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Review Article

Role of Transient Receptor Potential Vanilloid 1 in Health and Disease

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Abstract

Transient receptor potential vanilloid 1 (TRPV1) channel is a non-selective cation channel that plays a pivotal role in pain transduction. However, more than a pain sensor, it is involved in an array of vital processes in different body systems. The findings of several studies illustrated that many disorders are associated with alterations in the function and/or expression of the TRPV1 channel. Accordingly, the TRPV1 channel has become an important target in numerous therapeutic interventions. Several TRPV1 antagonists are already in the market, however, there is a need for new drugs with fewer or no side effects. This review highlights the involvement of the TRPV1 channel in a plethora of physiological and pathological conditions and points to its importance as a therapeutic target.

Introduction

Transient receptor potential vanilloid 1 (TRPV1)

In 1997, TRPV1 receptor was cloned from the dorsal root ganglia (DRGs) neurons of rats.[1] Since then, multiple studies have been conducted to elucidate the structure, mechanisms and roles of the TRPV1 channel in health and disease. The TRPV1 channel is a non-selective cation channel characterized by cation influx when activated[1] with a very high calcium (Ca^{2+}) permeability ($P_{Ca}/P_{Na} \sim 10$).[1] Previous research highlights that several endogenous and exogenous stimuli activate the TRPV1 channel. More specifically, the channel is activated by noxious heat (>43 °C), anandamide, low extracellular pH, redox state, prostaglandins (PGs), nerve growth factor (NGF), substance P (SP), oxytocin, lysophosphatidic acid, 9, 13 and 20-hydroxyoctadecadienoic acid, linoleic acid as well as the highly selective agonists capsaicin and resiniferatoxin (RTX).[1–3]

Keywords: TRPV1; Expression; Function; Health; Disease; Target.

Abbreviations: ATP, adenosine triphosphate; BAT, black adipose tissue; BoNTA, botulinum toxin a; Ca^{2+}, calcium; CaMKII, calmodulin dependent kinase II; CBD, cannabidiol; CGRP, calcitonin gene-related peptide; CNS, central nervous system; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; dlPAG, dorsolateral periaqueductal gray; DRGs, dorsal root ganglia; ER, endoplasmic reticulum; GABA, gamma- amino butyric acid; GI, gastrointestinal; IBS, irritable bowel syndrome; ICV, intracerebroventricular; Na^{+}, sodium; NGF, nerve growth factor; NSAIDs, non-steroidal anti-inflammatory drugs; PAG, periaqueductal gray; PAR2, protease-activated receptor 2; PGs, prostaglandins; PKA, protein kinase A; PNS, peripheral nervous system; ROS, reactive oxygen species; RTX, resiniferatoxin; S5, segment 5; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SNPs, single nucleotide polymorphisms; SP, substance P; Src, sarcoma; TGs, trigeminal ganglia; TRPA1, transient receptor potential ankyrin 1; TRPV1, transient receptor potential vanilloid 1.

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TRPV1 structure

Figure 1 depicts TRPV1 structure. TRPV1 channel possesses a tetrameric structure with 6 transmembrane domains and pore-forming hydrophobic stretch linking segment 5 (S5) and S6.[4] The channel has an unusual characteristic in which it has cytosolic intracellular C and N termini.[5] Notably, a considerable amount of literature showed that the TRPV1 channel contains multiple phosphorylation sites whereby its activity can be regulated by various kinases, including protein kinase A (PKA), PKC, Ca^{2+}/calmodulin dependent kinase II (CaMKII), sarcoma (Src) kinase, and the Ca^{2+}-dependent phosphatase, calcineurin.[6]

TRPV1 activation

There are several mechanisms for TRPV1 activation. In more detail, TRPV1 agonists (e.g. capsaicin and anandamide) activate the channel by direct binding while the non-agonist activators can induce sensitization for the channel through post-translational modifications, changing one or more of the following parameters: membrane potential, pH, temperature threshold, or trafficking to the plasma membrane.[7,8] Overall, when the TRPV1 channel is activated, sodium (Na^{+}) and Ca^{2+} channels open leading to ion influx, initiation of depolarization, additional Ca^{2+} entry through voltage-gated Ca^{2+} channels, propagation of action potential into the central nervous system (CNS) and finally, different sensations such as stinging, burning, itching or a feeling of warmth.[9,10] Xin *et al*. (2005) reported the involvement of the TRPV1 channel in Ca^{2+} release from intracellular stores due to its expression in the

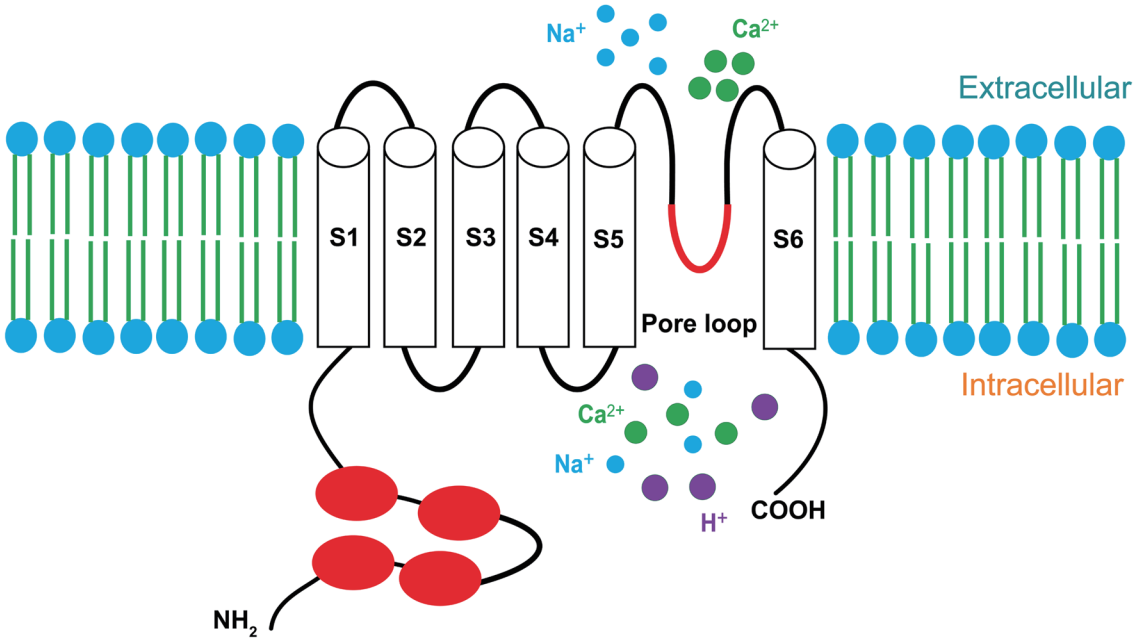

Fig. 1. Transient receptor potential vanilloid 1 (TRPV1) structure. The TRPV1 channel possesses a tetrameric structure with six transmembrane domains and a pore-forming hydrophobic stretch linking segment 5 (S5) and S6. The channel has an unusual characteristic in which it has cytosolic intracellular C and N termini. When the TRPV1 channel is activated, sodium (Na^+) and calcium (Ca^{2+}) channels open leading to ion influx, initiation of depolarization, additional Ca^{2+} entry through voltage-gated Ca^{2+} channels, propagation of action potential into the central nervous system (CNS) and finally, different sensations. H^+ refers to protons.

