Fig. 6).

CaSR in the cardiovascular system

The CaSR is located on the membrane of vascular cells and is a key player in cardiovascular physiology. The constant activation and reactivation of CaSR with the changing levels of Ca^{2+} owing to feedback mechanism aid in normalizing the contractility of the muscle cells. CaSR thus does not only regulate ion channels but also regulates membrane potentials. Activating the CaSR in vascular smooth muscle cells and specifically the aortic SMCs permits the entry of calcium into the cells through the receptor-operated channels (ROC). Experimental mice in which CaSR was lacking were seen to show several compromises in the functioning of the vasculature like blood pressure and vessel tone (Wenceslau et al. 2021). Impairments in the contractility of the vasculature (mice were hypotensive) were also observed to be linked to CaSR (Schepelmann et al. 2016). CaSR also plays a role in the endothelial cells of the cardiovascular system.

Mitochondrial calcium ion transport

The mitochondria are one of the very vital cell organelles implicated in regulating the homeostasis of intracellular



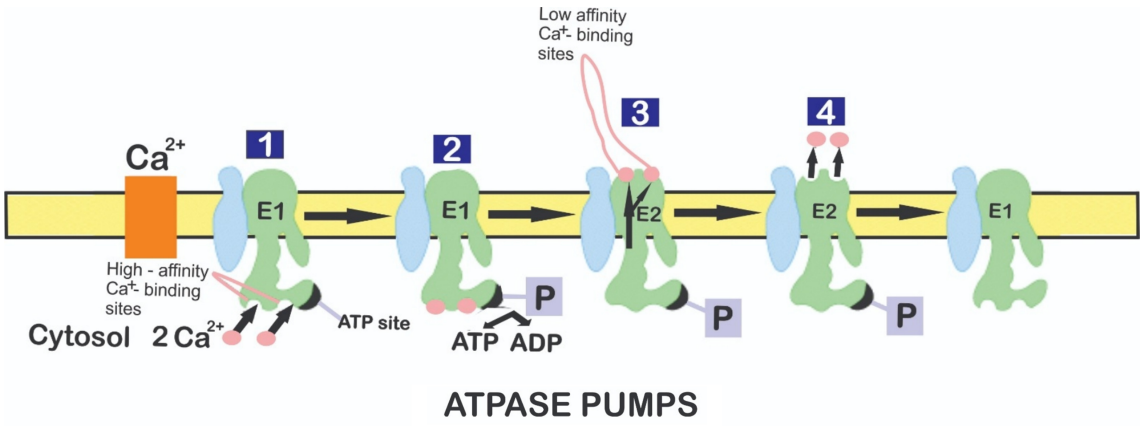


Fig. 5 The calcium sensing receptor

Fig. 6 ATPase pumps

calcium. In addendum to their roles of providing energy for the cell, mitochondria also plays a significant role in managing calcium within the cell. Mitochondria are ubiquitous and dynamic and decide both cell survival and cell death. Because of the ubiquitous nature of both calcium and mitochondria, the regulation of both is deeply intertwined, so that ca^{2+} regulates mitochondrial functions, and the mitochondria shapes ca^{2+} dynamics and again, deregulation of either ca^{2+} or mitochondrial signaling leads to abnormal cell function, cell damage or even cell death and a corresponding dysfunction in the muscle or cardiac system. Furthermore abnormalities in mitochondrial -ca^{2+} homeostasis are considered to be responsible for some metabolic diseases like pulmonary hypertension, cancer and obesity. The mitochondrial calcium transporter is represented in Fig. 7

Voltage-dependent anion channels (VDACs)

Existing on the outer mitochondrial membrane (OMM) of excitable cells (fibroblasts, retinal amacrine cell, neurons

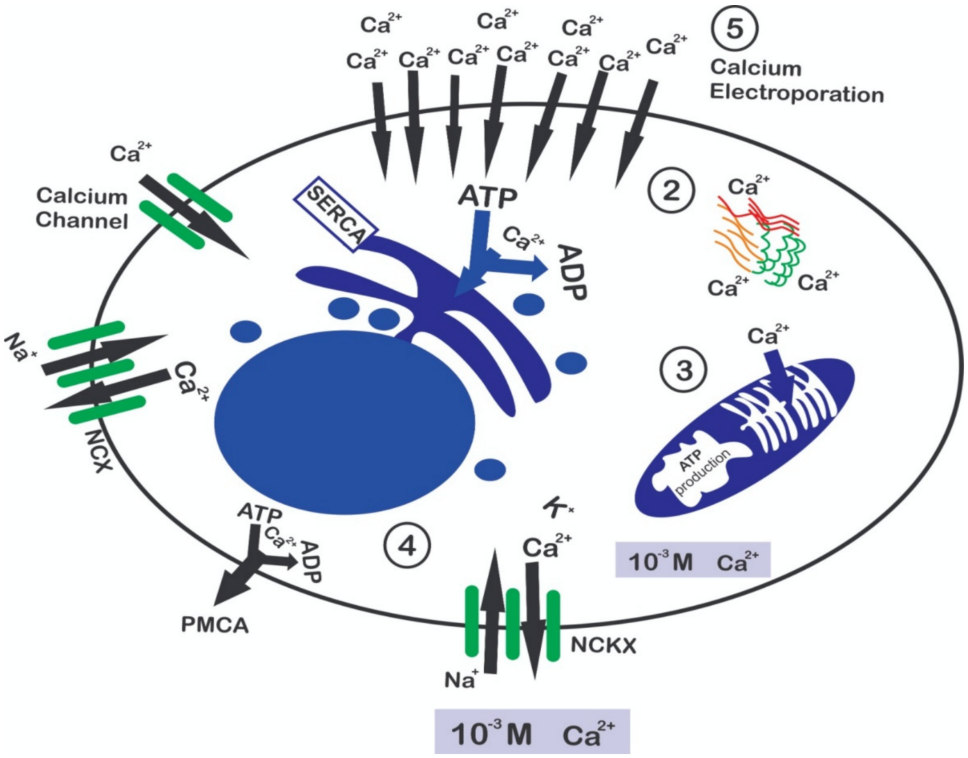


Fig. 7 The mitochondrial calcium transporter

and muscle cells) are responsible for transporting calcium into the mitochondria. They are the most copious proteins found on the outer mitochondrial membrane. VDACs in addition to calcium also transport other small ions and molecules. The activities of VDACs are regulated by calcium which also controls what ions and molecules enter in so that calcium levels as high as the micromolar range make for greater conductance and keep VDAC opened because VDACs are usually closed conformations under physiological ionic conditions (Rostovtseva et al. 2021). VDACs are implicated in energy production and metabolism regulation and energy production.

