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Review

Transient receptor potential vanilloid (TRPV) channels: Basal properties and physiological potential

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Abstract. Transient receptor potential vanilloid (TRPV) channels are TRP homologs and have been classified into six subfamilies. They are unique mediators of sensory signals with multiple physiological effects and are potential targets for developing new therapies targeting human diseases. TRPV channels play crucial roles in normal physiological processes, and their dysfunction has been implicated in various disease states. Several small-molecule compounds, such as TRPV1 and TRPV3 antagonists, have been developed as novel analgesic agents. A better understanding of the physiological functions of TRPV channels would lead to progress in life science. In this review, we focus on various functions of TRPV channels, including pain sensing, temperature sensing, and metabolic control, as well as summarize the basal properties and pathophysiological contributions of six TRPV channels. Moreover, we discuss the pharmacological effects of endogenous and exogenous ligands on TRPV channels and related diseases.

Key words: TRPV channels — Sensory system — Channel diseases — Drug discovery

Abbreviations: CB, cannabinoid; CGRP, calcitonin gene-related peptide; CNS, central nervous system; COVID-19, coronavirus disease 2019; cryo-EM, cryo-electron microscopy; DIO, diet-induced obesity; DPN, diabetic peripheral neuropathy; DRG, dorsal root ganglion; GLP-1, glucagon-like peptide-1; GPR, G-protein coupled receptor; KO, knockout; MMP, metalloproteinase; PPAR, peroxisome proliferator-activated receptor; STZ, streptozotocin; TRP, transient receptor potential; TRPA, transient receptor potential ankyrin; TRPC, transient receptor potential canonical; TRPM, transient receptor potential melastatin; TRPML, transient receptor potential mucolipin; TRPN, transient receptor potential "nompC" (from no mechanoreceptor potential C); TRPP, transient receptor potential polycystin; TRPV, transient receptor potential vanilloid.

Introduction

Transient receptor potential (TRP) channels have been extensively studied worldwide since the identification of the Drosophila *trp* gene in 1989 (Montell and Rubin 1989). A large number of *trp*-encoded proteins form non-selective cationic channels. As a result of gene analysis, many TRP homologs have been identified and classified into seven subfamilies: TRPC (canonical), TRPM (melastatin), TRPV (vanilloid), TRPML (mucolipin), TRPP (polycystin), TRPA (ankyrin), and TRPN (nompC) (Gees et al. 2012). Among these, members of the TRPV family are activated by mechanical stimulation, thermal stimulation, and changes in pH or osmotic pressure. Importantly, TRPV channels are activated/inactivated by a number of ligands and are associated with various diseases, in

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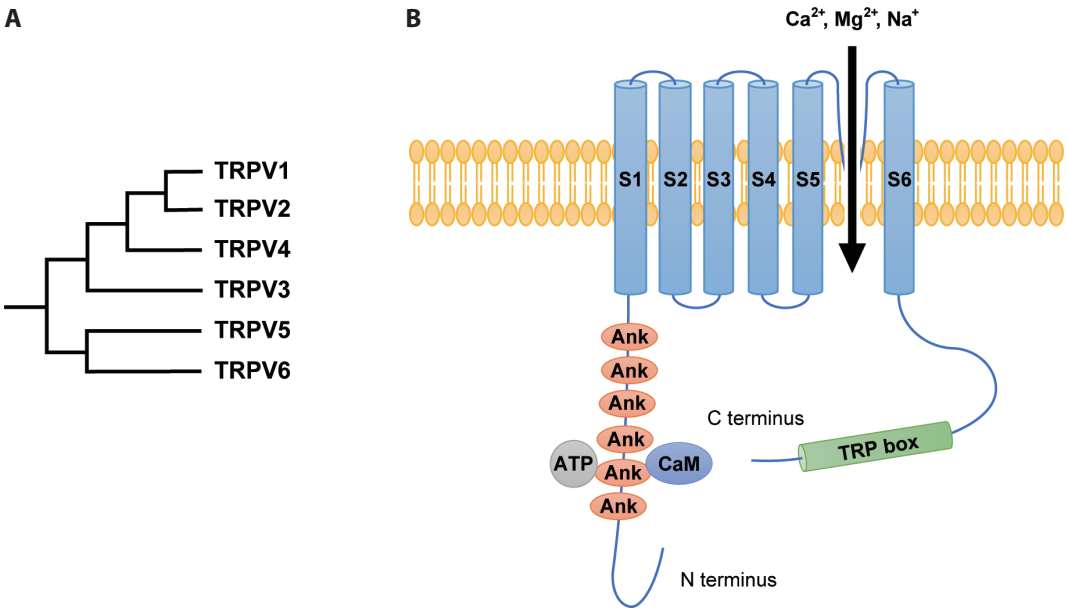


Figure 1. Phylogenetic tree (**A**) and common structure (**B**) of TRPV family. Structurally, TRPV family has two domains. S1–S4 voltage-sensing domains associates with the transmembrane segments S5–S6 containing the pore region. TRPV1 is a tetramer, and its pore-like structure comprises the large basket-shaped cytoplasmic and transmembrane regions. TRPV family has six ankyrin (Ank) repeat domains at their N-termini. Ank repeat of TRPV1 has an ATP-binding site and a calmodulin (CaM)-binding site, important for channel activation and inactivation, respectively. TRP-box in the C-terminal region is important for activating channel gating and protein tetramerization.

addition to acting as temperature receptors and noxious stimulus receptors.

The TRPV family is composed of TRPV1–6 (Fig. 1A), and there are six ankyrin (Ank) repeat domains at their N-termini in mammals (Montell 2001; Clapham 2003). The three-dimensional structure of Ank repeat has been determined for TRPVs; Ank repeat of TRPV1 has an ATP-binding site and a calmodulin (CaM)-binding site, which are important for channel activation and inactivation, respectively (Lishko et al. 2007). On the other hand, the TRPV family has a TRP-box in the C-terminal region, which is important for activating channel gating and protein tetramerization (Garcia-Sanz et al. 2004, 2007) (Fig. 1B). In recent years, the structure of the TRPV family has been analyzed using cryo-electron microscopy (cryo-EM). For example, TRPV1 is a tetramer, and its pore-like structure comprises the large basket-shaped cytoplasmic and transmembrane regions (Moiseenkova-Bell et al. 2008).

Although there are several reports focus on TRPVs' ligands and specific diseases (Woudenberg-Vrenken et al. 2009; Robbins et al. 2013; Seebohm and Schreiber 2021; Zhang et al. 2021; Liu et al. 2022), no review article widely covers TRPV family and development of their ligands and diseases. In this review article, we focus on various functions of TRPV channels, including pain sensing, temperature sensing, and metabolic control; moreover, we summarize the basal properties and pathophysiological contributions of six characterized TRPV channels. In addition, we discuss the pharmacological effects of endogenous and exogenous ligands of TRPV channels including clinically developing drugs as well as diseases associated with TRPV channels (Table 1).

TRPV1

The capsaicin receptor TRPV1 was identified as vanilloid receptor subtype-1 (VR1) in 1997 by Caterina and colleagues (Caterina et al. 1997). Evidence suggests a crucial role for the TRPV1 channel in various physiological functions (Szallasi and Blumberg 1999). Multiple painful stimuli, electrical voltage, lipids, and phosphorylation activate the TRPV1 channel, and TRPV1 knockout (KO) mice reduce thermal hyperalgesia in response to inflammatory mediators. TRPV1 agonists induce pain-related behavior in mice, and such behavior is diminished in TRPV1-null animals. Pharmacological blockade shows analgesic effects in various pain models, including arthritic and cancer pain. On the other hand, TRPV1 channels in sensory nerve afferents play a key role in physiological glucose control, and deregulated TRPV1 activity is implicated in pathological mechanisms involved in diabetes. A TRPV1-deficient mouse model demonstrated

Table 1. Distribution, ligands, and related human diseases of temperature sensitive TRPV channels