endoplasmic reticulum (ER), sarcoplasmic reticulum and membrane.[11] Accordingly, the TRPV1 channel contributes to the increase in Ca^{2+} concentration through four sources including the TRPV1 channel in the plasma membrane and ER; Ca^{2+}-induced Ca^{2+} release and store-operated Ca^{2+} entry.[12] On the other hand, Ferrini *et al*. (2007) reported that the administration of capsaicin to the spinal lamina II neurons causes SP release that excites inhibitory neurons in laminae I, III and IV, leading to an increase in the release of inhibitory neurotransmitters (e.g. gamma-amino butyric acid (GABA)/glycine) in mice.[13] Thus, capsaicin enhances the inhibitory neurotransmission as a parallel alternative pathway to glutamate in the transfer of nociceptive signals.[13]

TRPV1 expression

It is well documented that the TRPV1 channel is highly expressed in DRGs, trigeminal ganglia (TGs) and the spinal cord.[1] Also, it is found in the striatum, amygdala, thalamus, microglia, astrocytes and other regions in the CNS as well as non-neuronal tissues such as hair follicles, mast cells, smooth muscles, keratinocytes, liver, tongue, oral cavity, bladder, kidneys, lungs, spleen and cochlea.[10,14] Related research shows that low levels of the TRPV1 channel are expressed in the entorhinal cortex, olfactory bulb, hippocampus, periaqueductal gray (PAG) and other regions.[15] Moreover, the TRPV1 channel is widely present in multiple peripheral tissues/systems including the vasculature, gastrointestinal (GI) tract, urinary bladder, and immune system.[16–18]

TRPV1 in health

Appealing evidence shows that the TRPV1 channel plays key roles in thermosensation, oral sensation, proteasome activity, modulation of autophagy, energy homeostasis, muscle physiology, GI motility, and the release of inflammatory mediators as well as crosstalk between the immune system and sensory nervous system.[1,18–24] In addition, the TRPV1 channel is involved in the modulation of synaptic transmission through pre- and post-synaptic mechanisms and microglia-to-neuron communication.[10] To elaborate, the TRPV1 channel modulates glutamatergic and GABAergic transmission and causes changes in neuronal firing.[25,26] Thus, it has a role in brain plasticity and development.[10,27] Moreover, numerous studies have shown that the TRPV1 channel is implicated in the regulation of long-term potentiation of excitatory postsynaptic potentials in the hippocampus which is responsible for learning and memory.[28]

In the urinary bladder, the TRPV1 channel is involved in the micturition reflex, regulation of the contractility in muscle cells, blood flow and nerve excitability.[17,29] In addition, the TRPV1 channel is involved in the regulation of vascular tone and blood pressure due to its wide expression in smooth muscle cells, perivascular nerves, and endothelial cells of the cardiac system.[30] Moreover, previous studies point to the vasodilatory effect of the TRPV1 channel and its role in the stimulation of mucus secretion in the gut.[31] In the stomach and duodenum, the TRPV1 channel takes part in the maintenance of tissue integrity in addition to its protective role against aggressive compounds.[32] Also, the TRPV1 channel plays a role in the control of motor function in the GI tract.[10] Also, the TRPV1 channel is a key component in the fertility outcome in men.[33] In other contexts, it is increasingly recognized that the channel is a fundamental contributor to the healing of different wounds as reviewed by Bagood and Isseroff (2021) and other researchers.[34] The TRPV1 channel acts as a mechanosensor in the lens and contributes to the regulation of water and ion transport to restore lens volume and maintain internal lens hydrostatic pressure gradient.[35]

Figure 2 shows body systems that have TRPV1 expression.