The role of voltage dependent anion channels in cardiovascular disease The role of VDACs in the pathogenesis of cardiac abnormalities is far from been elucidated, however, mounting evidence suggests that VDACs might have critical roles in several settings. In the case of ischemia–reperfusion, the upregulation of the expression and phosphorylation of VDACs have been demonstrated to increase damage of cardiomyocytes. Inhibition of these processes was mechanistically associated to the nutritional preconditioning of roles of resveratrol (*No Title*, n.d.). Oxidative stress damage in H9c2 was demonstrated to augment the expression levels of VDACI and its oligomerization. Additionally, VDACs were reported to be implicated in the disadvantageous transfer of calcium ions from the endoplasmic reticulum to the mitochondria (Shen et al. 2022). During chronic cardiac abnormalities, changes in the expression and function of VDAC are less clear compared to the acute ischemia–reperfusion set up. Moreover, upregulated transcriptional levels of a diverse array of genes including VDAC were seen in the septal tissue of human patients with hypertrophic cardiomyopathy (Klapper-Goldstein et al. 2020). The prominent upregulaton of VDAC expressional levels in a rat model of cardiac hypertrophy induced by renal artery ligation was also reported by Klapper-Goldstein et al. (2020). The team discovered that the apoptotic cell death of the model could be partially inhibited by in in-vivo treatment by siRNA against VDAC. In the same investigation, the upregulation of VDAC was not detected ten day post-myocardial infarction. Contrary to the findings by Klapper-Goldstein et al. (2020), the expressional levels of VDAC were down-regulated in a cellular model of cariomyocyte hypertrophy triggered by the alpha 1 adrenergic agonist phenylephrine. Furthermore, the anti-hypertrophic effects of activating peroxisome proliferator activated receptor α could prevent this down-regulated of VDAC. Therefore it is still unclear how the expression of VDAC is affected by common cardiac pathologies including ischemic cardiomyopathy and pathological hypertrophy (Kar and Bandyopadhyay 2018).

The $Na^+/Ca^{2+}/LI.^+$ exchanger (NCLX)

The first identification and isolation of the role of NCLX was done in a Ca^{2+} loaded cardiac mitochondria (Boyman

et al. 2013). The lack of Na^+ was observed to restrict Ca^{2+} efflux. But upon an addition of Na^+, there was a rapid efflux of Ca^{2+} from the mitochondrial. NCLX is thus the extrusion route for calcium ions from the cells. Li^+ was later found to be capable of replacing Na^+ in catalyzing the efflux of calcium from the mitochondria (Rysted et al. 2021). The function of NCLX therefore is to exchange calcium contained in the mitochondrial for sodium or lithium in the external environment. The transporter transports $3Na^+$ per $1Ca^{2+}$ meaning that more Na^+ get into the mitochondrial than Ca^{2+} go out. A sustained balance is therefore critical between MUC and NCLX in order to maintain $mtCa^{2+}$ homeostasis as imbalances in $mtCa^{2+}$ homeostasis are causative of many diseases (Luongo et al. 2017). The activity of NCLX is about a 100 times slower than MUC thus, the rate-limiting factor in the homeostasis of $mitCa^{2+}$ is the NCLX operation. Despite this, NCLX remains the main mitochondrial matrix Ca^{2+} extrusion mediator (B. Kim et al. 2016). Investigations conducted on isolated cardiac mitochondria revealed that the regulation of NCLX is carried out by Ca^{2+} so that elevated Ca^{2+} levels lead to partial inhibition of its activity. The decreased expression or complete loss of NCLX causes $mtCa^{2+}$ overload which in turn, results in the depolarization of the mitochondria (Modesti et al. 2021).

The mitochondrial calcium uniporter (MUC)

This channel also transports calcium ions. The MUC is a 40KDa highly selective Ca^{2+} channel uniporter through which mitochondrial takes up calcium ions in order to regulate its cystosolic calcium ion signalling, energy production, and cell death. This uniporter (Fig. 8) is situated in the IMM and (in mammals,) it is composed of four monomer subunits: the pore-forming MCU, MICU1 and MICU2 which are the gatekeepers and a supplementary EMRE (Essential MCU regulator) subunit. Each of the pore forming units in

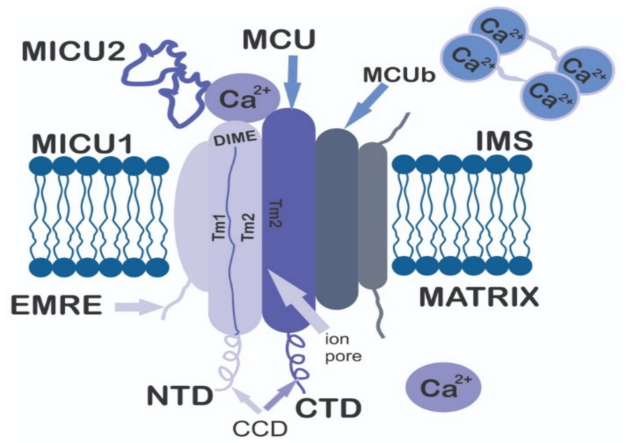


Fig. 8 The calcium uniporter

MUC consists of a short loop containing a "DIME" motif that connects two helical membrane spanning domains. Furthermore, an electron microscopy showed both the N- and the C- terminus of MCU to face the matrix of the cell of mitochondria overexpressing MICU1 and MICU2 regulate the activity of MCU, switching it on or off to prevent an instance of the damaging calcium ion overload (Davis et al. 2023). In an instance the downregulation of MUC, uptake of mitochondrial calcium ions ($mitCa^{2+}$) into living cells is greatly reduced. The concentration of calcium and the membrane potential of the inner mitochondrial membrane determine the flow of this channel. When the cell is at rest, the MUC stays inactive and only becomes active following a rise in local calcium ion levels (above 1 µM). This MICU1-MICU2 mediated calcium dependent activation of MUC is of great importance as it hinders an excessive influx of calcium ions that are capable of increasing the oxidative stress of the mitochondria and triggering apoptosis.

Calcitionin receptor (CTR)

The calcitonin (CT) is a 32 aminoacids polypeptide hormone (having a molar mass of 3418 Da) that is primarily syntetized primarily by the thyroid although some evidences agree that there exist nonthyrodial sources of CT. Coop and his team first discovered the hormone in their bid to find hormones that modulate serum levels of calcium (Masi and Brandi 2007). CT by directly inhibiting mediated bone resorption and promoting the elimination of calcium from the kidneys, is able to decrease blood levels of calcium (Davey and Findlay 2013). Calcitonin receptors (CTRs) on the other hand are high affinity proteins that mediate the activities of calcitonin. Furthermore, CTRs like several other peptides, belong to the subfamily of the seven-transmembrane domain G-protein coupled receptor superfamily. The human CTR however, was cloned from the carcinoma cell line (BIN-67) of an ovary. CTRs have the ability to couple signal transduction pathways, one of the most imperative pathways is coupled with cAMP signal transduction. Some agents (dibutyryl cAMP $(Bu)_2$ cAMP, forskolin e.t.c) either up-regulate or down-regulate the expression of CTR which regulation is vital component in the physiological response to CT. CT by itself, down-regulates the expression of a number of tissues that are CTR positive. A good example of this CTR down-regulation by CT was demonstrated in T47D breast cancer cells (Varghese et al. 2018). The mechanism by which CT down-regulates CTR is however not very clear. While CT, forskolin and Bu_2 cAMP down-regulates CTR, glucocorticoids up-regulate or in other words, increase the quantity of cell surface CTRs. The glucocorticoid: dexamethasone for example is seen to increase the expression of CTR in T47D, in the management of osteoclasts and in a number of other cells. These processes are however slow

and take a long time (three weeks) of exposing the agent to the cells (Lee et al. 2022).