TRPV channel	Distribution	Agonists	Antagonists	Related diseases
TRPV1	Brain Sensory nerve Lung Kidney Liver Pancreas	Anandamide Oleoylethanolamide Palmitoylethanolamide Capsaicin Zucapsaicin Resiniferatoxin Gingerol Evodiamine Cannabidiol Palvanil	Capsazepine JTS-653 SAF-312 JNJ-38893777 α-Spinasterol Tivanisiran (siRNA)	Diabetic neuropathy Migraine Dry eye disease Irritable bowel syndrome
TRPV2	Brain Sensory nerve Spinal cord Liver Lung Spleen Colon Muscle Bladder endothelium Immune cells	Lysophospholipids Cannabidiol 2-APB Probenecid	Tranilast	Dilated cardiomyopathy Scapuloperoneal spinal muscular atrophy Intraocular lymphoma
TRPV3	Brain Sensory nerve Spinal cord Skin Stomach Colon	Farnesyl pyrophosphate Camphor Carvacrol Menthol	17(R)-resolvin D1	
TRPV4	Brain Skin Lung Kidney Bladder endothelium Vascular endothelium	Epoxyeicosatrienoic acids 4α-Phorbol 12,13-didecanoate Apigenin GSK1016790A	HC-067047 GSK205	Motor and sensory neuropathy Metatropic dysplasia Spondylometaphyseal dysplasia
TRPV5	Brain Kidney Pancreas Prostate Testes	17β-Estradiol 1α,25-Dihydroxy vitamin D3	ZINC17988990 Econazole Miconazole	Nephrolithiasis Kidney stone disease
TRPV6	Brain Lung Intestine Kidney Liver Pancreas Uterus Placenta Skin	1α,25-Dihydroxy vitamin D3	2-APB cis-22a 3OG CBP-1008 SOR-C13	Hyperparathyroidism Pancreatitis Kidney stone formation Bone resorptive diseases Cancer

TRPV, transient receptor potential vanilloid; 2-APB, 2-aminoethoxydiphenyl borate.

improved glycemic control in a diet-induced obesity (DIO) model. A cryo-EM structure of TRPV1 at 3.4 Å resolution was determined and reported by Liao et al. (2013). An overview of representative endogenous and exogenous ligands of TRPV1 is presented in Figure 2 and Table 2.

Human diseases related to TRPV1

Neuropathic pain

Diabetic peripheral neuropathy (DPN) is a major microvascular complication of diabetes that frequently occurs in the early stages of diabetes and involves the peripheral nerves. Generally, when DPN develops, the small nerve fibers are initially affected, and large nerve fibers are gradually damaged, leading to neuropathic pain. Because TRPV1 is highly expressed in dorsal root ganglion (DRG) and small sensory C and Aδ fibers, TRPV1 is involved in DPN. Streptozotocin (STZ)-induced diabetic mice show thermal hyperalgesia in the initial phase (1–2 weeks after STZ injection) and thermal hypoalgesia in the late phase (>6 weeks after STZ injection). In the initial phase, expression of TRPV1 in the DRG was upregulated, and in the later phase, it was downregulated. Both phenotypes were diminished in TRPV1 KO mice treated with STZ (Pabbidi et al. 2008).

Some TRPV1 antagonists, such as JTS-653, are expected to be therapeutic drugs for neuropathic pain, such as DPN and post-herpetic pain (Kitagawa et al. 2013). In addition, excessive stimulation by agonists desensitizes TRPV1, which may be caused by tachyphylaxis, leading to the topical application of TRPV1 agonists as long-lasting analgesic drugs. Qutenza is a first approved capsaicin transdermal patch indicated for the treatment of neuropathic pain associated with DPN and postherpetic neuralgia (PHN) (Anand and Bley 2011). In addition to capsaicin and its derivatives, compounds with other structures have been developed as topical analgesic drugs.

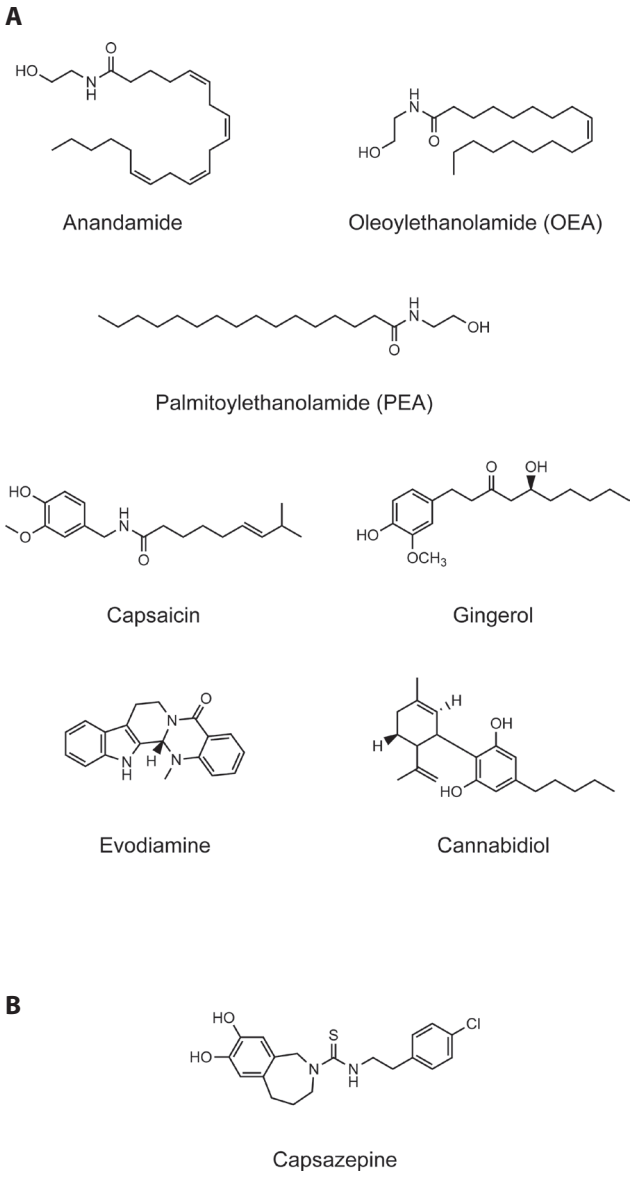


Figure 2. Chemical structures of TRPV1 agonists (**A**) and antagonist (**B**).

Migraine

Migraine is a neurological condition that causes various symptoms such as pulsing, debilitating headaches in one area of the head; it is a disorder of the brain. The pathogenesis of migraine is not fully understood; however, abnormal trigeminal and central nervous system (CNS) are deeply involved. TRPV1 is co-localized with calcitonin gene-related peptide (CGRP) in trigeminal ganglion neurons and is implicated in the pathophysiology of migraine (Shibata and Tang 2020). Activation of TRPV1 excites nociceptive afferent fibers and causes pain. Therefore, modulation of TRPV1 activity is thought to be able to control migraine. Zucapsaicin, a *cis*-isomer of capsaicin, has been developed as an acute care medication for episodic cluster headache (Rapoport 2012). The TRPV1 antagonists JNJ-38893777 and JNJ-17203212 are effective in animal models of migraine (Meents et al. 2015).

Dry eye disease (DED)

DED has become a growing problem over recent decades, owing to multiple factors, including increased office work using visual display terminals (VDT) or worsening of air pollution. These harsh environments lead to chronic pain on the ocular surface. DED is characterized by an alteration of tear film stability with ocular inflammation and neurosen-

sory abnormalities, such as ocular symptoms of discomfort and irritation. In severe cases, patients frequently complain of chronic pain and fluctuating vision, which significantly reduces their quality of life. Although the mechanisms underlying DED remain unclear, several TRP channels have been implicated in this syndrome. Among them, TRPV1 has been well-studied because of its important role in mediating enhanced nocifensive behaviors. In the cornea, TRPV1-immunoreactive nerve fibers co-express substance P or CGRP and potently contribute to nociceptive transduction. Furthermore, hypertonic stress, which might occur on the surface of the cornea in DED, increases pro-inflammatory cytokine interleukin (IL)-6 levels *via* activation of TRPV1 in human corneal epithelial cells (Pan et al. 2011). This evidence clearly indicates the involvement of TRPV1 activation in DED.

Table 2. Endogenous and exogenous ligands of TRPV1 channels and the pharmacological effects

Ligand	Pharmacological effects	Others
Endogenous agonist		
Anandamide	Vasodilation	MMP-2 induction
	Hypotension	Inflammation
		Behavioral disruption
Oleoylethanolamide	Modulation in lipid and glucose metabolism	Decrease in feeding behavior and motor activity
	Immunomodulation	
	Neuroprotection	
	Analgesic effect	
Palmitoylethanolamide	Anti-inflammation	
	Modulation of gut permeability	
	Hypotension	
Exogenous agonist		
Capsaicin	Modulation in glucose and lipid metabolism	
	Anti-inflammation	
	Anti-oxidation	
	Antidepressant-like effect	
	Anti-cancer	
Gingerol	Anti-diabetes	Increase of sodium absorption in colon
	Anti-inflammation	Decrease of gastric acid secretion
	Anti-cancer	Osteopenia
	Anti-vomiting	
	Modulation of intestinal contraction	
Evodiamine	Anti-obesity	
	Anti-inflammation	
	Atheroprotection	
	Neuroprotection	
	Anti-cancer	
	Anti-Alzheimer`s disease	
	Anti-anoxia	
	Anti-nociception	
Cannabidiol	Anti-inflammation	
	Anti-oxidation	
	Cytoprotection/neuroprotection	
	Anti-cancer	
	Modulation of intestinal permeability	
	Anti-anoxia	
Exogenous antagonist		
Capsazepine	Anti-neuropsychiatric disorder	
	Decrease of hyperalgesia	

MMP, matrix metalloproteinase.