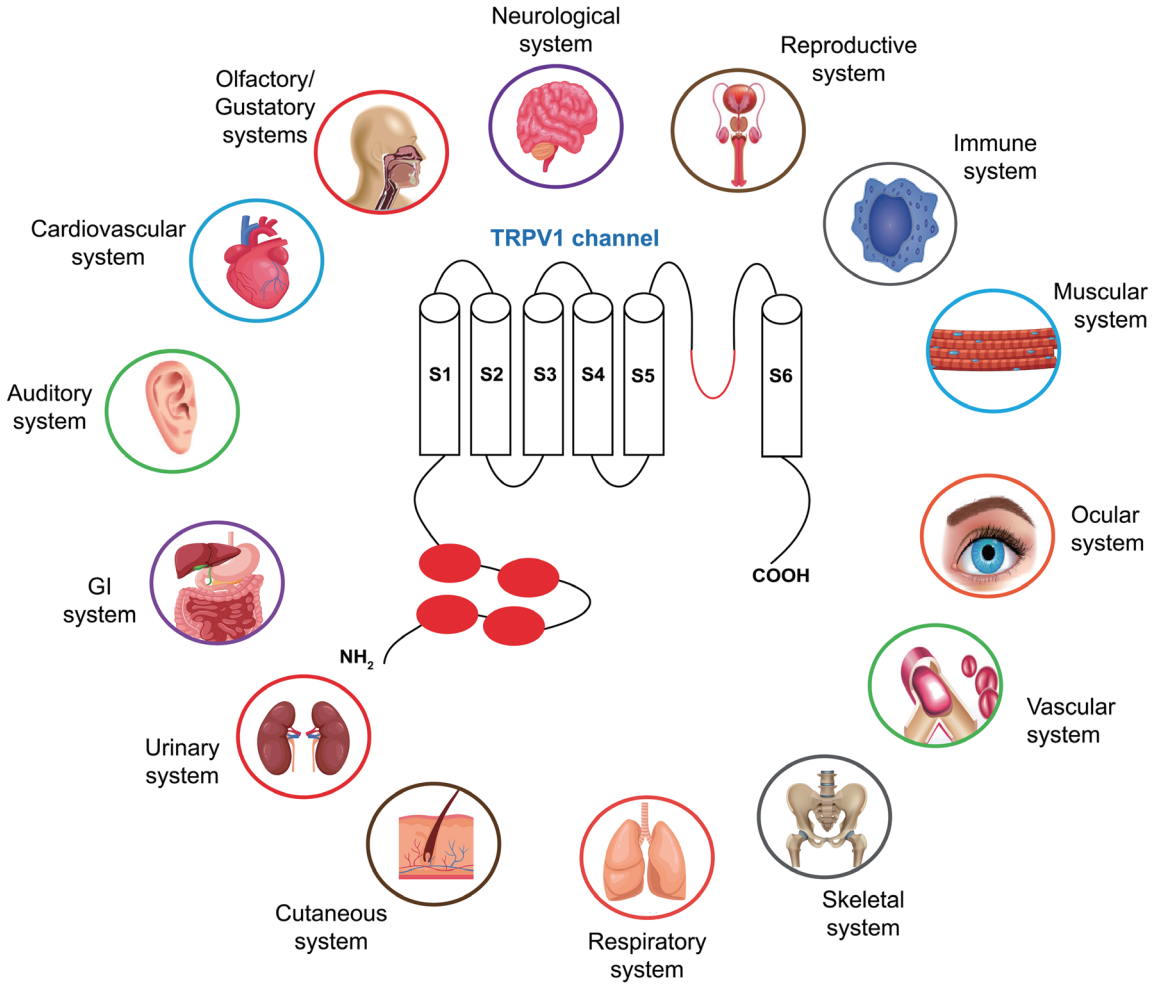

Fig. 2. Body systems that have transient receptor potential vanilloid 1 (TRPV1) expression. GI, gastrointestinal; S, segment.

TRPV1 in disease

As the TRPV1 channel is implicated in several physiological processes, many disorders have been associated with alterations in the function and/or expression of the TRPV1 channel. Close attention is currently paid to the involvement of the TRPV1 channel in diseases, pointing to its importance as a promising therapeutic target. This review highlights up to date findings regarding the involvement of the TRPV1 channel in diseases.

TRPV1 and dysregulation of temperature

It is widely accepted that TRPV1 knockout mice show altered responses to heat.[36,37] The animals exhibited little thermal hypersensitivity during inflammation and impairment in painful heat detection.[37] In another study, it was revealed that the sensitivity to noxious heat was attenuated after silencing the TRPV1 gene by short hairpin ribonucleic acid.[38] Other research implicated that the expression of the TRPV1 channel accounted for the activity of hypothalamus in thermoregulation.[39] Importantly, the use of several TRPV1 antagonists was associated with side effects such as hyperthermia and accidental burns (e.g. AMG0347) or hypothermia (e.g. 1165901) as a further indication to the link between TRPV1 and thermoregulation.[40,41]

TRPV1 and pain

Many studies have depicted that the TRPV1 channel is expressed in sensory neurons.[1] In more detail, the TRPV1 channel is expressed in the unmyelinated C-fibers and the myelinated Aδ-fibers.[1] Thus, the TRPV1 channel is involved in the nociception of mechanical, thermal, and chemical stimuli during pain.[42] In detail, it has been long recognized that the TRPV1 channel plays a fundamental role in inflammatory and neuropathic types of pain.[43] By virtue of this fact, mice that lack the TRPV1 channel display a significant decrease in pain sensation.[37] Additionally, emerging evidence shows that TRPV1 expression changes after nerve injury.[44] In addition, it was revealed that the alterations in TRPV1 expression and function were major contributors to diabetes-induced variations in thermal pain.[45] Furthermore, cumulative evidence confirms that the TRPV1 channel is implicated in inflammatory pain through the activation of kinases (e.g. PKA and PKC) and an increase in TRPV1 activity by many inflammatory mediators.[46] Additionally, the TRPV1 channel is a major contributor to cases of neuropathic pain such as chemotherapy-induced peripheral neuropathy.[47] In this regard, one study has shown that paclitaxel causes TRPV1 sensitization through the release of mast cell tryptase that causes activation for the protease-activated receptor 2 (PAR2) and other kinases.[48] On the other hand, abundant evidence shows that the TRPV1 channel contributes

to fibromyalgia which is a chronic pain disorder characterized by fatigue, widespread body pain, and mental health problems.[49,50] Importantly, the TRPV1 channel, among other pain receptors, has been implicated in different types of pain during coronavirus disease 2019 (COVID-19) and after recovery (post-COVID-19).[51,52]

Since the TRPV1 channel is involved in the nociception of different stimuli, it is widely considered a promising target for pain control.[42] Notably, despite the fact that the first exposure to TRPV1 activators causes pain, repeated exposure to these activators inhibits pain perception due to TRPV1 desensitization, thus representing a unique form of analgesia.[9]

TRPV1 and inflammation

It is well known that tissue injury is associated with inflammation and the release of multiple inflammatory mediators such as PGE_2 NGF, and bradykinin as well as protons that are responsible for tissue acidosis indicating that there is interplay between the TRPV1 channel and inflammation.[53] Many inflammatory mediators sensitize the TRPV1 channel by lowering its threshold leading to its activation at body temperature by several mechanisms that differ according to the types of nociceptors and inflammatory mediators.[43,54] These mediators have significant effects on the TRPV1 channel. Also, growing evidence demonstrates that inflammation promotes the sensitized state of the TRPV1 channel through increased activity of PKC and PKA. Thereby, the TRPV1 channel is considered a key detector for brain inflammation and autoimmune encephalitis.[27,55] Besides, the literature supports the fact that inflammation causes TRPV1 anterograde transport from the cell body to the periphery via the sciatic nerve.[56] Evidently, inflammation-induced reactive oxygen species (ROS) increased the translation of TRPV1 mRNA and caused anterograde transport of the TRPV1 protein to the periphery.[57] In this context, it has been found that the trafficking and expression of the TRPV1 channel change at the transcriptional, translational, and post-translational levels during nerve injury and inflammation.[58] Moreover, there is growing evidence indicating that the recruitment of vesicular TRPV1 pools to the membrane and the surface insertion of the TRPV1 channel onto the surface of DRGs are complementary mechanisms required for the enhancement of TRPV1 functionality by some inflammatory mediators such as NGF, insulin-like growth factor 1 and adenosine triphosphate (ATP).[54] Supporting this contention, earlier reports showed that numerous inflammatory mediators lower the threshold of TRPV1 activation via phosphorylation.[4] Likewise, there is substantial evidence revealing that NGF produced after inflammation and/or tissue injury has an impact on a regulatory region located upstream of the TRPV1 gene and hence evokes TRPV1 expression in nociceptors, partly through transcription.[59] Additionally, it was demonstrated that the administration of TRPV1 antagonists inhibits ovalbumin-induced coughing in guinea pigs, indicating that the TRPV1 channel plays a crucial role in inflammatory coughing.[60] Additionally, Orliac *et al*. (2007) proposed that the effect of anandamide during endotoxic shock (a case of severe inflammatory response) was enhanced by TRPV1 overexpression in rats.[61]