G protein-coupled receptors (GPCRs)

More than 40% of drugs produced by the pharmaceutical industries today are created to target and modulate G protein-coupled receptor (GPCR) signalling (Hauser et al. 2017). This is because this group of receptors (diagram in Fig. 9) play vital roles in several biological functions. Their non-selectivity of actions in numerous tissues though poses a challenge to the production of these therapies. GPCRs are one of the most copious protein classes (approximately 800) in the genome of mammals, they comprise of structurally analogous proteins that share some distinguishing characteristics placed into classes. GPCRs are activated by structurally heterogenous agonists like nucleotides, peptides, lipids, natural odorants, ions, light, neurotransmitters and proteins (Weis and Kobilka 2018). Primarily, GPCRs are implicated in the transduction of extracellular stimuli into the interior of the cell permitting cells to both intercommunicate and to sense the extracellular environment (Thomsen et al. 2018). GPCR mediated calcium ion signalling transduction is still critical for the production of medications for different complex diseases like chronic heart failure, neurodegenration and respiratory disease (Dhyani et al. 2020). Upon the activation of GPCRs, cascades of events are triggered.

The SERCA pumps

The SERCA which was the first ATP- driven calcium ion was discovered in a skeletal muscle fraction known at the time as the Marsh relaxing factor. The pump was soon acknowledged as the main system for the control of cytoplasmic calcium ions in muscle cells, where its ability to remove calcium ions from the cytosol induced relaxation. Early investigations demonstrated that the pump transported two calcium ions per ATP hydrolyzed and that it is counterwise transported hydrogen ion in exchange for calcium channels. Nevertheless, fewer than four hydrogen ions were released to the cytosol per two calcium ion pumped, demonstrating that the transport reaction was partly electrogenic (Das et al. 2017). Some inhibitors of the SERCA pump are orthovanadate, thapsigargin and cyclopiazonic acid. During excitation–contraction events related with muscle force generation, the ryanodine receptor channels releases calcium ions and this increases the cytosolic calcium ions to 1–2 μM for a few milliseconds. This high concentration of calcium ions enhances the interaction of troponin with calcium to initiate the sequence of events resulting in force production (Xu and Van Remmen 2021). Prolonged levels of high cytosolic calcium ions however can be unfavourable to cellular homeostasis, triggering calcium signalling pathway and resulting in the activation of proteases such as matrix metalloproteinases and calpains (Xu and Van Remmen 2021) which can degrade cellular components. Furthermore, calcium ions can directly regulate contractile function in muscles, particularly in the cardiac muscles where the release of intracellular calcium from the sarcoplasmic reticulum is activated by a small calcium influx which is termed; calcium-induced calcium release. High dysregulated concentration of calcium can directly add to unpleasant cardiac remodelling and disruption of diastolic and systolic functions (Valentim et al. 2022). Thus dysfunctional SERCA pumps could add to high cytosolic calcium, restricting not only the functioning of the muscles, but also impairing cellular function and

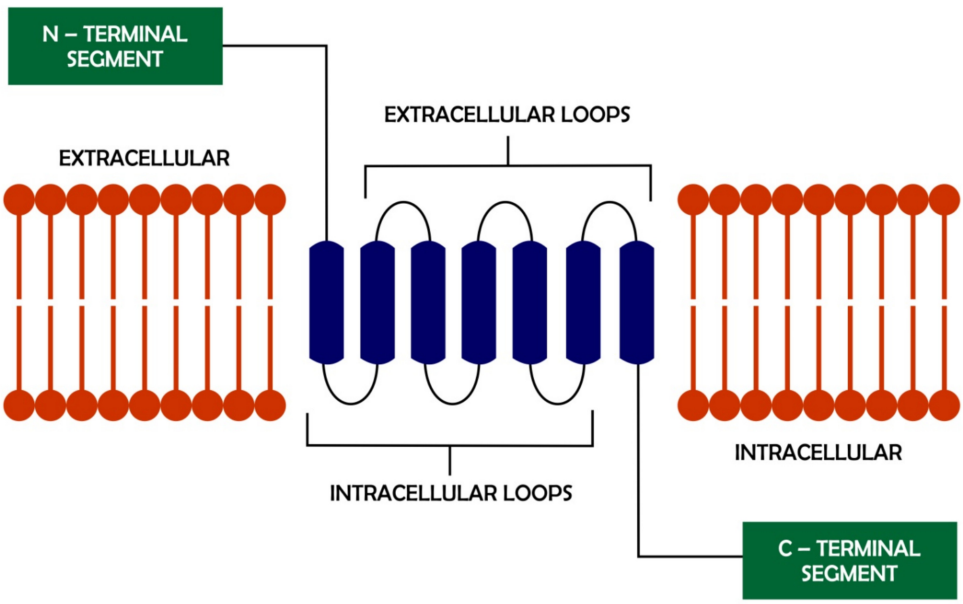


Fig. 9 The G-protein coupled receptors

metabolism. Moreover, the activity of SERCA pumps is controlled by a sequence of small molecular weight proteins present in muscle including myoregulin, phospholamban, dwarf open reading frame and sarcolipin (Xu and Van Remmen 2021). All these regulatory proteins are expressed differently in muscle, phospholamban inhibits the activity of SERCA through reduction of the pump's affinity to calcium ions hence reducing the activity of ATPase. While sarcolipin does not affect the functioning of ATPase, the maximum rate of calcium uptake is reduced indicating that sarcolipin has a calcium ion uncoupling function to SERCA (Xu and Van Remmen 2021). Intriguingly, sarcolipin also has important functions in regulating thermogenesis in muscles. Sarcolipin mediates the uncoupling function of SERCA and calcium ions, which lets SERCA to perform an ineffective cycle of hydrolysis of ATP to ADP which produces heat without releasing calcium ions thus aiding temperature homeostasis of the body, another vital function of muscle other than contraction (Wang et al. 2021). The function of myoregulin is still a novel area in research and currently investigations suggest that myoregulin exercises an inhibitory regulation on the activity of SERCA; really, the genetic ablation of myoregulin had ability to improve the function of SERCA as well as to enhance exercise performance (Xu and Van Remmen 2021). Contrariwise, dwarf open reading frame has different functioning from the others since it activates SERCA. In cardiac muscles, the genetic manipulation of replacing phospholamban with dwarf open reading frame leads to a dramatic increase in the activity of SERCA as well as the enhancement of muscle contractility (Fisher et al. 2021).