Tivanisiran, a small interfering RNA (siRNA) of TRPV1, has been developed as a new drug for DED. Once-daily ocular instillation of 1.125% Tivanisiran for 10 days improved both signs – visual analogue scale (VAS) score and ocular surface disease index (OSDI) questionnaire score, and symptoms – corneal fluorescein staining (CFS) and conjunctival hyperemia – of the disease in clinical trials (Benitez-Del-Castillo et al. 2016).

Other diseases

TRPV1 in the visceral nerve is involved in hypersensitivity to gastrointestinal disorders such as irritable bowel syndrome (IBS). The TRPV1 agonist palvanil modulates intestinal motility and reduces visceral pain such that this modification of TRPV1 function may be applied in the treatment of IBS (Szymaszkiewicz et al. 2020).

Fibromyalgia is characterized mainly by symptoms of chronic widespread pain and comorbidities, such as depression. In a fibromyalgia model, TRPV1 was noted to be involved in nociception and depressive-like behavior. α-Spinasterol, a bioavailable phytosterol that acts as a TRPV1 antagonist, reduces both pain and depressive-like behavior in mice (Fischer et al. 2020).

Acute respiratory distress syndrome (ARDS) is one of the causes of death related to severe cytokine storm that leads to respiratory failure in coronavirus disease 2019 (COVID-19). TRPV1-positive nerve fibers are intimately related to immune cells that mediate airway inflammation after viral infection (Nahama et al. 2020). Activation of TRPV1 enhances the release of pro-inflammatory molecules such as substance P, CGRP, and cytokines that are upregulated in patients with COVID-19. Therefore, targeting TRPV1-expressing nerve fibers in the lungs with resiniferatoxin, an ultra-potent TRPV1 agonist, is expected to regulate inflammation and immune signals in order to reduce mortality in COVID-19 (Nahama et al. 2020).

Pharmacological effects of TRPV1 ligands

Endogenous agonists

• **Anandamide** is recognized as a brain constituent that can bind to the cannabinoid (CB) receptor, and it has the ability to modulate TRPV1 levels (Toth et al. 2009). Activation of the TRPV1 receptor by anandamide exposure produces hypotension and a decrease in systemic vascular resistance, suggesting a potential implication for the treatment of cardiovascular diseases (Hogestatt and Zygmunt 2002). The efficacy of anandamide as a TRPV1 agonist is affected by several factors, including CB1 receptor activation, voltage, temperature, and pH (Ross 2003). On the other hand, undesirable effects caused by anandamide treatment include matrix metalloproteinase (MMP)-2 induction, inflammation, and behavioral disruption (Miyashita et al. 2012).

• **Oleoylethanolamide (OEA)**, an endocannabinoid analog, is a natural fatty acid and an endogenous lipid mediator associated with control of feeding, body weight, and energy homeostasis (Laleh et al. 2019). OEA modulates lipid and glucose metabolism *via* TRPV1 activation; its potential efficacy is also exerted *via* other receptors, including peroxisome proliferator-activated receptor (PPAR)-α and G-protein coupled receptor (GPR) 119 (Laleh et al. 2019). PPAR-α agonists promote lipolysis, and GPR119 agonists improve glucose sensitivity in peripheral tissues. OEA is expected to be a novel supplement for the management of obesity in human (Laleh et al. 2019).

Immunomodulatory effects of OEA have also been reported. OEA downregulates toll-like receptor (TLR) 4/nuclear factor (NF)-κB and dendritic cell (DC) maturation through activation of TRPV1 and AMP-activated protein kinase (AMPK) (Yao et al. 2019). In addition, OEA possesses neuroprotective and analgesic properties in visceral and inflammatory pain (Portavella et al. 2018). The effects of OEA on feeding behavior and motor activity were investigated, and it was found that OEA suppresses feeding without causing visceral discomfort (Proulx et al. 2005; Wang et al. 2005).

• **Palmitoylethanolamide (PEA)** is an endogenous congener of anandamide and potentiates its actions *via* TRPV1 channels, CB1 and CB2 receptors, GPR55 receptor, and PPAR-α (Borrelli et al. 2015). PEA is a pleiotropic endogenous lipid mediator with anti-inflammatory and analgesic effects (Ambrosino et al. 2013). In *in vitro* studies, PEA regulates mast cell degranulation and substance P-induced histamine release and suppresses increased cytokine production. PEA prevents inflammation-induced hyperpermeability in the human colon, suggesting that its treatment ameliorates disorders related to increased gut permeability, including inflammatory bowel disease (IBD) (Couch et al. 2019). PEA plays a key role in digestive regulation through modulation of intestinal permeability. In STZ-induced diabetic rats, PEA administration reduces retinal inflammation, exhibiting retinal protective effects against diabetic retinopathy (Paterniti et al. 2015).

Anti-allodynic and anti-hyperalgesic effects in murine models are mediated *via* CB1 and PPAR-γ receptors, as well as TRPV1 channel (Costa et al. 2008), and protective effects in allergic dermatitis are exerted by activation of these receptors/channel (Petrosino et al. 2010). Additionally, PEA treatment induced hypotensive effects in a murine model (Marichal-Cancino et al. 2020).

Exogenous agonists

• **Capsaicin**, a direct agonist of TRPV1, is a key component of natural chili peppers. When capsaicin binds to TRPV1,

intramolecular twisting motion is caused within microsecond to millisecond time scale to take pore-opening structure (Fujimura et al. 2020). Capsaicin activates TRPV1 and induces cation influx to generate action potential. This action potential is followed by anion efflux-mediated depolarization *via* Ca^{2+}-activated chloride channel anoctamin 1 (Takayama et al. 2015).

The benefits of capsaicin have been investigated for the treatment of several diseases, such as metabolic syndrome, neuropathic pain, and cancer (Baskaran et al. 2019). Dietary capsaicin reduces insulin resistance and hepatic steatosis in DIO models by suppressing inflammatory responses and improving lipid metabolic disorders (Kang et al. 2010). Moreover, chronic dietary capsaicin promotes lipolysis by increasing levels of hepatic phosphorylated hormone-sensitive lipase, carnitine palmitoyltransferase (CPT) 1, and PPAR-δ (Li et al. 2013). In a renal ischemia-reperfusion model, capsaicin treatment prevented renal tissue damage through anti-inflammatory and anti-oxidative activities (Yu et al. 2018).

Capsaicin exhibited immunomodulatory effects in a rat model of experimental autoimmune neuritis, wherein reduced inflammation of the sciatic nerve was observed with histological changes, including reduction of T-cells, macrophages, and nerve demyelination (Motte et al. 2018). Rats administered capsaicin showed a reduction in immobility in forced swimming tests, suggesting antidepressant-like effects. Generally, in any tumor cell, anti-cancer effects have been reported after capsaicin treatment (Qian et al. 2016).

• **Gingerol** is a bioactive component of ginger, which is used not only as a spice but also as an herbal medicine (Tsuchiya et al. 2014; Tsuchiya and Kawamata 2018). Recent computational modelling showed that gingerol and other ginger compounds, which have a vanillyl moiety similar to capsaicin, interact with the S4–S5 linker of the TRPV1 channel like capsaicin (Yin et al. 2019). Gingerol exerts a variety of pharmacological and therapeutic effects, such as anti-diabetic, anti-inflammatory, anti-carcinogenic, and anti-emetic activities (Yu et al. 2017; Tsuchiya and Kawamata 2018). In obese type 2 diabetic *db/db* mice, gingerol treatment promoted glucose disposal in skeletal muscles and potentiated glucagon-like peptide (GLP)-1-mediated glucose-stimulated insulin secretion in pancreatic β-cells (Samad et al. 2017). In STZ-induced diabetic rats, gingerol minimized myocardial damage by inhibiting inflammation and oxidative stress (Yu et al. 2017).

Gingerol treatment reduced carcinoma incidence in a urethane-induced lung cancer model. A combination therapy of gingerol and capsaicin enhanced the inhibitory effects on lung carcinoma incidence (Geng et al. 2016). Gingerol regulates intestinal contraction and induces electrogenic sodium absorption in the rat colon (Tsuchiya et al. 2014; Tsuchiya and Kawamata 2018). Moreover, gingerol inhibits gastric acid secretion in mice (Okumi et al. 2012). As an undesired effect, gingerol reportedly induced trabecular osteopenia *via* activation of osteoclast formation (Khan et al. 2012).