TRPV1 and cancer

Research evidence has proved the involvement of the TRPV1 channel in tumorigenesis (cell proliferation, death, and metastasis) as the channel contributes to cell division.[62,63] The effects and mechanisms of using various TRPV1 agonists/antagonists on different cancer cells were reviewed by Li *et al*. (2021).[63] Accumulating knowledge shows that the anti-tumor potential of capsaicin is demonstrated in different cancer cell lines via one or more of the following mechanisms: suppressing angiogenesis, increasing apoptosis, changing different signaling pathways or inhibiting proliferation and motility of cells.[63,64] The fact that TRPV1 activation leads to Ca^{2+} influx indicates that there is interplay between the TRPV1 channel and intracellular Ca^{2+} concentration, which is needed in many processes such as cell migration, cytotoxicity and ultimately cell death.[65,66] In this regard, one study demonstrated that the administration of the TRPV1 agonist, RTX, induced cell death in pancreatic cancer cells.[66] More precisely, it was revealed that the TRPV1 channel contributes to the proliferation of different human cancer cell lines and tumors such as osteosarcoma, colorectal cancer cells, dermal cancer cells, pancreatic cancer cells, urothelial cancer cells, renal cancer cells, hepatocellular carcinoma, nasopharyngeal carcinoma, breast carcinoma, neuroblastoma, and melanoma.[63] Meanwhile, the channel has an impact on the apoptosis/necrosis of breast carcinoma, osteosarcoma, lung cancer cells, gastric cells, oral squamous cell carcinoma, nasopharyngeal carcinoma, uterine cervix cancer, endometrial cancer, cutaneous melanoma, cervical carcinoma and bladder cancer cells.[63] Additionally, evidence suggests that the TRPV1 channel has a role, via different mechanisms, in cancer cell metastasis and invasiveness in different cells such as colorectal cancer cells, pancreatic cancer cells, urothelial cells, papillary thyroid carcinoma, dermal cancer cells, lung cancer cells, cervix adenocarcinoma, hepatoblastoma, nasopharyngeal carcinoma, neuroblastoma and melanoma.[63] In addition, the TRPV1 channel plays a role in bone cancer due to its activation by tissue acidosis mediated by osteoclasts.[67] In the oral cavity, TRPV1 expression was detected in the cell carcinoma of the human tongue.[68] Also, in cultured DRGs, it was found that treating the animals with the anticancer drugs oxaliplatin and cisplatin caused upregulation for TRPV1 mRNA.[69] Besides, a considerable body of work shows that the TRPV1 channel is implicated in several hematological malignancies due to its expression in macrophages, monocytes, and dendritic cells.[70] Moreover, previous research has shown that there is a link between TRPV1 expression and the efficiency of chemotherapy as well as radiotherapy.[63] Notably, caution has been raised in some studies regarding the association between the long term use of capsaicin and the emergence of cancer in animals.[71]

TRPV1 and psychiatric/neurological disorders

It is widely recognized that the TRPV1 channel is involved in several psychiatric and neurological disorders such as anxiety, conditioned fear, depression, drug-addiction disorders, epilepsy and Alzheimer's disease.[10,35,65,72] In more detail, earlier reports revealed that the TRPV1 channel was expressed in the hippocampus and cortex of patients who had epilepsy.[73] Additionally, it was found that the administration of the TRPV1 antagonist capsazepine suppressed seizures in genetically epilepsy-prone animals.[74] Remarkably, multiple studies have demonstrated that the TRPV1 channel promotes the migration of astrocytes and release of pro-inflammatory cytokines from astrocytes into the nearby neurons to maintain epileptogenesis.[75] In the substantia nigra, it is evident that the activation of astrocytic TRPV1 prevents the degeneration of dopaminergic neurons in a model of Parkinson's disease in rats.[76] Furthermore, You *et al*. (2012) reported that TRPV1 knockout mice exhibited antidepressant behavior.[77] Also, TRPV1 activation reversed memory impairment and hippocampal damage caused by the cytotoxic effects of Amyloid-β peptide.[65] Additional lines of evidence documented the potential role for the TRPV1 channel in schizophrenia.[78] Importantly, it merits consideration that the

TRPV1 channel has been detected in brain areas that are involved in the control of stress such as the hippocampus, locus coeruleus, medial prefrontal cortex, hypothalamus, and dorsolateral periaqueductal gray (dlPAG).[79] In this regard, the TRPV1 channel in dlPAG has been implicated in the attenuation of cannabidiol (CBD)-mediated anxiolysis.[79]

TRPV1 and disorders of the auditory system

In the study of Takumida *et al*. (2005), the authors documented that the TRPV1 channel was detected in the inner ear of guinea pigs; more specifically, in hair cells and supporting cells of the organ of Corti; spiral ganglia of the cochlea; and the vestibular end organs.[80] Further, multiple studies showed that the cochlear expression of the TRPV1 channel was involved in drug-induced cochleotoxicity (hearing loss) during systemic inflammation.[81] Additionally, TRPV1 expression was up-regulated in the vestibular and spiral ganglia in the inner ear of mice after kanamycin challenge.[82] Besides, earlier studies shed new light on the role of the TRPV1 channel in cisplatin ototoxicity as its absence provided protection against hearing loss.[83] In addition, a significant amount of research has shown that several cochlear stressors (e.g. noise and ototoxic drugs) affect the TRPV1 channel indicating the role of this channel in the regulation of cytoprotection and/or cell death pathways.[83] Consistent with these findings, it was found that inhibiting inflammation or oxidative stress decreased TRPV1 expression, modulated the apoptotic and inflammatory signals and provided protection against cochlear damage and hearing loss.[83]

TRPV1 and disorders of the ocular system

It is well documented that the TRPV1 channel is expressed in different regions of the lens including the epithelium, outer cortex and inner cortex.[35,84] *In vivo*, TRPV1 absence was associated with impairment in the healing of the epithelium in debrided corneal defects in rodents.[84] Furthermore, a considerable body of work has revealed that TRPV1 activation by mechanical injury causes cytoskeletal rearrangement, an increase in Ca^{2+} concentration, and enhances the migration of isolated retinal astrocytes.[85] In ganglion cells, it has been published that the increase in intraocular pressure augments TRPV1 expression, which is involved in protecting ganglion cells from apoptosis.[86] Additionally, the application of capsaicin to the corneal epithelium causes TRPV1 activation, an increase in intracellular Ca^{2+} concentration, the release of inflammatory mediators, and protection against infection by microorganisms.[87]

TRPV1 and anosmia/ageusia

People experience a burning sensation on their tongues when eating chili peppers. Thus, multiple studies have highlighted the involvement of the TRPV1 channel in taste perception.