The function of SERCA in neurodegenerative disorders and muscle disease

Neurodegenerative diseases such as amyotrophic lateral sclerosis change neuromuscular transmission via the disruption of neuromuscular junction functions and structures and are also linked with a number of denervation phenotypes in skeletal muscles (Verma et al. 2022). The neuromuscular junction has been demonstrated to be a highly age-related structure with its morphology of the pre and post-synaptic regions changed and the number of neurotransmitter-containing synaptic vesicles reduced (Verma et al. 2022). The impact of neuromuscular dysfunction on skeletal muscles has been reported and the activity of SERCA has been reported to be noticeably lessened in denervated muscles. This may be caused by the oxidative stress initiated by the generation of LOOH and mitochondrial dysfunction in response denervation (Motanova et al. 2024); nevertheless, the precise mechanisms underlying mechanisms are not yet completed understood. A recent study demonstrated that the overexpression of catalase targeted to skeletal muscle mitochondria in *S*od1KO mouse muscle atrophy model resulted in decreased oxidative stress in muscle associated with full rescue of oxidative stress induced alternations in neuromuscular junction function and morphology, the activity of SERCA also returns to wildtype levels (Ahn et al. 2022).

Other than neurodegenerative disorders, muscular dystrophies are also a group of degenerative muscle disorders categorized by progressive muscle wasting and often untimely death. Usually, the primary defect to most muscular dystrophies implicate disruption of the dystrophin-glycoprotein complex which results in sarcolemma instability and an abnormal calcium ion influx including cellular necrosis (Shin et al. 2013). Duchenne muscular dystrophy is a severe form of muscular dystrophy that has been comprehensively studied using the dystrophic mdx mouse model. Based on the model, the activity of SERCA is reduced for more than 20% in comparison to wild type muscle in both hindlimb and diaphragm muscles. The impaired function of SERCA contributes to the dysregulation of dystrophic muscles. Enhancing the activity of SERCA through overexpression of the SERCA suppresses the muscle degenerative phenotypes (Qaisar et al. 2020). Put together, these investigations suggest the vital role of SERCA function under the diseased status of skeletal muscle.

Conclusion

The regulation of calcium ion transport and its participation in both physiological and pathological processes greatly lies on calcium channels and transporters. The authors of this review were concerned to report about various calcium channels and transporters (TRPVI, TRPV2, TRPV4, CaSR, MCU, G-Protein coupled receptors, mitochondrial calcium transporters, Calcitonin receptors, SERCA and PMCA) and their roles in regulating the influx and efflux of calcium ion across cells. Intrinsic calcium binding sites regulate several calcium channels hence serve functional or structural roles. Further study of these systems should birth new understanding of how these regulatory systems evolved; a better understanding of these channels may also sponsor significant innovation in the field of medicine. Moreover, enhanced knowledge of the molecular mechanisms behind calcium dependent control from these channels could also lead to novel strategies for anti-arrhythmia, myocardial infarction and other cardiovascular and human diseases.

Author contributions AJ, GE, PA, JO, EI, UI, EO, EY, KZ, AE, DO, HU, AA were responsible for the conception and design of the study; AJ, GE, PA, JO, EI, UI, EO, EY, KZ, AE, DO, HU, AA performed data collection. AJ, GE, PA, JO, EI, UI, EO, EY, KZ, AE, DO, HU, AA performed data analysis and drafted the article. GE, EY supervised the study, contributed to data analysis, interpretation, and critical revisions. All authors approved the final manuscript.

Funding This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability All data will be made available upon reasonable request.

Declarations

Conflict of interest The authors have no competing interests.

Ethical approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

References

Abdalla, S.S., Harb, A.A., Almasri, I.M., Bustanji, Y.K.: The interaction of TRPV1 and lipids: insights into lipid metabolism. Front. n Physiol. (2022). https://doi.org/10.3389/fphys.2022.1066023

Adhikary, D., Barman, S., Ranjan, R., Stone, H.: A systematic review of major cardiovascular risk factors: a growing global health concern. Cureus (2022). https://doi.org/10.7759/cureus.30119

Ahn, B., Ranjit, R., Kneis, P., Xu, H., Piekarz, K.M., Freeman, W.M., Van Remmen, H.: Scavenging mitochondrial hydrogen peroxide by peroxiredoxin 3 overexpression attenuates contractile dysfunction and muscle atrophy in a murine model of accelerated sarcopenia. Aging Cell (2022). https://doi.org/10.1111/acel.13569

Aleixandre-Carrera, F., Engelmayer, N., Ares-Suárez, D., Acosta, M.D.C., Belmonte, C., Gallar, J., Meseguer, V., Binshtok, A.M.: Optical assessment of nociceptive TRP channel function at the peripheral nerve terminal. Int. J. Mole. Sci. **22**(2), 481 (2021). https://doi.org/10.3390/ijms22020481

Andresen, M.: Understanding diverse TRPV1 signaling: an update. F1000Research (2019). https://doi.org/10.12688/f1000research.20795.1

Arjun McKinney, A., Petrova, R., Panagiotakos, G.: Calcium and activity-dependent signaling in the developing cerebral cortex. Development (2022). https://doi.org/10.1242/dev.198853

Beghi, S., Furmanik, M., Jaminon, A., Veltrop, R., Rapp, N., Wichapong, K., Schurgers, L.J.: Calcium signalling in heart and vessels: role of calmodulin and downstream calmodulin-dependent protein kinases. Int. J. Mole. Sci. **23**(24), 16139 (2022). https://doi.org/10.3390/ijms232416139

Bennett, D.L., Clark, A.J., Huang, J., Waxman, S.G., Dib-Hajj, S.D.: The role of voltage-gated sodium channels in pain signaling. Physiol. Rev. **99**(2), 1079–1151 (2019). https://doi.org/10.1152/physrev.00052.2017

Bernardini, M., Brossa, A., Chinigo, G., Grolez, G.P., Trimaglio, G., Allart, L., Gkika, D.: Transient receptor potential channel expression signatures in tumor-derived endothelial cells: functional roles in prostate cancer angiogenesis. Cancers (2019). https://doi.org/10.3390/cancers11070956

Billman, G.E.: Homeostasis: the underappreciated and far too often ignored central organizing principle of physiology. Front. Physiol. (2020). https://doi.org/10.3389/fphys.2020.00200

Bootman, M.D., Bultynck, G.: Fundamentals of cellular calcium signaling: a primer. Cold Spring Harb. Perspect. Biol. **12**(1), a038802 (2020). https://doi.org/10.1101/cshperspect.a038802

Boutin, J.A., Bedut, S., Jullian, M., Galibert, M., Frankiewicz, L., Gloanec, P., Leprince, J.: Caloxin-derived peptides for the inhibition of plasma membrane calcium ATPases. Peptides **154**, 170813 (2022). https://doi.org/10.1016/j.peptides.2022.170813

Boyman, L., Williams, G.S.B., Khananshvili, D., Sekler, I., Lederer, W.J.: NCLX: the mitochondrial sodium calcium exchanger. J. Mol. Cell. Cardiol. **59**, 205–213 (2013). https://doi.org/10.1016/j.yjmcc.2013.03.012

Brini, M., Carafoli, E.: Calcium pumps in health and disease. Physiol. Rev. **89**(4), 1341–1378 (2009). https://doi.org/10.1152/physrev.00032.2008