• **Evodiamine** is a quinozole alkaloid extracted from *Evodia rutaecarpa* Bentham, a plant used in Chinese herbal medicine (Liu et al. 2013b). TRPV1 is known to show species-specific sensitivity to capsaicin. Both rat and human TRPV1 is sensitive to capsaicin but rabbit TRPV1 is insensitive to capsaicin. T550 residue located in the ligand binding area directly impact capsaicin binding and is an important determinant for capsaicin sensitivity in rat and human. Rabbit TRPV1 has I553 residue in this site and this substitution affects the space of the binding pocket to disturb the binding of the nonenyl tail of capsaicin (Gavva et al. 2004; Wang et al. 2012). On the other hands, pharmacophore modeling revealed that evodiamine occupies binding pockets of TRPV1 in various species include rabbit (Wang et al. 2012). Evodiamine exerts a variety of pharmacological effects, such as the following: anti-obesity, atheroprotective, neuroprotective, anti-inflammatory, anti-cancer, anti-Alzheimer's disease, antimetastatic, antianoxic, and antinociceptive (Fei et al. 2003; Wang et al. 2008, 2009; Liu et al. 2013b, 2015; Wei et al. 2013). Evodiamine inhibits adipogenesis in 3T3-L1 mice pre-adipocytes and alleviates diet-induced obesity in mice (Wang et al. 2008, 2009). In apolipoprotein E deficient mice, chronic administration of evodiamine inhibits the development of atherosclerosis and alleviates hyperlipidemia and systemic inflammation (Wei et al. 2013). Moreover, evodiamine increases the influx of extracellular calcium, which leads to c-Jun NH2-terminal kinase (JNK)-mediated protective autophagy, suggesting a new therapy for ischemic stroke (Liu et al. 2013b).

Evodiamine treatment induces anti-cancer effects, including the induction of apoptosis in tumor cells (Yuan et al. 2017) and calcium/JNK-mediated autophagy in human glioblastoma cells (Liu et al. 2013a). Anti-invasive and metastatic activities of evodiamine have also been reported in previous studies (Ogasawara et al. 2002). In an Alzheimer's disease model, evodiamine improves cognitive abilities by suppressing inflammatory cytokines and oxidative stress, which indicates neuroprotective ability (Zhang et al. 2018).

• **Cannabidiol** is a non-psychomimetic compound derived from *Cannabis sativa*, which is one of the oldest plants cultivated by humans. It exerts a number of pharmacological effects, such as anti-inflammatory, antioxidative, cytoprotective, and neuroprotective effects, and has anxiolytic properties (Atalay et al. 2019). Cannabidiol administration exerted an anti-hyperalgesic effect in a rat model of acute inflammation (Costa et al. 2004). In other reports, its potential in the treatment of inflammatory diseases, such as asthma, colitis, arthritis, and allergic dermatitis, has been revealed (Cuba et al. 2017; Petrosino et al. 2018; Klein et al. 2020). In a Caco-2

(human colorectal adenocarcinoma cells) cell culture system, cannabidiol modulates intestinal permeability.

Cannabidiol delivers vasodilatory effects in human pulmonary and rat small mesenteric arteries, and hypotension in rat models of hypertension (Baranowska-Kuczko et al. 2020). Alzheimer's disease and Parkinson's disease are the most common neurodegenerative disorders. Cannabidiol treatment prevents the development of cognitive deficits in rodent models of Alzheimer's disease and shows potential effects in an *in vitro* Parkinson's disease model (Cassano et al. 2020). Cannabidiol reportedly inhibits cancer cell invasion and metastasis *via* the upregulation of intracellular adhesion molecule (ICAM)-1 or tissue inhibitors of metalloproteinase (TIMP)-1 (Ramer et al. 2012).

Exogenous antagonist

• **Capsazepine** is the first reported TRPV1 receptor antagonist that has been widely used as a competitive antagonist in pharmacological studies. Capsazepine is synthesized as a structural analog of the capsaicin molecule, and binds to the channel pore region (Messeguer et al. 2006). Hydrophobic pocket in S4–S5 linker of TRPV1 including L515, V518, M547, I573, and L669 accommodates the heterocyclic region of capsazepine (Gao et al. 2016). Capsazepine treatment has pharmacological effects in several diseases, such as neuropsychiatric disorders, neuralgic disorders, and cancer (Gonzalez-Reyes et al. 2013).

In a forced swimming test using mice, capsazepine displayed antidepressant-like effects, which were facilitated by the inhibition of neuronal nitric oxide synthase (nNOS) or *via* blockade of *N*-Methyl-*D*-aspartate (NMDA) (Sartim et al. 2019). In addition, capsazepine inhibited 4-aminopyridine (AP)-induced epileptiform activity in *in vitro* studies and modulated 4-AP- or capsaicin-induced epileptiform activity in *in vivo* experiments (Gonzalez-Reyes et al. 2013). Acute capsazepine treatment potentiated the antinociceptive effects of morphine in mice, *via* the hot-plate test (Nguyen et al. 2010). In STZ-induced diabetic rats, capsazepine injection reduced facial heat hyperalgesia (Araya et al. 2017), and in models of inflammatory and neuropathic pain, it reversed mechanical hyperalgesia (Walker et al. 2003). Reportedly, capsazepine potentiated the apoptotic effects of tumor necrosis factor-related apoptosis-inducing ligand, and it suppressed the proliferation of human prostate cancer cells (Huang et al. 2006).

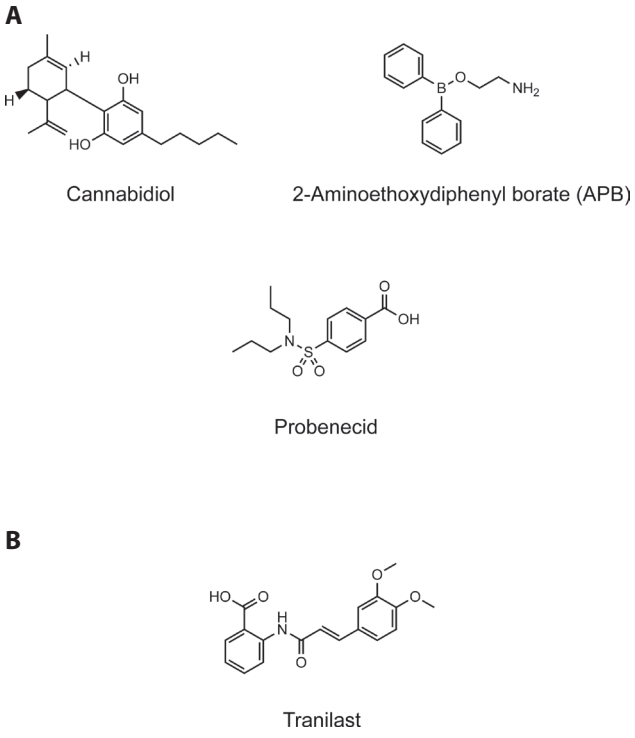


Figure 3. Chemical structures of TRPV2 agonists (**A**) and antagonist (**B**).

TRPV2

TRPV2 is a non-specific cation channel activated by noxious temperatures >52°C. TRPV2 was isolated as vanilloid receptor-like protein 1 (VRL1) and is localized in DRG, CNS, lung, spleen, and intestine (Caterina et al. 1999). TRPV2 is highly expressed in cardiomyocytes and is involved in stretch-dependent responses in the heart (Aguettaz et al. 2017). Mice deficient in TRPV2 showed impaired cardiac function (Naticchioni et al. 2015). The structure of TRPV2 is close to that of the potassium channel. A 13.6 Å cryo-EM structure of TRPV2 was reported by Huynh et al. (2014). Known TRPV2 agonists and antagonists are listed in Figure 3 and Table 3.

Human diseases related to TRPV2

Heart failure

TRPV2 functions as both a mechanosensory and a mediator of calcium regulation and plays important roles in cardiomyocyte structure and function; it functionally integrates neighboring cardiomyocytes (Katanosaka et al. 2014). In the left ventricle, as well as in the whole heart, TRPV2 expression is highest among members of TRPV family (Koch et al. 2012). TRPV2 KO mice show decreased systolic function and impaired cardiac functional responses to forced treadmill exercise (Naticchioni et al. 2015). Additionally, heart-specific TRPV2-deficient mice exhibited decreased heart pump function with disorganization of the intercalated disc structure, conduction defects, and

Table 3. Endogenous and exogenous ligands of TRPV2 channels and the pharmacological effects

Ligand	Pharmacological effects	Others
Endogenous agonist		
Lysophospholipids	Stimulate prostate cancer cell migration Apoptosis/necrosis in osteoblast-like cells Inhibit differentiation of brown adipocyte	Stimulate GLP-1 secretion
Exogenous agonist		
Cannabidiol	Anti-cancer	Activate TRPV1, TRPV2, TRPV3, TRPV4 Release CGRP in cultured DRG
Probenecid	Improve cardiac function in Fontan circulation	
Exogenous antagonist		
Tranilast	Anti-allergic Anti-cancer	

GLP-1, glucagon-like peptide-1; CGRP, calcitonin gene-related peptide; DRG, dorsal root ganglion.

accelerated mortality (Katanosaka et al. 2014). Reduced insulin-like growth factor (IGF-1) signaling is strongly associated with heart failure found in TRPV2 KO mice (Katanosaka et al. 2014).