Remarkably, the TRPV1 channel is expressed in neurons innervating the oral cavity.[88,89] There are several pieces of evidence indicating that the TRPV1 channel responds to a number of substances (e.g. allicin, capsaicin, alcohol and gingerol) and modifies salt stimuli.[90] Also, appealing evidence shows that a TRPV1 channel variant is expressed in the epithelial cells and taste buds of the tongue.[89] Besides, it has been reported that TRPV1 polymorphisms are linked to alterations in the sensitivity to the taste of salts.[91] Notably, earlier research mentions that capsaicin can decrease sucrose preference and inhibit voltage-dependent Na^{+} channels in taste cells in TRPV1 knockout mice.[91] In this context, Hu *et al*. (2016) reported that the TRPV1 channel was involved in rimonabant-induced olfactory discrimination deficit and that the impaired olfactory discrimination was rescued by the TRPV1 antagonist capsazepine.[92] Further, the TRPV1 channel seems to be linked to the anosmia/ageusia symptoms in COVID-19 patients.[51,52]

TRPV1 and infections

Several reports demonstrated that the TRPV1 channel plays important roles in bacterial, fungal and viral infections.[51,52,93–95] In more detail, Maruyama *et al*. (2017) reported that the topical *Candida albicans* skin infection stimulated the release of calcitonin gene-related peptide (CGRP) in a TRPV1 dependent manner during bone infection.[93] Another study showed the beneficial effects of TRPV1 ablation on inducing immunosuppression against *Streptococcus pyogenes* in the skin.[94] Likewise, the TRPV1 channel has been implicated in the anti-inflammatory and immunosuppressive responses in animals infected with *Staphyloccocus aureus* in the skin and lung.[95,96] In a model of sepsis (cecal ligation and puncture), it was revealed that the animals that are deficient in the TRPV1 channel suffered from severe symptoms such as decreased phagocytosis in macrophages, increased apoptosis of peritoneal mononuclear cells, increased levels of inflammatory mediators, decreased levels of ROS, and reduced bacterial clearance.[21] In fact, the link between the TRPV1 channel, Ca^{2+} concentration and ROS provides evidence for the involvement of the TRPV1 channel in viral infections.[97] More precisely, an accumulation of knowledge showed that Ca^{2+} entry into the cells is of key importance to the viral lifecycle at several steps including its entry, replication, assembly, and release.[98] Further, it has been reported that there is interplay between the increase in intracellular Ca^{2+} and ROS levels in mitochondria, which is crucial for the lifecycle of many viruses.[99]

As shown from previous studies, the TRPV1 channel is one of the receptors that provide favorable environments for viruses including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[51,52] The wide expression of the TRPV1 channel in tissues that were frequently infected by SARS-CoV-2 suggests that the channel plays a crucial role in COVID-19, one of the world's worst pandemics in the current century. In the review of Jaffal and Abbas (2021), the authors summarized the studies that demonstrated a correlation between the TRPV1 channel and several symptoms of COVID-19 including fever, pain, myalgia, inflammation, cough, headache, pulmonary edema, anosmia, ageusia, as well as problems of the GI and cardiovascular systems.[51] Also, the TRPV1 channel can be implicated in other manifestations of COVID-19 disease such as anxiety as well as visual, renal, and hepatic problems.[51] Figure 3 shows a representation of a SARS-CoV-2-induced cytokine storm,[52] which is considered the leading cause of death in COVID-19 patients. The activation of the TRPV1 channel in the peripheral nervous system (PNS) and CNS contributes to Ca^{2+} influx and the release of neuropeptides that induce liberation of more inflammatory mediators. These mediators cause sensitization of more TRPV1 channels, among others leading to excessive stimulation and providing a favorable environment for SARS-Cov-2. In summary, the inflammatory cytokine storm produces a loop of amplified release of mediators at different levels leading to more adverse outcomes.

TRPV1 and disorders of the reproductive system

It is well known that the TRPV1 channel is expressed in the head, midpiece, and tail of sperm and is involved in the regulation of acrosomal reaction and sperm capacitation.[33,100] As such, there is correlation between TRPV1 expression and the fecundity po-