Brini, M., Carafoli, E.: The plasma membrane Ca2+ ATPase and the plasma membrane sodium calcium exchanger cooperate in the regulation of cell calcium. Cold Spring Harb. Perspect. Biol. **3**(2), a004168–a004168 (2011). https://doi.org/10.1101/cshperspect.a004168

Chen, X., Wang, L., Cui, Q., Ding, Z., Han, L., Kou, Y., Geng, Y.: Structural insights into the activation of human calcium-sensing receptor. Elife (2021). https://doi.org/10.7554/eLife.68578

Ciardo, M.G., Ferrer-Montiel, A.: Lipids as central modulators of sensory TRP channels. Biochimica Et Biophysica Acta (BBA) Biomembranes **1859**(9), 1615–1628 (2017). https://doi.org/10.1016/j.bbamem.2017.04.012

Coles, J.A., Myburgh, E., Brewer, J.M., McMenamin, P.G.: Where are we? The anatomy of the murine cortical meninges revisited for intravital imaging, immunology, and clearance of waste from the brain. Prog. Neurobiol. **156**, 107–148 (2017). https://doi.org/10.1016/j.pneurobio.2017.05.002

Cordier, C., Prevarskaya, N., Lehen'kyi, V.: TRPM7 ion channel: oncogenic roles and therapeutic potential in breast cancer. Cancers **13**(24), 6322 (2021). https://doi.org/10.3390/cancers13246322

Corradi, V., Sejdiu, B.I., Mesa-Galloso, H., Abdizadeh, H., Noskov, S.Y., Marrink, S.J., Tieleman, D.P.: Emerging diversity in lipid-protein interactions. Chem. Rev. **119**(9), 5775–5848 (2019). https://doi.org/10.1021/acs.chemrev.8b00451

Das, A., Rui, H., Nakamoto, R., Roux, B.: Conformational transitions and alternating-access mechanism in the sarcoplasmic reticulum calcium pump. J. Mol. Biol. **429**(5), 647–666 (2017). https://doi.org/10.1016/j.jmb.2017.01.007

Davey, R.A., Findlay, D.M.: Calcitonin: physiology or fantasy? J. Bone Miner. Res. **28**(5), 973–979 (2013). https://doi.org/10.1002/jbmr.1869

Davis, L.C., Morgan, A.J., Galione, A.: Optical profiling of autonomous Ca2+ nanodomains generated by lysosomal TPC2 and TRPML1. Cell Calcium **116**, 102801 (2023). https://doi.org/10.1016/j.ceca.2023.102801

Dhyani, V., Gare, S., Gupta, R.K., Swain, S., Venkatesh, K.V., Giri, L.: GPCR mediated control of calcium dynamics: a systems perspective. Cell. Signal. **74**, 109717 (2020). https://doi.org/10.1016/j.cellsig.2020.109717

Dixon, R.E., Trimmer, J.S.: Endoplasmic reticulum-plasma membrane junctions as sites of depolarization-induced ca 2+ signaling in excitable cells. Annu. Rev. Physiol. **85**(1), 217–243 (2023). https://doi.org/10.1146/annurev-physiol-032122-104610

Entin-Meer, M., Keren, G.: Potential roles in cardiac physiology and pathology of the cation channel TRPV2 expressed in cardiac cells and cardiac macrophages: a mini-review. Am. J. Physiol.-Heart Circulat. Physiol. **318**(1), H181–H188 (2020). https://doi.org/10.1152/ajpheart.00491.2019

Ernst, I.M.A., Fliegert, R., Guse, A.H.: Adenine dinucleotide second messengers and t-lymphocyte calcium signaling. Front. Immunol. (2013). https://doi.org/10.3389/fimmu.2013.00259

Fisher, M.E., Bovo, E., Aguayo-Ortiz, R., Cho, E.E., Pribadi, M.P., Dalton, M.P., Young, H.S.: Dwarf open reading frame (DWORF) is a direct activator of the sarcoplasmic reticulum calcium pump SERCA. Elife (2021). https://doi.org/10.7554/eLife.65545

Froghi, S., Grant, C.R., Tandon, R., Quaglia, A., Davidson, B., Fuller, B.: New insights on the role of TRP channels in

calcium signalling and immunomodulation: review of pathways and implications for clinical practice. Clin. Rev. Allergy Immunol. **60**(2), 271–292 (2021). https://doi.org/10.1007/s12016-020-08824-3

Geng, Y., Mosyak, L., Kurinov, I., Zuo, H., Sturchler, E., Cheng, T.C., Fan, Q.R.: Structural mechanism of ligand activation in human calcium-sensing receptor. Elife (2016). https://doi.org/10.7554/eLife.13662

Giudice, M.L., Mihalik, B., Dinnyés, A., Kobolák, J.: The nervous system relevance of the calcium sensing receptor in health and disease. Molecules **24**(14), 2546 (2019). https://doi.org/10.3390/molecules24142546

Gomez, K., Vallecillo, T.G.M., Moutal, A., Perez-Miller, S., Delgado-Lezama, R., Felix, R., Khanna, R.: The role of cyclin-dependent kinase 5 in neuropathic pain. Pain **161**(12), 2674–2689 (2020). https://doi.org/10.1097/j.pain.0000000000002027

Gorvin, C.M.: Calcium-sensing receptor signaling — How human disease informs biology. Curr. Opin. Endocrine Metab. Res. **16**, 10–18 (2021). https://doi.org/10.1016/j.coemr.2020.06.007

Hannan, F.M., Kallay, E., Chang, W., Brandi, M.L., Thakker, R.V.: The calcium-sensing receptor in physiology and in calcitropic and noncalcitropic diseases. Nat. Rev. Endocrinol. **15**(1), 33–51 (2019). https://doi.org/10.1038/s41574-018-0115-0

Hauser, A.S., Attwood, M.M., Rask-Andersen, M., Schiöth, H.B., Gloriam, D.E.: Trends in GPCR drug discovery: new agents, targets and indications. Nat. Rev. Drug Discovery **16**(12), 829–842 (2017). https://doi.org/10.1038/nrd.2017.178

Haustrate, A., Prevarskaya, N., Lehen'kyi, V.: Role of the TRPV channels in the endoplasmic reticulum calcium homeostasis. Cells **9**(2), 317 (2020). https://doi.org/10.3390/cells9020317

Held, K., Tóth, B.I.: TRPM3 in brain (patho)physiology. Front. Cell Develop. Biol. (2021). https://doi.org/10.3389/fcell.2021.635659

Jiang, Z.-J., Li, W., Yao, L.-H., Saed, B., Rao, Y., Grewe, B.S., Gong, L.-W.: TRPM7 is critical for short-term synaptic depression by regulating synaptic vesicle endocytosis. Elife (2021). https://doi.org/10.7554/eLife.66709

Jin, X., Zhang, Y., Alharbi, A., Hanbashi, A., Alhoshani, A., Parrington, J.: Targeting two-pore channels: current progress and future challenges. Trends Pharmacol. Sci. **41**(8), 582–594 (2020). https://doi.org/10.1016/j.tips.2020.06.002