Currently, only a small number of TRPV2-selective ligands have been reported. Probenecid, a TRPV2 agonist that is also known as multidrug resistance-associated protein 1 (MRP-1; ABCC1) inhibitor, has been shown to have its inotropic effects and potential for use in the treatment of cardiomyopathy in both non-clinical and clinical studies (Robbins et al. 2018). A retrospective cohort study suggested that TRPV2 expression increased in patients with single ventricle physiology. In this congenital heart defect, systemic and pulmonary blood flow returns mix with each other and lead to lower systemic oxygen saturations (between 75% to 85% in patients, ≥96% in normal). Therefore, the single ventricle causes systemic arterial oxygen desaturation (Chopra and Rao 1992). Fontan procedure is a surgery that connects the inferior vena cava to the pulmonary artery so that all systemic venous blood can flow directly into the lungs (Fontan circulation) (Fontan and Baudet 1971). A phase 4 clinical study showed that probenecid improved cardiac function in patients with Fontan circulation treated for functionally univentricular circulation (Rubinstein et al. 2020).

Pharmacological effects of TRPV2 ligands

Endogenous agonist

• **Lysophospholipids**, such as lysophosphatidylcholine (LPC) and lysophosphatidylinositol (LPI), induce Ca^{2+} influx *via* the TRPV2 channel. This Ca^{2+} entry is due to translocation of TRPV2 protein to the plasma membrane. TRPV2 activation depends on the length of the unsaturated side chain of lysophospholipids and needs a specific combination of head-group composition and side chain length of the lysophospholipid (Monet et al. 2009). LPC and LPI stimulate prostate cancer cell migration (Monet et al. 2009). In bone-forming MG-63 osteoblast-like cells, LPC induces cell death *via* both apoptosis and necrosis and impairment of intracellular calcium homeostasis (Fallah et al. 2013). Moreover, LPC inhibited the differentiation of brown adipocytes (Sun et al. 2016). In contrast, LPI stimulated GLP-1 secretion by enteroendocrine L cells *via* TRPV2 activation (Harada et al. 2017).

Exogenous agonists

• **Cannabidiol** has been reported as a high-affinity agonist of the TRPV2 channel, in addition to being an agonist of the TRPV1 channel. Pumroy and colleagues have identified the cannabidiol binding site in TRPV2 that is different from other ligand/lipid binding sites in other TRP channels. Cannabidiol interacts with TRPV2 through a hydrophobic pocket located between S5 and S6 helices of adjacent subunits (Pumroy et al. 2019). The effect of cannabidiol has been poorly investigated in *in vitro* (Luo et al. 2019). Cannabidiol induced cell proliferation, migration, tubulogenesis, and integrity in human brain endothelial cells, suggesting its potential ability to modulate the human blood-brain barrier (BBB) (Luo et al. 2019). Cannabidiol treatment induced autophagy in glioma stem-like cells (Nabissi et al. 2015) and expression of the pro-inflammatory chemokine IL-8 in human testicular peritubular cells (Eubler et al. 2018).

• **2-Aminoethoxydiphenyl borate (2-APB)** is a common activator of TRPV1, TRPV2, and TRPV3 channels, exerting its effects on cardiorespiratory reflex, pulmonary C fiber afferents, and isolated pulmonary neurons (Gu et al. 2005). Although K571 residue in the intracellular S4–S5 linker of TRPV1 is critical for interaction with 2-APB, homologous K529 residues in TRPV2 is less important for 2-APB binding (Boukalova et al. 2010). In anesthetized spontaneously

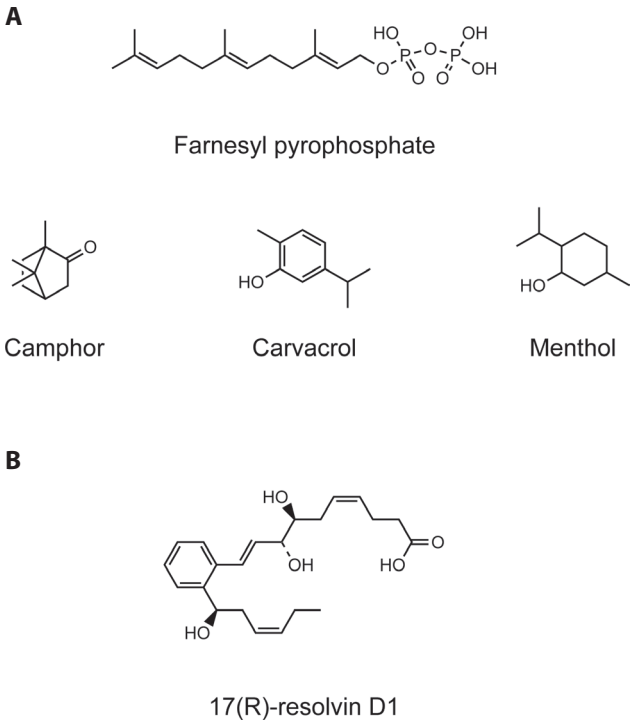


Figure 4. Chemical structures of TRPV3 agonists (**A**) and antagonist (**B**).

breathing rats, 2-APB treatment induces pulmonary chemoreflex responses, such as apnea, bradycardia, and hypotension. In open-chest and artificially ventilated rats, 2-APB treatment induced an abrupt and intense discharge in the vagal pulmonary C fibers (Gu et al. 2005).

• **Probenecid**, a lipid-soluble benzoic acid derivative, was initially used to increase serum antibiotic levels (Koch et al. 2012; Robbins et al. 2012). It is also expected to be a new therapeutic target in the fields of cardiology and neurology. In a mouse model of peripartum cardiomyopathy, probenecid treatment decreased mortality, hypertrophy, and molecular parameters of heart failure (Onusko et al. 2020). In a clinical trial, probenecid treatment improved cardiac function accompanied by heart failure with reduced ejection fraction (Robbins et al. 2018).

Exogenous antagonist

• **Tranilast**, a non-selective blocker of TRPV2, is widely used as an anti-allergic drug and can be an effective treatment for heart failure (Koch et al. 2018; Matsumura et al. 2018). Anticancer effects of tranilast have also been reported (Santoni et al. 2020).

TRPV3

TRPV3, also known as vanilloid receptor-like protein 3 (VRL3), is a Ca^{2+}-permeable temperature-sensitive cation channel that responds to noxious heat with a threshold of approximately 39°C (Smith et al. 2002). TRPV3 was cloned from newborn mouse skin and was specifically detected in keratinocytes, for example, in the epidermal layer and hair follicles (Peier et al. 2002). It was also cloned from brain cDNA and is expressed in the tongue, DRG, and CNS (Xu et al. 2002). TRPV3 KO mice do not respond to innocuous/noxious heat (Moqrich et al. 2005) and exhibit a wavy hair coat and curly whiskers (Cheng et al. 2010). TRPV3 is also essential for skin barrier formation (Cheng et al. 2010). A cryo-EM structure of TRPV3 was reported by Zubcevic et al. (2019). TRPV3 agonists and antagonists are presented in Figure 4 and Table 4.

Human diseases related to TRPV3

Olmsted syndrome

The characteristic features of Olmsted syndrome include palmoplantar keratoderma, periorificial hyperkeratotic lesions, and alopecia. Palmoplantar keratoderma is a keratinization disorder with hyperkeratotic thickening of the palms and soles. TRPV3 is abundantly expressed in the skin and hair follicles, in addition to the CNS (brain and spinal cord) (Lin et al. 2012). *De novo* missense mutations (gain-of-function)

Table 4. Endogenous and exogenous ligands of TRPV3 channels and the pharmacological effects

Ligand	Pharmacological effects	Others
Endogenous agonist		
Farnesyl pyrophosphate	Elicits nociceptive behaviors/pain	
Exogenous agonist		
Camphor	Topical analgesia (by desensitizing TRPV1)	Produce warm sensation
Carvacrol	Hypothermic effect Hypotention	Skin sensitizer/allergen
Exogenous antagonist		
17(R)-resolvin D1	Peripheral antinociception	

in TRPV3 have been found in the skin of patients with Olmsted syndrome (Lin et al. 2012). Furthermore, TRPV3 transgenic mice spontaneously develop dermatitis (Yoshioka et al. 2009). Thus, inhibition of overactive TRPV3 could possibly have therapeutic potential for Olmsted syndrome patients.