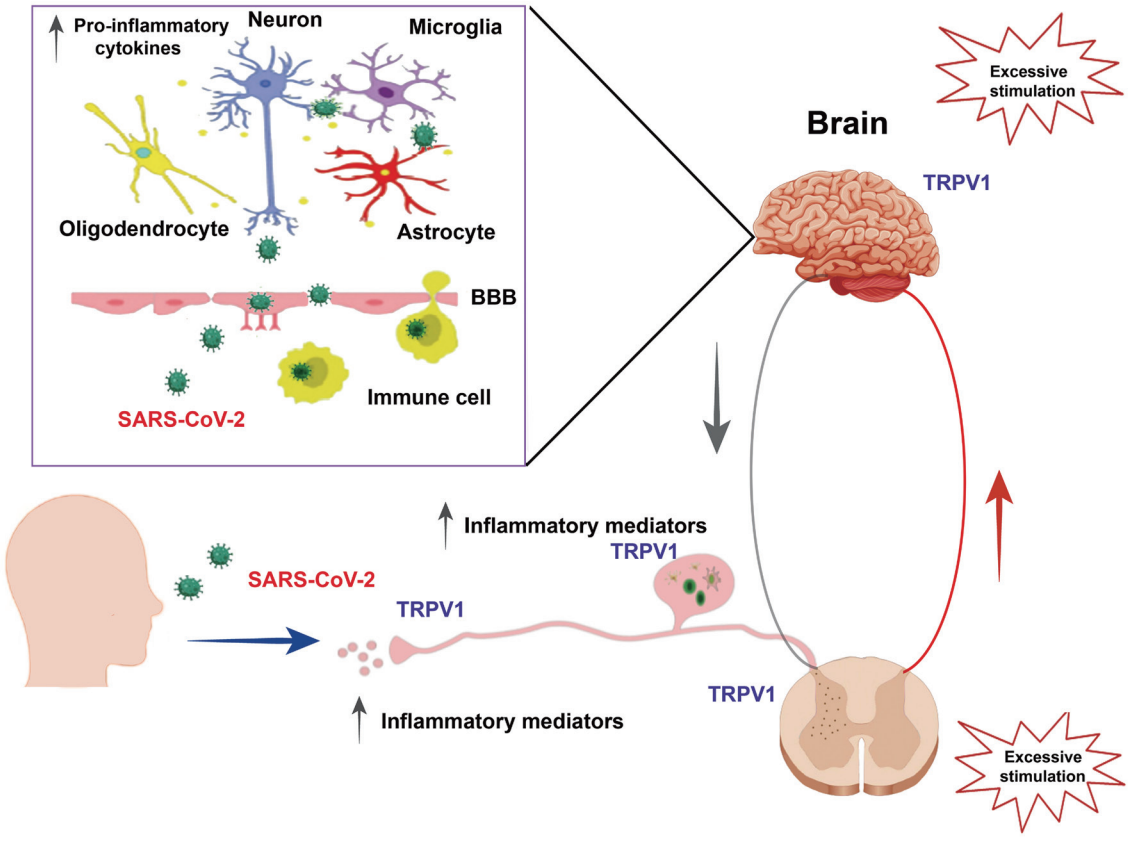

Fig. 3. Representative sketch for the cytokine storm in Coronavirus disease 2019 (COVID-19) and the involvement of the transient receptor potential vanilloid 1 (TRPV1) channel (Modified from Jaffal, 2021).[52] Severe acute respiratory syndrome coronavirus (SARS-CoV-2) can cross the blood brain barrier (BBB) and cause more devastating effects. During COVID-19, the activation of the TRPV1 channel in the peripheral nervous system (PNS) and central nervous system (CNS) contributes to calcium (Ca^{2+}) influx and the release of neuropeptides that induce the liberation of more inflammatory mediators. These mediators cause sensitization of more TRPV1 channels, among others leading to excessive stimulation and providing a favorable environment for SARS-Cov-2. DRGs, dorsal root ganglia.

tential of sperm.[33] In this context, earlier reports have shown that the TRPV1 channel is downregulated in the spermatozoa of idiopathic infertile men, subfertile men, and normozoospermic infertile males.[33] Further, in TRPV1 knockout mice, it was found that the testes of mice were more susceptible to oxidative stress, testicular damage, and dysfunctional sperm development.[101] It was also found that vulvodynia (a condition of pain in the opening of vagina) is linked to more epithelial innervation when accompanied by more TRPV1 expression in vulva.[102] Besides this, the TRPV1 channel contributes to the sensory symptoms experienced by patients who suffer from hyperalgesia, allodynia, and a burning sensation in the vulvar vestibulus region.[102]

TRPV1 and disorders of the respiratory system

A remarkable amount of literature demonstrates that the TRPV1 channel is expressed in several regions in the upper and lower respiratory tracts such as the vascular endothelial cells, submucosal gland cells, smooth muscle cells, cholinergic neurons, inflammatory cells, laryngeal epithelial cells, blood vessels, fibroblast cells, T cells, and the airway epithelium.[103,104] Also, the TRPV1 channel is expressed in neurons of the vagal nerve that innervate the airways.[38] Moreover, previous studies highlighted that TRPV1 antagonism decreased airway hyperresponsiveness in guinea pigs and exerted anti-tussive effects in a capsaicin-induced cough model of guinea pigs.[105,106] In line with the involvement of the TRPV1 channel in respiratory disorders, it was found that TRPV1 expression increased in patients suffering from chronic obstructive pulmonary disease (COPD) and chronic cough.[107,108] In addition, the TRPV1 channel was critical for the effect of NGF (when administered via inhalation or intracerebroventricular (ICV) injection) in enhancing cough and airway obstruction in guinea pigs.[109,110] Moreover, accumulated data suggest that the activation of the TRPV1 channel on respiratory effector cells can lead to tracheal mucosal edema, bronchoconstriction, protein secretion and inflammatory cell chemotaxis.[109,111] Interestingly, earlier reports have shown a relationship between TRPV1 single nucleotide polymorphisms (SNPs) and protective effects against wheezing in patients who suffer from asthma.[112] Additionally, a recent study documented the increase in TRPV1 expression in rhinovirus that contributes to asthma exacerbations.[113] In this regard, several studies have shown that capsaicin nasal spray is useful in the treatment of idiopathic rhinitis.[114]

TRPV1 and obesity

Previous reports have demonstrated that the TRPV1 channel is expressed in adipocytes and plays a key role in the regulation of metabolic processes that are related to obesity.[115,116] Capsaicin promotes weight loss by increasing the sympathetic nervous system activity, decreasing appetite as well as increasing energy expendi-

ture, fat oxidation, insulin and leptin resistance.[117,118] Furthermore, capsaicin improves endurance capacity and energy metabolism in skeletal muscles.[119]

The findings of a recent meta-analysis of clinical trials showed that the daily consumption of capsiate (a non-pungent vanilloid) or capsaicin increased thermogenesis and decreased appetite, and can thus be useful in weight management.[120] Further, it has been published that dietary capsaicin and capsinoids increase energy expenditure and thermogenesis mediated by an increase in brown adipose cells and a decrease in white adipogenesis.[115] It is evident that the administration of low-dose dietary capsaicin improved insulin sensitivity, increased fat oxidation, decreased body fat and improved the functions of liver.[116] Despite that, there are conflicting results about the role of the TRPV1 channel in weight management due to the risk of developing myocardial infarction.[121] Of note, the effects of capsaicin depend on the administered dose and duration of its application. Further research is needed in this regard.

TRPV1 and disorders of the GI tract

In the GI tract, the TRPV1 channel is expressed in the afferent neurons (vagal and spinal) in the esophagus, jejunum, stomach, rectum, colon as well as the small intestine.[16,119,122] In fact, accumulated evidence supports the findings that TRPV1-labeled nerve fibers are distributed in each layer of the GI tract including submucosa, mucosa, muscle, and myenteric plexus.[123] Thus, the TRPV1 channel is implicated in the cases of irritable bowel syndrome (IBS), neurogenic pancreatitis, and ileus.[123] It is well established that CGRP released after TRPV1 activation in primary nociceptive nerves leads to a strong inhibitory effect on gastric acid induced irritation.[124] Additionally, many substances (e.g. tachykinins) are released when the TRPV1 channel is activated causing gastric motility and acceleration for gastric emptying.[125] Furthermore, it has been illustrated that ulcer formation in rats is suppressed by the injection of low dose capsaicin and that the perfusion of capsaicin into the stomach of rats can inhibit gastric mucosal injury.[126,127] Evidently, several studies have been published about the effects of capsaicin on reducing the symptoms of functional dyspepsia caused by duodenal and gastric dysfunction, reducing upper abdominal symptoms as well as increasing GI dysfunction, leading to IBS-related symptoms.[19] Interestingly, TRPV1 expression increased in a rat model of chronic pancreatitis and in patients of ulcerative colitis and Crohn's disease.[128,129] Further, it is increasingly apparent that the channel is involved in gastric pain hypersensitivity and gastroesophageal reflux disease.[123] Moreover, it was revealed that capsaicin could improve liver function in a mouse model of hepatic failure.[130] The fact that TRPV1 expression has been found to increase in oesophagitis, colonic inflammation, acute haemorrhoidal disease, and distal colitis is further evidence of the involvement of the TRPV1 channel in the disorders of the GI tract.[8]