Kalinovskii, A.P., Osmakov, D.I., Koshelev, S.G., Lubova, K.I., Korolkova, Y.V., Kozlov, S.A., Andreev, Y.A.: Retinoic acid-differentiated neuroblastoma SH-SY5Y is an accessible in vitro model to study native human acid-sensing ion channels 1a (ASIC1a). Biology **11**(2), 167 (2022). https://doi.org/10.3390/biology11020167

Kar, D., Bandyopadhyay, A.: Targeting peroxisome proliferator activated receptor α (PPAR α) for the prevention of mitochondrial impairment and hypertrophy in cardiomyocytes. Cell. Physiol. Biochem. **49**(1), 245–259 (2018). https://doi.org/10.1159/000492875

Kemény, K.K., Ducza, E.: Physiological cooperation between aquaporin 5 and TRPV4. Int. J. Mol. Sci. **23**(19), 11634 (2022). https://doi.org/10.3390/ijms231911634

Kim, B., Takeuchi, A., Hikida, M., Matsuoka, S.: Roles of the mitochondrial Na+-Ca2+ exchanger, NCLX B lymphocyte chemotaxis. Sci. Rep. **6**(1), 28378 (2016). https://doi.org/10.1038/srep28378

Kim, J.J., Park, H.-M., Kyoung, A.Y., Lim, S.-K., Lee, J.E., Park, B.C.: Redefining copy number variation and single-nucleotide polymorphism counting via novel concepts based on recent PCR enhancements. Biochem. Biophys. Res. Commun. **740**, 150988 (2024). https://doi.org/10.1016/j.bbrc.2024.150988

Klapper-Goldstein, H., Verma, A., Elyagon, S., Gillis, R., Murninkas, M., Pittala, S., Etzion, Y.: VDAC1 in the diseased myocardium and the effect of VDAC1-interacting compound on atrial fibrosis induced by hyperaldosteronism. Sci. Rep. **10**(1), 22101 (2020). https://doi.org/10.1038/s41598-020-79056-w

Koivisto, A.-P., Belvisi, M.G., Gaudet, R., Szallasi, A.: Advances in TRP channel drug discovery: from target validation to clinical studies. Nat. Rev. Drug Discovery **21**(1), 41–59 (2022). https://doi.org/10.1038/s41573-021-00268-4

Lee, W.H., Choong, L.Y., Jin, T.H., Mon, N.N., Chong, S., Liew, C.S., Lim, Y.P.: TRPV4 plays a role in breast cancer cell migration via Ca2+-dependent activation of AKT and down-regulation of E-cadherin cell cortex protein. Oncogenesis **6**(5), e338–e338 (2017). https://doi.org/10.1038/oncsis.2017.39

Lee, S., Krüger, B.T., Ignatius, A., Tuckermann, J.: Distinct glucocorticoid receptor actions in bone homeostasis and bone diseases. Front. Endocrinol. (2022). https://doi.org/10.3389/fendo.2021.815386

Levy, D.: The progression from hypertension to congestive heart failure. JAMA: J. Am. Med. Assoc. **275**(20), 1557 (1996). https://doi.org/10.1001/jama.1996.03530440037034

Liu, T.-Y., Chu, Y., Mei, H.-R., Chang, D., Chuang, H.-H.: Two vanilloid ligand bindings per channel are required to transduce capsaicin-activating stimuli. Front. Mole. Neurosci. (2020). https://doi.org/10.3389/fnmol.2019.00302

Luongo, T.S., Lambert, J.P., Gross, P., Nwokedi, M., Lombardi, A.A., Shanmughapriya, S., Elrod, J.W.: The mitochondrial Na+/Ca2+ exchanger is essential for Ca2+ homeostasis and viability. Nature **545**(7652), 93–97 (2017). https://doi.org/10.1038/nature22082

Marini, M., Titiz, M., Monteiro, S., de Araújo, D., Geppetti, P., Nassini, R., De Logu, F.: TRP channels in cancer: signaling mechanisms and translational approaches. Biomolecules **13**(10), 1557 (2023). https://doi.org/10.3390/biom13101557

Masi, L., Brandi, M.L.: Calcitonin and calcitonin receptors. Clin. Cases Mine. Bone Metabol. : off. J. Ital. Soc. Osteoporosis Mineral Metabol. Skeletal Dis. **4**(2), 117–122 (2007)

Matsushita, Y., Manabe, M., Kitamura, N., Shibuya, I.: Adrenergic receptors inhibit TRPV1 activity in the dorsal root ganglion neurons of rats. PLoS ONE **13**(1), e0191032 (2018). https://doi.org/10.1371/journal.pone.0191032

Matuz-Mares, D., González-Andrade, M., Araiza-Villanueva, M.G., Vilchis-Landeros, M.M., Vázquez-Meza, H.: Mitochondrial calcium: effects of its imbalance in disease. Antioxidants **11**(5), 801 (2022). https://doi.org/10.3390/antiox11050801

Mecawi, A.S., Varanda, W.A., da Silva, M.P.: Osmoregulation and the hypothalamic supraoptic nucleus: from genes to functions. Front. Physiol. (2022). https://doi.org/10.3389/fphys.2022.887779

Meza, R.C., Ancatén-González, C., Chiu, C.Q., Chávez, A.E.: Transient receptor potential vanilloid 1 function at central synapses in health and disease. Front. Cell. Neurosci. (2022). https://doi.org/10.3389/fncel.2022.864828

Mickle, A., Shepherd, A., Mohapatra, D.: Nociceptive TRP channels: sensory detectors and transducers in multiple pain pathologies. Pharmaceuticals **9**(4), 72 (2016). https://doi.org/10.3390/ph9040072

Modesti, L., Danese, A., Vitto, A.M., Ramaccini, V., Aguiari Gafà Pinton, D.G.R.: Mitochondrial Ca2+ signaling in health. Dis. Ther. Cells **10**(6), 1317 (2021). https://doi.org/10.3390/cells10061317

Motanova, E., Pirazzini, M., Negro, S., Rossetto, O., Narici, M.: Impact of ageing and disuse on neuromuscular junction and mitochondrial function and morphology: current evidence and controversies. Ageing Res. Rev. **102**, 102586 (2024). https://doi.org/10.1016/j.arr.2024.102586

Nazıroğlu, M., Öz, A., Yıldızhan, K.: Selenium and neurological diseases: focus on peripheral pain and TRP channels. Curr. Neuropharmacol. **18**(6), 501–517 (2020). https://doi.org/10.2174/1570159X18666200106152631

Newton, A.C., Bootman, M.D., Scott, J.D.: Second messengers. Cold Spring Harb. Perspect. Biol. **8**(8), a005926 (2016). https://doi.org/10.1101/cshperspect.a005926

No Title. (n.d.). https://doi.org/10.1038/s41392-023-01688-x

Odieka, A.E., Obuzor, G.U., Oyedeji, O.O., Gondwe, M., Hosu, Y.S., Oyedeji, A.O.: The medicinal natural products of cannabis sativa linn: a review. Molecules **27**(5), 1689 (2022). https://doi.org/10.3390/molecules27051689