However, there are only limited treatments available for palmoplantar keratodermas. Treating the background condition or removing possible triggers is effective for treating palmoplantar keratodermas. Current options for drug treatment are emollients, topical keratolytics, topical/systemic retinoids, and topical vitamin D ointment; however, these treatments only result in temporary improvement. Development of TRPV3 antagonists can potentially lead to therapeutic application for treating inflammatory skin diseases, including palmoplantar keratoderma. However, there is currently no active developing TRPV3 antagonist.

Other diseases

In patients with atopic dermatitis, increased TRPV3 expression in lesions has been reported (Yamamoto-Kasai et al. 2013). Clinical data suggest that TRPV3 expression is increased in the lesional skin. In addition, mice with a gain-of-function mutation in TRPV3 develop allergic and pruritic dermatitis (Yamamoto-Kasai et al. 2013). Furthermore, expression of TRPV3 is reportedly increased in the epidermis of psoriatic lesional skin. Since TRPV3 antagonist inhibits 2-APB/carvacrol-induced IL-1α release from keratinocytes, in addition to the epidermal growth factor receptor (EGFR) signaling pathway that is activated in lesional skin in psoriasis patients, TRPV3 antagonists may be effective for treating psoriasis (Scott et al. 2016). TRPV3 KO mice exhibit impaired responses to noxious heat. An animal model of TRPV3 gain-of-function mutation (WBN/Kob-Ht rat) is hypersensitive to heat and cold stimuli. These results suggest that TRPV3 contributes to the sensation of thermal pain (Maruyama et al. 2015).

Pharmacological effects of TRPV3 ligands

Endogenous agonist

• **Farnesyl pyrophosphate** is an intermediate in the synthesis of steroid hormones and the mevalonate pathway, and it activates GPR92 (also known as lysophosphatidic acid receptor 5 [LPA5]) (Lee et al. 2010). LPA receptors are associated with signal transduction during noxious stimuli. Farnesyl pyrophosphate is distributed in the rodent brain, suggesting a relationship with pain perception (Lee et al. 2010). In cultured keratinocytes, farnesyl pyrophosphate reduces the TRPV3 heat threshold, and its intraplantar injection acutely induces nociceptive behaviors in animal inflammatory models (Bang et al. 2010a).

Exogenous agonists

• **Camphor** is known to potentiate both heat and cold sensations. Sensitization to heat is caused by the activation of TRPV1 and TRPV3 channels, and sensitization to cold is induced by the activation of TRPM8 (Selescu et al. 2013). In Wistar rats, camphor induces self-grooming behavior, which is a defensive action against heat and a part of thermoregulatory grooming (Ishikawa et al. 2019).
• **Carvacrol** is a pungent ingredient of oregano oil and is a highly potent agonist of TRPV3 channels (Vogt-Eisele et al. 2007). In rodents, carvacrol treatment shows a hypothermic effect accompanied by a decrease in whole-body heat generation. It also induces hypotension (Feketa and Marrelli 2015). In mice, intradermal injection of carvacrol induces scratching behavior, demonstrating that carvacrol is a skin sensitizer or allergen (Cui et al. 2018). In addition, carvacrol elicits warmth- and noxious heat-evoked responses of trigeminal neurons and enhances warmth and heat pain in the human tongue (Klein et al. 2013, 2014).
• **Menthol** is known for its cooling effect *via* activation of TRPM8, which is a cold-activated thermal TRP ion channel. It also activates TRPV3, which is capable of being heat-activated. In contrast, menthol inhibits TRPA1 activity, and induces an analgesic effect (Macpherson et al. 2006).

Endogenous antagonist

• **17(R)-Resolvin D1**, a naturally occurring anti-inflammatory and pro-resolving lipid, affects TRPV3 activity. TRPV3 is expressed in primary sensory neurons and keratinocytes, and plays a key role in thermal and chemical nociception in the peripheral tissues (Bang et al. 2010b, 2012). In an *in vivo* study using Hargreaves, Randall-Selitto and von Frey tests, 17(R)-resolvin D1 exhibited acute analgesic potential *via* TRPV3-specific mechanisms (Bang et al. 2012).

TRPV4

TRPV4 is a Ca^{2+}-permeable, non-selective cation channel that is gated by exposure to physiological hypotonicity. TRPV4 was isolated as a cDNA encoding the VR1-related osmotically activated channel (VR-OAC) by Liedtke et al. (2000). It was also cloned by Strotmann et al. (2000) as OTRPC4 and by Wissenbach et al. (2000) as TRP12. It is highly expressed in kidney, liver, heart, lung, spleen, testis, fat, DRG, and CNS. TRPV4-deficient mice show reduced sensitivity of the tail to pressure and acidic nociception. Therefore, TRPV4 is essential for detecting the nociceptive levels of mechanical stimuli (Suzuki et al. 2003). Moreover, 3.8 Å resolution cryo-EM structure and X-ray crystallographic analyses of TRPV4 have been reported (Deng et al. 2018).

Systemic administration of a TRPV4 agonist induces increased pulmonary vascular permeability and hemorrhage. TRPV4 inhibition prevents increased vascular permeability and pulmonary edema in animals. The concept of selecting the TRPV4 channel as a pharmacological target, such as in metabolic diseases and pain, is controversial. TRPV4 blockade improves glucose tolerance and diet-induced obesity in rodents (Hu et al. 2020), whereas another study showed the opposite effects. An overview of representative endogenous and exogenous ligands of TRPV4 is presented in Figure 5 and Table 5.

Human diseases related to TRPV4

Skeletal dysplasia

Spondylometaphyseal dysplasia is a short-stature disorder characterized by vertebral abnormalities and metaphyses of the tubular bones. Metatropic dysplasia is a more severe skeletal dysplasia characterized by short and flexible limbs, a short trunk with progressive kyphoscoliosis, and craniofacial abnormalities, such as a high forehead. In patients with hereditary skeletal dysplasia, gene mutations involving *TRPV4* have been reported. In patient-derived metatropic dysplasia primary cells, temperature-dependent intracellular calcium oscillations were inhibited by the TRPV4-specific antagonist GSK205 (Hurd et al. 2015). However, no compounds are currently being developed to treat these bone disorders.

Neuromuscular disorders

Charcot-Marie-Tooth disease type 2C (CMT2C) is an autosomal dominant peripheral sensorimotor neuropathy characterized by weakness of the distal hands and feet, impairment of respiratory muscles, and sensorineural hearing loss. Missense mutations in the *TRPV4* gene have been reported in this neuromuscular disorder (Landoure et al. 2010). In addition to the skeletal dysplasia described above, gain-of-function mutations involving TRPV4 can cause degenerative disorders of the peripheral nerves. In a cell viability assay using *TRPV4*-mutated cells, cell death caused by increased intracellular calcium levels was suppressed by blocking of TRPV4 with the non-selective TRPV antagonist, ruthenium red (Klein et al. 2011). Therefore, TRPV4 antagonists are expected to be possible therapeutic options for neuromuscular disorders.

Pharmacological effects of TRPV4 ligands

Endogenous agonist

• **Epoxyeicosatrienoic acids (EETs)** are cytochrome P450 epoxygenase metabolites of arachidonic acid secreted by vascular endothelial cells. TRPV4 is a potential target for 5,6-EET and 11,12-EET, which are biological active regioisomeric EETs directly bind to TRPV4 and gate