TRPV1 and disorders of the cardiovascular system

Previous studies have confirmed that the TRPV1 channel is densely expressed in the sensory neurons that innervate the ventricles, endothelial cells, epicardial surface of the heart, myocardium, cardiomyocytes, the adventitia of the ascending aorta, aortic arch, and the vascular smooth muscle cells.[131] Moreover, TRPV1 expression is detected in large arteries, aorta and carotid arteries.[132] Following this, other studies have shown that the TRPV1 channel plays a role in sensing blood pressure fluctuations.[133] Furthermore, it has been found that TRPV1 activation mediates the hypotensive action and is implicated in myogenic vasoconstriction in the Bayliss reflex in the resistance arteries.[10,134] In this regard, previous studies showed that the administration of capsaicin increased coronary flow and decreased left ventricular end diastolic pressure and infarct size in wild type mice.[135] In addition, it has been found that TRPV1 activation can alleviate atherosclerosis induced by a high-fat diet in mice through cellular cholesterol cleavage.[136] Specifically, dietary capsaicin decreased atherosclerosis by regulating lipid metabolism and decreasing endothelial dysfunction.[136,137] According to Harper *et al*. (2010), TRPV1 receptors that exist on platelets can promote inflammatory mediators leading to platelet activation and the formation of atherosclerosis.[138] The TRPV1 channel, being expressed in the perivascular nerves, also plays a crucial role in cardioprotection by stimulating the release of potent neuropeptides such as CGRP and SP that cause vasodilation or vasoconstriction.[138–140] Moreover, it has been documented that there is association between decreased expression of the TRPV1 channel in metabolic syndrome and increased ischemic reperfusion injury in isolated mice hearts.[141] Further, emerging evidence indicates that the TRPV1 channel mediates relaxation of smooth muscle cells in the endothelium.[142] However, previous studies have implicated that high consumption of capsaicin can cause myocardial infarction and vasospasm.[143] In this regard, Song *et al*. (2017) documented that TRPV1 activation is responsible for the contraction of smooth muscle cells in pulmonary artery, vasoconstriction and the pathogenesis of idiopathic pulmonary arterial hypertension.[144]

TRPV1 and diabetes

A considerable body of work shows that nerve fibers that express the TRPV1 channel innervate Langerhans islets in the pancreas.[145] Also, previous research has confirmed an alteration in the activity and/or expression of the TRPV1 channel in insulin resistance.[118] In the long-term diabetic microenvironment, earlier studies demonstrated that TRPV1 desensitization in DRGs decreased TRPV1 activity and contributed to peripheral diabetic neuropathy.[146] Furthermore, the injection of capsaicin attenuated hyperglycaemia in Zucker diabetic fatty animals which is a model of human type 2 diabetes mellitus.[145] In this sense, TRPV1 knockout mice exhibited impairment in glucose metabolism manifested by a decrease in glucose-induced insulin secretion.[147] Importantly, it has been found that the TRPV1 channel is a modulator for clock gene oscillations in black adipose tissue (BAT) and is involved in the regulation of hepatic functions and glucose metabolism.[148,149] Besides, earlier studies revealed that hepatic glycogen storage was compromised in TRPV1 knockout mice due to impairment in glucose homeostasis.[149] Further, it was shown that the livers of TRPV1 knockout mice exhibited changes in proteomics and a decrease in glycogen storage in addition to an enhancement in glycogenolysis, gluconeogenesis, and the levels of inflammatory parameters.[149]

TRPV1 and disorders of the cutaneous system

The burning feeling of capsaicin in the skin was discovered by Hogyes in 1878 before the discovery of the TRPV1 channel.[33] Since then, several studies have been conducted to unravel the effects and mechanisms of the TRPV1 channel on different systems including the cutaneous system. In the skin, it is evident that the TRPV1 channel presents in epidermal keratinocytes, mast cells, epithelial cells of hair follicles, blood vessels, eccrine sweat glands, keratinocytes, nociceptors, immune cells, sebocytes, fibroblasts, and melanocytes.[33,150] Interestingly, it has been documented that TRPV1 positive nociceptors in hair follicles play a role in the proliferation and migration of stem cells to improve healing.[151] Many people have used capsaicin to treat psoriasis, atopic dermatitis, and aller-

gic contact dermatitis.[152–154] Also, the channel plays an important role in the healing of wounds in different models such as incision wounds, tape striping, burn wounds, corneal wounds and ultraviolet B wounds.[33] Therapeutically, it has been found that honokiol (a natural compound extracted from magnolia plants) is effective in treating third degree burns by decreasing the mRNA and protein expression of TRPV1.[155] Moreover, in one study, mice lacking the TRPV1 gene showed reduction in histamine-induced scratching and itching sensation compared to wild-type mice.[156] Regarding hair growth, Bodo *et al*. (2005) suggested that the TRPV1 channel can influence human hair growth and that TRPV1-based therapy can be used for the treatment of hirsutism (unwanted hair growth), effluvium, and alopecia (hair loss).[157]

TRPV1 and headache

Several studies have unraveled the role of the TRPV1 channel in migraines. It is well known that one of the factors that contribute to migraines is the release of neuropeptides through the activation of trigeminal afferents in the cranial vasculature (trigeminovascular system).[158] Due to the expression of the TRPV1 channel in TGs and dural nerves, it is well documented that this channel is implicated in headache and migraine mechanisms.[159] In this regard, previous studies have shown that the anti-migraine drug sumatriptan alleviates headache in a TRPV1 dependent manner.[159] Other pieces of research elucidated the mechanisms of botulinum toxin A (BoNTA) in treating chronic migraine. The studies shed new light on the inhibition of TRPV1 trafficking to the plasma membrane in TGs and the decrease in capsaicin-induced pain after BoNTA treatment.[160,161] Moreover, many studies used TRPV1 agonists and antagonists to probe meningeal afferents and reported the effectiveness of TRPV1 agonists, rather than antagonists, in treating migraines.[162,163] In this regard, the repeated administration of intranasal capsaicin to chronic migraine patients resulted in 50–80% amelioration of migraine attack due to TRPV1 desensitization.[163] Likewise, it was found that the use of an intranasal TRPV1 agonist (civamide) decreased the frequency of headache attacks in 72.7% of patients and caused absence of pain in 33% of patients.[164] Importantly, it has been revealed that neurogenic vascular effects of the TRPV1 channel are implicated in migraine pathophysiology through CGRP release and dural vasodilation.[158] Widely popular, pro-inflammatory mediators stimulate trigeminal nociceptors possibly via the TRPV1 channel highlighting the role of the TRPV1 channel in migraines and the role of non-steroidal anti-inflammatory drugs (NSAIDs) in treating them.[165,166] Of relevance, it was found that the transient receptor potential ankyrin 1 (TRPA1) channel requires co-activation of the TRPV1 channel to initiate afferent signaling from the meninges and that ethanol triggers migraine attacks through release of CGRP in a TRPV1-dependent manner.[167–169]