Öster, C., Tekwani Movellan, K., Goold, B., Hendriks, K., Lange, S., Becker, S., Lange, A.: Direct detection of bound ammonium ions in the selectivity filter of ion channels by solid-state NMR. J. Am. Chem. Soc. **144**(9), 4147–4157 (2022). https://doi.org/10.1021/jacs.1c13247

Pistritto, G., Trisciuoglio, D., Ceci, C., Garufi, A., D'Orazi, G.: Apoptosis as anticancer mechanism: function and dysfunction of its modulators and targeted therapeutic strategies. Aging **8**(4), 603–619 (2016). https://doi.org/10.18632/aging.100934

Pottosin, I., Delgado-Enciso, I., Bonales-Alatorre, E., Nieto-Pescador, M. G., Moreno-Galindo, E. G., Dobrovinskaya, O. (2015) Mechanosensitive Ca2+-permeable channels in human leukemic cells: Pharmacological and molecular evidence for TRPV2. *Biochimica et Biophysica Acta (BBA) Biomembranes*, *1848*(1), 51–59. https://doi.org/10.1016/j.bbamem.2014.09.008

Predescu, C., Crețoiu, P., SuciuVoinea, R.: G protein-coupled receptors (GPCRs)-mediated calcium signaling in ovarian cancer: focus on GPCRs activated by neurotransmitters and inflammation-associated molecules. Int. J. Mol. Sci. **20**(22), 5568 (2019). https://doi.org/10.3390/ijms20225568

Qaisar, R., Pharaoh, G., Bhaskaran, S., Xu, H., Ranjit, R., Bian, J., Van Remmen, H.: Restoration of sarcoplasmic reticulum Ca2+ ATPase (SERCA) activity prevents age-related muscle atrophy and weakness in mice. Int. J. Mole. Sci. **22**(1), 37 (2020). https://doi.org/10.3390/ijms22010037

Qu, Y., Sun, Y., Yang, Z., Ding, C.: Calcium ions signaling: targets for attack and utilization by viruses. Front. Microbiol. (2022). https://doi.org/10.3389/fmicb.2022.889374

Ribeiro, H., Sarmento-Ribeiro, A.B., Andrade, J.P., Dourado, M.: Apoptosis and (in) pain—potential clinical implications. Biomedicines **10**(6), 1255 (2022). https://doi.org/10.3390/biomedicines10061255

Rorsman, P., Ashcroft, F.M.: Pancreatic β-cell electrical activity and insulin secretion: of mice and men. Physiol. Rev. **98**(1), 117–214 (2018). https://doi.org/10.1152/physrev.00008.2017

Rosenbaum, T., Benítez-Angeles, M., Sánchez-Hernández, R., Morales-Lázaro, S.L., Hiriart, M., Morales-Buenrostro, L.E., Torres-Quiroz, F.: TRPV4: a physio and pathophysiologically significant ion channel. Int. J. Mol. Sci. **21**(11), 3837 (2020). https://doi.org/10.3390/ijms21113837

Rostovtseva, T.K., Bezrukov, S.M., Hoogerheide, D.P.: Regulation of mitochondrial respiration by VDAC is enhanced by membrane-bound inhibitors with disordered polyanionic C-terminal domains. Int. J. Mol. Sci. **22**(14), 7358 (2021). https://doi.org/10.3390/ijms22147358

Rysted, J.E., Lin, Z., Walters, G.C., Rauckhorst, A.J., Noterman, M., Liu, G., Usachev, Y.M.: Distinct properties of Ca2+ efflux from brain, heart and liver mitochondria: the effects of Na+, Li+ and the mitochondrial Na+/Ca2+ exchange inhibitor CGP37157. Cell Calcium **96**, 102382 (2021). https://doi.org/10.1016/j.ceca.2021.102382

Saldías, M.P., Maureira, D., Orellana-Serradell, O., Silva, I., Lavanderos, B., Cruz, P., Cerda, O.: TRP channels interactome as a novel therapeutic target in breast cancer. Front. Oncol. (2021). https://doi.org/10.3389/fonc.2021.621614

Salzer, I., Ray, S., Schicker, K., Boehm, S.: Nociceptor signalling through ion channel regulation via GPCRs. Int. J. Mol. Sci. **20**(10), 2488 (2019). https://doi.org/10.3390/ijms20102488

Santoni, G., Amantini, C.: The transient receptor potential vanilloid type-2 (TRPV2) ion channels in neurogenesis and gliomagenesis: cross-talk between transcription factors and signaling molecules. Cancers **11**(3), 322 (2019). https://doi.org/10.3390/cancers11030322

Schepelmann, M., Yarova, P.L., Lopez-Fernandez, I., Davies, T.S., Brennan, S.C., Edwards, P.J., Riccardi, D.: The vascular Ca 2+ -sensing receptor regulates blood vessel tone and blood pressure. Am. J. Physiol.-Cell Physiol. **310**(3), C193–C204 (2016). https://doi.org/10.1152/ajpcell.00248.2015

Senatore, A., Raiss, H., Le, P.: Physiology and evolution of voltage-gated calcium channels in early diverging animal phyla: cnidaria placozoa porifera and ctenophora. Front. Physiol. (2016). https://doi.org/10.3389/fphys.2016.00481

Shen, C., Wang, J., Feng, M., Peng, J., Du, X., Chu, H., Chen, X.: The mitochondrial-derived peptide MOTS-c attenuates oxidative stress injury and the inflammatory response of H9c2 cells through the Nrf2/ARE and NF-κB pathways. Cardiovasc. Eng. Technol. **13**(5), 651–661 (2022). https://doi.org/10.1007/s13239-021-00589-w

Shin, J., Tajrishi, M.M., Ogura, Y., Kumar, A.: Wasting mechanisms in muscular dystrophy. Int. J. Biochem. Cell Biol. **45**(10), 2266–2279 (2013). https://doi.org/10.1016/j.biocel.2013.05.001

Shuba, Y.M.: Beyond neuronal heat sensing: diversity of TRPV1 heat-capsaicin receptor-channel functions. Front. Cell. Neurosci. (2021). https://doi.org/10.3389/fncel.2020.612480

Sinenko, S.A., Starkova, T.Y., Kuzmin, A.A., Tomilin, A.N.: Physiological signaling functions of reactive oxygen species in stem cells: from flies to man. Front. Cell Develop. Biol. (2021). https://doi.org/10.3389/fcell.2021.714370

Siveen, K.S., Nizamuddin, P.B., Uddin, S., Al-Thani, M., Frenneaux, M.P., Janahi, I.A., Azizi, F.: TRPV2: A cancer biomarker and potential therapeutic target. Dis. Markers **2020**, 1–10 (2020). https://doi.org/10.1155/2020/8892312

Sun, Y., Sukumaran, P., Singh, B.B.: Magnesium-induced cell survival is dependent on TRPM7 expression and function. Mol. Neurobiol. **57**(1), 528–538 (2020). https://doi.org/10.1007/s12035-019-01713-7