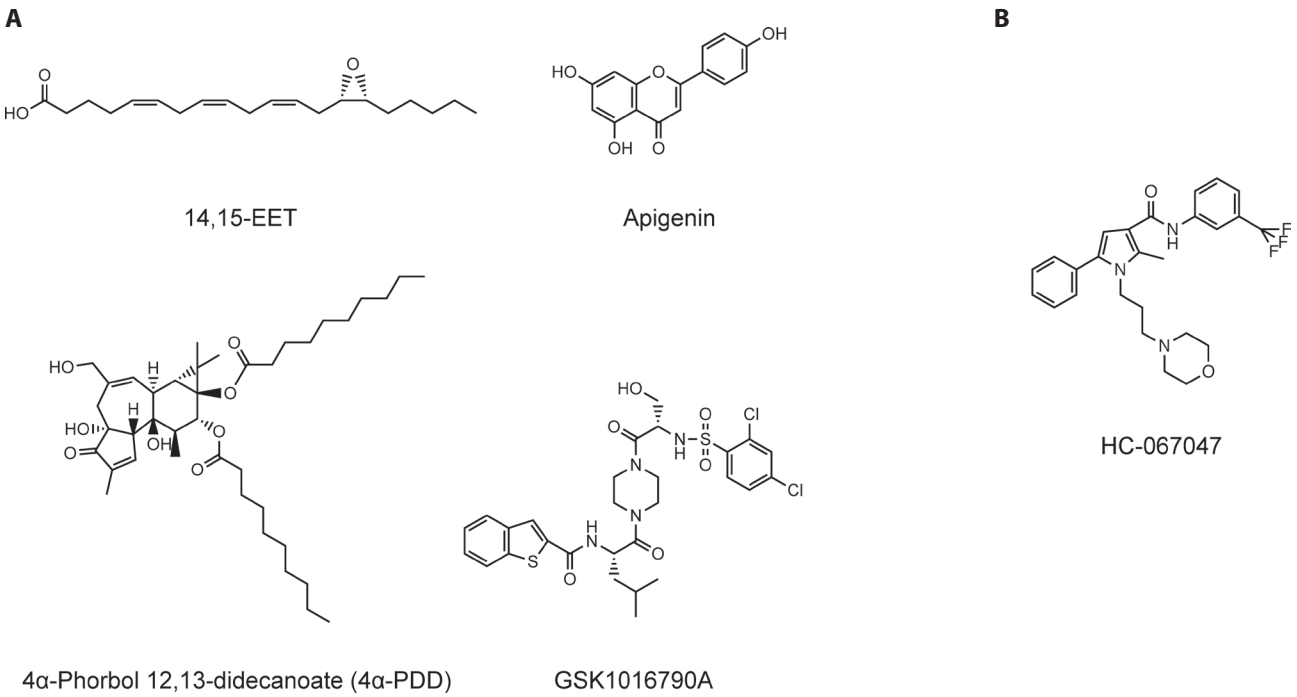


Figure 5. Chemical structures of TRPV4 agonists (**A**) and antagonist (**B**).

Table 5. Endogenous and exogenous ligands of TRPV4 channels and the pharmacological effects

Ligand	Pharmacological effects	Others
Endogenous agonist		
EETs	Vasodilation Hypotension Protection in myocardial and brain ischemia Protection in lung ischemia/reperfusion injury	
Exogenous agonist		
4α-PDD	Insulin secretion Vascular relaxation Neovascularization Microglial activation	Antidipsogenic effect
Apigenin	Modulation in glucose and lipid metabolism Anti-inflammation Anti-oxidation Renal protection	Melanogenesis
GSK1016790A	Vasodilation	Increase of cellular permeability Increase of glioma migration and invasion
Exogenous antagonist		
HC-067047	Analgesic effect Neuroprotection Cardioprotection Anti-inflammation Anti-oxidation Function maintenance in BBB Anti-fibrosis Anti-cancer	Increase in core body temperature Anti-apoptosis

EETs, epoxyeicosatrienoic acids; 4α-PDD, 4α-phorbol 12,13-didecanoate; BBB, blood-brain barrier.

the channel. EET binding site on TRPV4 is identified as residues from S2–S3 linker (K535, F549 and Q550), S4 (Y591) and S4–S5 linker (R594) (Berna-Erro et al. 2017). 11,12-EET induces smooth muscle cell hyperpolarization and vascular relaxation in human left internal mammary arteries (Campbell and Fleming 2010; Ma et al. 2015). In addition, TRPV4 channels in arterial myocytes are activated by EETs and regulate vascular smooth muscle function, suggesting that it is an important target for drug therapy in vascular disorders, such as hypertension, stroke, and vasospasm (Campbell and Fleming 2010). In another study, 14,15-EET induced vasodilation through inhibition of the thromboxane receptor. However, its relationship with the TRPV4 channel is unknown (Behm et al. 2009). In isolated rat lungs, 11,12- or 11,15-EET demonstrated a protective effect in lung ischemia-reperfusion injury by limiting the permeability response to ischemia-reperfusion (Townsley et al. 2010). In Nax-positive glial cells, 5,6- and 8,9-EETs stimulated water intake in response to increased Na^+ in body fluids, probably *via* TRPV4 activation (Sakuta et al. 2020). In contrast, 5,6-, 8,9-, 11,12-, and 14,15- EETs exacerbated inflammatory responses in the context of cystic fibrosis (Henry et al. 2016).

Exogenous agonists

• **4α-Phorbol 12,13-didecanoate (4α-PDD)** is known to bind TM3–TM4 domain of TRPV4 as agonist with three important ring structures: Ring A and B junctions are essential for Ca^{2+}-depend activity of the TRPV4 and the lipophilic ester groups on ring C affects the orientation of binding (Klausen et al. 2009). TRPV4 is a Ca^{2+}- and Mg^{2+}-permeable cation channel that affects insulin secretion and insulin sensitivity. In INS-1E pancreatic β cells, 4α-PDD treatment increases intracellular Ca^{2+} levels and enhances glucose-stimulated insulin secretion (Skrzypski et al. 2013). Furthermore, in rodents, 4α-PDD induces endothelial-dependent NO-mediated relaxation in the mesenteric arteries (Boudaka et al. 2019). 4α-PDD treatment elicits the dilation of mesenteric arteries in aged rats by increasing intracellular Ca^{2+} levels (Du et al. 2016). In rat prefabricated skin flaps, 4α-PDD increases the survival of prefabricated flaps through neovascularization induction *via* vascular endothelial growth factor (VEGF) secretion (Bae et al. 2018).

Glial cells are abundant in the CNS and play key roles in the regulation of neuronal activity, vascular function, and gliotransmitter release. In rat glial cells, 4α-PDD suppressed

lipopolysaccharide (LPS)-induced microglial activation, indicating its pathophysiological roles in microglial activation (Shirakawa et al. 2010). On the other hand, 4α-PDD activated mouse dorsal ganglia neurons independently of TRPV4 (Alexander et al. 2013). 4α-PDD affected the TRPV4-p38 mitogen-activated protein kinase (MAPK) pathway, with respect to neuropathic pain in rats (Qu et al. 2016). In mice, intra-cerebroventricular injection of 4α-PDD inhibited water intake, suggesting the regulation of drinking behavior *via* the TRPV4 channel (Tsushima and Mori 2006).

• **Apigenin** is a TRPV4 agonist that is abundant in fruits and vegetables and belongs to the flavone subclass of flavonoids, possessing good anti-diabetic properties (Vinayagam and Xu 2015). In rats with type 2 diabetes induced by STZ and high-fat diet, apigenin treatment ameliorated glucose and lipid metabolism, leading to a decrease in the levels of blood glucose and serum lipid and an improvement in the insulin resistance index. Furthermore, pathological damage to the thoracic aorta was alleviated. In palmitic acid-treated endothelial cells, apigenin inhibited NF-κB activation and *ICAM-1* mRNA expression (Ren et al. 2016). Apigenin administration alleviated diabetic neuropathy in STZ-induced rats by inhibiting the MAPK pathway (Malik et al. 2017). The anti-oxidative effect of apigenin enhanced glucose uptake in L6 cells (rat skeletal myoblast cell line) and hypolipidemic action in 3T3-L1 cells (Krishna et al. 2015). In deoxycorticosterone acetate (DOCA)-salt hypertension model, apigenin administration reduced renal lesions, which was accompanied by inhibition of the expression of transforming growth factor (TGF)-β1 signaling pathway and MMPs (Wei et al. 2017). In contrast, apigenin increased melanogenesis in B16 cells (mouse skin melanoma cell line) by activating the p38 MAPK pathway (Ye et al. 2011).

• **GSK1016790A.** Vascular functions of GSK1016790A, a synthetic TRPV4 activator, have been reported. In isolated mesenteric arteries of rats, GSK1016790A treatment elicited endothelial hyperpolarization and subsequent vasodilation (Ho et al. 2015; Naik et al. 2016). Additionally, in human skin, GSK1016790A injection in skin induced cutaneous vasodilation (Fujii et al. 2019). GSK1016790A increased fluorescein isothiocyanate-dextran permeability in monolayer colonic cells by modulating serine-phosphorylated claudin-7 (Huang et al. 2018). GSK1016790A promoted the migration and invasion of glioma cells through ATP-dependent tyrosine kinase (Akt)/Ras-related C3 botulinum toxin substrate 1 (Rac 1) signaling (Ou-Yang et al. 2018).

Exogenous antagonist

• **HC-067047.** The TRPV4 channel shows sensitivity to temperature over the range of 24–34°C in rats. Intravenous blockade of the TRPV4 channel with HC-067047 induced an increase in core body temperature at temperatures of 26°C and 30°C. In contrast, rats treated with TRPV4 agonist RN-1747 chose colder temperatures and exhibited cold-seeking behavior (Vizin et al. 2015).