TRPV1 and disorders of the urinary system

In the urinary tract, the TRPV1 channel is expressed in sensory nerve fibers, smooth muscles and the urothelium.[169] Importantly, the expression of the TRPV1 channel has been correlated with the severity of inflammation in interstitial cystitis or bladder pain syndrome.[170] According to clinical studies, capsaicin is recommended for the treatment of neurogenic bladder hyperreflexia as it causes a decrease in bladder capacity, pressure threshold for micturition and the patients' desire to void.[17] Also, the TRPV1 channel is expressed in the renal pelvis and contributes to the maintenance of diuresis, natriuresis, water and Na^+ homeostasis.[171] Additionally, previous findings have shown that the TRPV1 channel responds to many chemicals (e.g. allicin, alcohol, capsaicin, and gingerol) that are known to modify salt stimuli.[172] In this context, capsaicin has been effective in treating incontinence in people suffering from dysfunctional micturition reflex.[40] Additionally, recent preclinical data revealed that TRPV1 activators improved the outcome of ischemic acute kidney injury.[173]

TRPV1 and disorders of the muscular system

It is well established that the TRPV1 channel is expressed in muscle afferents and is involved in muscle nociception and muscle pain conditions.[8] Moreover, TRPV1 mutations are associated with muscle disorders such as exertional heat stroke and malignant hyperthermia.[24] Additionally, several studies have shown that TRPV1 activation leads to Ca^{2+} release, membrane excitability, neurotransmitter release, and muscle contraction.[174] Supporting this contention, it has been revealed that the upregulation of nitric oxide and peroxynitrite in overloaded muscle activates the TRPV1 channel.[175] Also, TRPV1 knockout mice exhibited stronger muscles with improvement in neuromuscular function compared to wildtype counterparts.[24] In frogs, it was documented that TRPV1 activation decreased the tension of fast skeletal muscle fibers causing a change in muscle activity.[176]

TRPV1 and disorders of the skeletal system

It has been long recognized that capsaicin attenuates key parameters that are responsible for symptoms of adjuvant arthritis.[177] Also, there is mounting evidence that the TRPV1 channel is involved in bone remodeling and bone diseases such as osteoporosis which is characterized by a decrease in bone density, increase in bone resorption, and fragile bones.[178,179] In this context, Alexander *et al*. (2013) reported the up-regulation of the TRPV1 channel in osteoclasts obtained from osteoporotic patients.[178] In addition, it was found that TRPV1 genetic deletion, inhibition, or desensitization in mice decreased the activity of osteoclasts *in vitro* and inhibited ovariectomy-induced bone loss as well as osteoporosis *in vivo*.[179] Moreover, previous studies documented that capsazepine inhibited the differentiation of osteoclasts and osteoblasts *in vitro* as well as ovariectomy-induced bone loss *in vivo*.[180] Accordingly, it is strongly suggested that the TRPV1 channel is involved in several bone problems.

Pharmacological agents that interact with the TRPV1 channel

As the TRPV1 channel is involved in multiple biological and pathological processes, several pharmacological agents that target this channel have been synthesized and it is increasingly recognized that there are multiple endogenous and exogenous agonists for the TRPV1 channel.[181] Capsaicin is an exogenous TRPV1 agonist extracted from the plant *Capsicum annuum* L.[182] The agonistic action of capsaicin has been exploited therapeutically by synthesizing patches that include high doses of capsaicin, leading to TRPV1 desensitization.[143] Remarkably, accumulating knowledge illustrates that capsaicin creams and patches attenuate pain due to TRPV1 desensitization on local cutaneous nociceptors and a loss of responsiveness to many sensory stimuli.[9] Accordingly, capsaicin (8% patch; Qutenza™) was approved by the United States Food and Drug Administration in 2009 for the treatment of postherpetic neuralgia-induced neuropathic pain.[143] Also, it has been revealed that capsaicin, formulated as a topical cream or a transdermal patch, is effective for the management of pain in minor muscle strains or cramps and joint pain.[143] On the other hand, many endogenous agonists (also called endovanilloids) for the TRPV1 channel have been identified including anandamide,

N-oleoylethanolamine, *N*-Arachidonoyl-dopamine, *N*-oleoyl dopamine, lysophosphatidic acid, 20-hydroxyeicosatetraenoic acid, AM-404, hydroperoxyeicosatetraenoic acids [5-(*S*), 8-(*S*), 12-(*S*) and 15-(*S*)], hepoxilins A3, ATP, ammonia, polyamines (e.g. spermine, spermidine, putrescine), linoleic acid, in addition to 9, 13 and 20-hydroxyoctadecadienoic acid.[181] TRPV1 antagonists are classified into competitive or non-competitive antagonists according to their binding sites.[181,182] Capsazepine is the first reported competitive TRPV1 antagonist that blocks capsaicin-or RTX-induced channel activation. Other examples include JYL-1421, A-425619, BCTC, JNJ-1720, SB-705498, SB-366791, AMG-9810, MK2295 and AMG-2674.[181,182] Examples of non-competitive antagonists are ruthenium red, RRRRWW-NH_2, methoctramine, AG-489, AG-505, DD-161515, and DD-191515.[181] In another context, TRPV1 antagonists can be classified according to their effects on body temperature. In more detail, the antagonists can increase, decrease, or un-change body temperature. Some antagonists (e.g. AMG-0347 and AMG-517) can cause hyperthermia, which is a drawback, while hypothermia can be caused by other antagonists such as A-1165901. Meanwhile, one group of antagonists do not change body temperature (thermoneutral antagonists).[182]

Future directions

There is no doubt that the TRPV1 channel is an important therapeutic target and that the pharmacological modulators of the TRPV1 channel can be potential drug targets for several disorders. The fact that there are drawbacks for several TRPV1 antagonists that are available in the market strengthens the need to discover novel TRPV1 modulators.[181,182]

TRPV1 modulation has been implicated in the anti-nociceptive effect of several medicinal plants, a finding that was proved by molecular docking studies.[183–185] In accordance with this idea, Abbas, (2020) reviewed 137 natural ingredients that affect TRPV1 activity in different *in vivo* and *in vitro* assays.[186] On the other hand, it has been long recognized that several toxins or venoms extracted from snakes, frogs, bees, spiders, scorpions, and marine organisms can act as TRPV1 modulators.[1,7,51] Continuing the search for novel compounds that can be exploited therapeutically and target the TRPV1 channel without adverse effects is of vital importance.

Conclusions

Since its cloning in 1997, research on the TRPV1 channel has grown rapidly. Several reports have documented the role of the TRPV1 channel in many biological and pathological conditions. Accordingly, attention has been directed towards the development of effective drugs that target the TRPV1 channel to treat different diseases. This review provides knowledge on the functions of the TRPV1 channel in health and diseases and highlights its importance as a target in pharmaceutical industries.

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