Sundararaman, S.S., van der Vorst, E.P.C.: Calcium-sensing receptor (CaSR), its impact on inflammation and the consequences on cardiovascular health. Int. J. Mol. Sci. **22**(5), 2478 (2021). https://doi.org/10.3390/ijms22052478

Tennakoon, S., Aggarwal, A., Kállay, E.: The calcium-sensing receptor and the hallmarks of cancer. Biochimica Et Biophysica Acta (BBA) Molecular Cell Research **1863**(6), 1398–1407 (2016). https://doi.org/10.1016/j.bbamcr.2015.11.017

Thomsen, A.R.B., Jensen, D.D., Hicks, G.A., Bunnett, N.W.: Therapeutic targeting of endosomal G-protein-coupled receptors. Trends Pharmacol. Sci. **39**(10), 879–891 (2018). https://doi.org/10.1016/j.tips.2018.08.003

Toft-Bertelsen, T.L., Yarishkin, O., Redmon, S., Phuong, T.T.T., Križaj, D., MacAulay, N.: Volume sensing in the transient receptor potential vanilloid 4 ion channel is cell type–specific and mediated by an N-terminal volume-sensing domain. J. Biol. Chem. **294**(48), 18421–18434 (2019). https://doi.org/10.1074/jbc.RA119.011187

Tureckova, J., Hermanova, Z., Marchetti, V., Anderova, M.: Astrocytic TRPV4 channels and their role in brain ischemia. Int. J. Mol. Sci. **24**(8), 7101 (2023). https://doi.org/10.3390/ijms24087101

Vahe, C., Benomar, K., Espiard, S., Coppin, L., Jannin, A., Odou, M.F., Vantyghem, M.C.: Diseases associated with calcium-sensing receptor. Orphanet J. Rare Dis. **12**(1), 19 (2017). https://doi.org/10.1186/s13023-017-0570-z

Valentim, M.A., Brahmbhatt, A.N., Tupling, A.R.: Skeletal and cardiac muscle calcium transport regulation in health and disease. Biosci. Rep. (2022). https://doi.org/10.1042/BSR20211997

Varghese, E., Samuel, S., Abotaleb, M., Cheema, S., Mamtani, R., Büsselberg, D.: The "Yin and Yang" of natural compounds in anticancer therapy of triple-negative breast cancers. Cancers **10**(10), 346 (2018). https://doi.org/10.3390/cancers10100346

Vergara, R.C., Jaramillo-Riveri, S., Luarte, A., Moënne-Loccoz, C., Fuentes, R., Couve, A., Maldonado, P.E.: The energy homeostasis principle: neuronal energy regulation drives local network dynamics generating behavior. Front. Comput. Neurosci. (2019). https://doi.org/10.3389/fncom.2019.00049

Verma, S., Khurana, S., Vats, A., Sahu, B., Ganguly, N.K., Chakraborti, P., Taneja, V.: Neuromuscular junction dysfunction in amyotrophic lateral sclerosis. Mole. Neurobiol. **59**(3), 1502–1527 (2022). https://doi.org/10.1007/s12035-021-02658-6

Wang, S., Gopinath, T., Larsen, E.K., Weber, D.K., Walker, C., Uddigiri, V.R., Veglia, G.: Structural basis for sarcolipin's regulation of muscle thermogenesis by the sarcoplasmic reticulum Ca 2+ -ATPase. Sci. Adv. (2021). https://doi.org/10.1126/sciadv.abi7154

Wang, C., Huang, W., Lu, J., Chen, H., Yu, Z.: TRPV1-mediated microglial autophagy attenuates Alzheimer's disease-associated pathology and cognitive decline. Front. Pharmacol. (2022). https://doi.org/10.3389/fphar.2021.763866

Weis, W.I., Kobilka, B.K.: The molecular basis of G protein-coupled receptor activation. Annu. Rev. Biochem. **87**(1), 897–919 (2018). https://doi.org/10.1146/annurev-biochem-060614-033910

Wenceslau, C.F., McCarthy, C.G., Earley, S., England, S.K., Filosa, J.A., Goulopoulou, S., Webb, R.C.: Guidelines for the measurement of vascular function and structure in isolated arteries and veins. Am. J. Physiol.-Heart Circul. Physiol. **321**(1), H77–H111 (2021). https://doi.org/10.1152/ajpheart.01021.2020

Wu, J., Li, Z., Deng, Y., Lu, X., Luo, C., Mu, X., Xie, R.: Function of TRP channels in monocytes/macrophages. Front. Immunol. (2023). https://doi.org/10.3389/fimmu.2023.1187890

Xie, Q., Ma, R., Li, H., Wang, J., Guo, X., Chen, H.: Advancement in research on the role of the transient receptor potential vanilloid channel in cerebral ischemic injury (Review). Exp. Ther. Med. **22**(2), 881 (2021). https://doi.org/10.3892/etm.2021.10313

Xu, H., Van Remmen, H.: The SarcoEndoplasmic reticulum calcium ATPase (SERCA) pump: a potential target for intervention in aging and skeletal muscle pathologies. Skeletal Muscle **11**(1), 25 (2021). https://doi.org/10.1186/s13395-021-00280-7

Yang, C.-F., Tsai, W.-C.: Calmodulin. Tzu Chi Med. J. **34**(1), 15–22 (2022). https://doi.org/10.4103/tcmj.tcmj_285_20

Yee, N., Kazi, A., Yee, R.: Cellular and developmental biology of TRPM7 channel-kinase: implicated roles in cancer. Cells **3**(3), 751–777 (2014). https://doi.org/10.3390/cells3030751

Yu, S., Huang, S., Ding, Y., Wang, W., Wang, A., Lu, Y.: Transient receptor potential ion-channel subfamily V member 4: a potential target for cancer treatment. Cell Death Dis. **10**(7), 497 (2019). https://doi.org/10.1038/s41419-019-1708-9

Zahola, P., Hanics, J., Pintér, A., Máté, Z., Gáspárdy, A., Hevesi, Z., Alpár, A.: Secretagogin expression in the vertebrate brainstem with focus on the noradrenergic system and implications for Alzheimer's disease. Brain Struct. Funct. **224**(6), 2061–2078 (2019). https://doi.org/10.1007/s00429-019-01886-w

Zhai, K., Liskova, A., Kubatka, P., Büsselberg, D.: Calcium entry through TRPV1: a potential target for the regulation of proliferation and apoptosis in cancerous and healthy cells. Int. J. Mol. Sci. **21**(11), 4177 (2020). https://doi.org/10.3390/ijms21114177

Zhang, M., Ma, Y., Ye, X., Zhang, N., Pan, L., Wang, B.: TRP (transient receptor potential) ion channel family: structures, biological functions and therapeutic interventions for diseases. Signal Transduct. Target. Ther. **8**(1), 261 (2023). https://doi.org/10.1038/s41392-023-01464-x

Zhong, W., Shahbaz, O., Teskey, G., Beever, A., Kachour, N., Venketaraman, V., Darmani, N.A.: Mechanisms of nausea and vomiting: current knowledge and recent advances in intracellular emetic signaling systems. Int. J. Mol. Sci. **22**(11), 5797 (2021). https://doi.org/10.3390/ijms22115797