The TRPV4 channel is also involved in sensory transduction and pain signaling. In STZ-induced diabetic mice, HC-067047 treatment prevented the development of mechanical allodynia, suggesting that TRPV4 antagonists have pharmacological potential to treat painful neuropathy in diabetes (Dias et al. 2019). In a mouse model of peripheral neuropathy, HC-067047 treatment reduced paclitaxel-induced mechanical allodynia or hyperalgesia (Dias et al. 2019). Furthermore, HC-067047 treatment attenuated cancer-induced thermal and/or mechanical hyperalgesia in Copenhagen rats (Maqboul and Elsadek 2018). In a pilocarpine model of temporal lobe epilepsy in mice, HC-067047 treatment prevented the pro-inflammatory cytokine levels and protein levels of nucleotide-binding oligomerization domain-like receptor pyrin domain containing 3 (NLRP3), apoptosis-related spotted protein (ASC), and caspase 1 from increasing, as well as displayed neuronal protection (Wang et al. 2019b).

Organ-protective effects have been reported in a rodent model of ischemia/reperfusion (I/R) injury. In a rat model of myocardial I/R injury, HC-067047 treatment exerted cardioprotective effects by elevating anti-oxidative enzyme activity *via* the kelch-like ECH-associated protein 1 (keap1)/nuclear factor erythroid-2-related factor-2 (Nrf2) pathway (Wu et al. 2019). In a mouse model of myocardial I/R injury, HC-067047 treatment attenuated cell viability reduction through an increase in hypoxia/reoxygenation-induced intracellular Ca^{2+} rise (Wang et al. 2019a). In addition, HC-067047 treatment ameliorated the BBB leakage *via* downregulation of caveolin-1 and caveolin-2 expression in focal cerebral ischemia and reperfusion (Xie and Lu 2018). TRPV4 inhibition by HC-067047 treatment alleviated neurological symptoms, brain edema, and neuronal death, as well as disruption of the BBB, and maintained the intestinal epithelial barrier by modulating levels of serine phosphorylated claudin-7 (Huang et al. 2018).

In human hepatocellular carcinoma cells, HC-067047 inhibits cell proliferation, induces apoptosis, and decreases migration capability by reducing the epithelial-mesenchymal transition process (Fang et al. 2018). In addition, in NOD/ShiJic-*scid* mouse xenograft models, HC-067047 administration suppressed tumor growth and induced apoptosis (Fang et al. 2018). Activation of the TRPV4 channel exacerbated liver fibrosis in a mouse model of carbon tetrachloride-induced liver fibrosis, but HC-067047 treatment ameliorated the fibrosis (Fu et al. 2019).

TRPV5

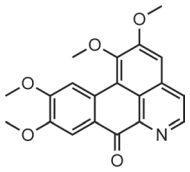
TRPV5 was cloned as a Ca^{2+}-permeable channel, namely ECaC1/CaT2 (Muller et al. 2000; Peng et al. 2001). It regu-

lates calcium homeostasis as a Ca^{2+}-selective TRP channel. Unlike other TRPV channels, TRPV5 and TRPV6 constitutively function under physiological membrane potential, and their activation is neither thermosensitive nor ligand dependent. TRPV5 and TRPV6 share ~75% sequence identity and show high selectivity for Ca^{2+} compared to other monovalent cations (den Dekker et al. 2003). In TRPV5, D542 residue in the pore region is an important molecular determinant of Ca^{2+} selectivity (Nilius et al. 2001). Similarly, D541 residue is identified as critical structure for Ca^{2+} selectivity in TRPV6 (Saotome et al. 2016). They localize in Ca^{2+}-transporting epithelial tissues and are highly responsive to 1,25-dihydroxyvitamin D3. These properties distinguish TRPV5 and TRPV6 from other TRPV subfamilies (TRPV1–4). TRPV5 is predominantly expressed in the apical membrane of renal distal tubules where Ca^{2+} is re-absorbed; therefore, TRPV5-deficient mice show dysfunction in Ca^{2+} reabsorption, which leads to severe hypercalciuria (Hoenderop et al. 2003). TRPV5 KO mice also exhibit significant abnormalities in bone structure (Hoenderop et al. 2003). The cryo-EM structure of TRPV5 has been reported recently (Hughes et al. 2018; Dang et al. 2019); however, no TRPV5 agonists/antagonists have been clinically tested. TRPV5 antagonists are shown in Figure 6 and Table 6.

Human diseases related to TRPV5

Nephrolithiasis (kidney stones)

Nephrolithiasis is the most common chronic kidney condition, in which stones made of minerals, frequently calcium, form inside the kidneys. Nephrolithiasis often causes severe pain because of movement of the stones from the renal pelvis to the ureter. Pain is suddenly relieved as the stones are expelled from the ureter into the bladder. Several risk factors such as family history, dehydration, diet containing high protein/salt/sugar, obesity, and hypercalciuria are known to contribute to this disease. TRPV5-deficient mice present serious hypercalciuria, which is a major risk factor for nephrolithiasis (Hoenderop et al. 2003). On the other hand, the A563T variant of TRPV5, which is widespread in African Americans, is reported to increase Ca^{2+} influx and lower urinary Ca^{2+} levels (Khaleel et al. 2015); therefore, the risk of nephrolithiasis in African Americans is less than half that in Caucasians (Stamatelou et al. 2003).



Oxoglaucine

Figure 6. Chemical structure of TRPV5 antagonist.

Pharmacological effects of TRPV5 ligands

Exogenous antagonists

• **Oxoglaucine**, a derivative of glaucine, is a calcium channel blocker that inhibits the expression and production of pro-inflammatory factors (Zhong et al. 2021). As a novel TRPV5 antagonist, oxoglaucine, exhibits pharmacological effects in rat osteoarthritis models and human osteoarthritis chondrocytes. Reportedly, oxoglaucine activates autophagy by inhibiting the TRPV5/calmodulin-dependent protein kinase 2/calmodulin pathway (Zhong et al. 2021).

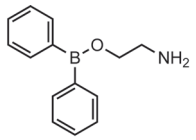
• **Others.** Some synthetic modulators of TRPV5, such as econazole, TH-1177, and select cannabinoids, have been reported. Moreover, a novel antagonist of TRPV5 which exhibits higher affinity and specificity for TRPV5 over other TRPs, has been discovered (Hughes et al. 2019).

TRPV6

TRPV6, a highly calcium-selective member of TRPs, is the main route for calcium absorption and is highly expressed in tissues of the duodenum, placenta, and exocrine. TRPV6 was cloned as a Ca^{2+}-permeable channel (ECaC2/CaT1) (Peng et al. 2000; Barley et al. 2001) and its amino acid sequence is similar to that of TRPV5 (75% amino acid sequence identity), whereas the similarity to TRPV1–4 homologs is lower (30–35%). Saotome et al. (2016) showed that high Ca^{2+} selectivity of TRPV6 is determined by direct coordination of Ca^{2+} by a ring of aspartate side chains in the selectivity filter binds to Ca^{2+}. Singh and colleagues solved cryo-EM and crystal

Table 6. Exogenous antagonists of TRPV5 channels and the pharmacological effects

Ligand	Pharmacological effects	Others
Oxoglaucine	Attenuate progression of osteoarthritis Anti-inflammation	Activate autophagy Anti-apoptosis
Econazole	Inhibit bone resorption in osteoclast-like cells	



2-Aminoethoxydiphenyl borate (APB)

Figure 7. Chemical structure of TRPV6 antagonist.

structures of TRPV6 bound to 2-APB, a small-molecule exogenous antagonist of TRPV6 (see below) originally identified as an inhibitor of Ins(1,4,5)P3-induced Ca^{2+} release (Maruyama et al. 1997), and showed that 2-APB modulates protein-lipid interactions to close the TRPV6 channel (Singh et al. 2018). Moreover, the promoter region of human *TRPV6* serves as a calcium absorption in duodenal and placental epithelia. Figure 7 and Table 7 list reported exogenous TRPV6 antagonists.

Human diseases related to TRPV6

Transient neonatal hyperparathyroidism (TNHP)

TNHP is an autosomal recessive disease. Reportedly, mutations in *TRPV6* cause impairment in maternal-fetal calcium transport and insufficient fetal bone mineralization impairs bone development (*e.g.*, generalized osteopenia, narrow chest, short ribs with multiple healing fractures, and bowing or fractures of long bones). Oral calcium intake completely ameliorates skeletal abnormalities in most patients (Suzuki et al. 2018). Suzuki and colleagues identified mutations in the *TRPV6* gene in children with TNHP (Suzuki et al. 2018). Recently, the sixth ankyrin repeat domain (AR6) of TRPV6 was reported to be necessary for the regulation of intracellular Ca^{2+} concentrations in TNHP patients (Suzuki et al. 2020).

Chronic pancreatitis (CP)

CP is a progressive inflammation of the pancreatic tissue that is caused genetically/environmentally. Some patients with CP experience pain from the upper abdomen to the back. Currently, pain management with nonopioids or opioids is the only approach to relieve pain, but there is no effective medical treatment. Therefore, new treatments for this disease are required. Recently, *TRPV6* was identified as a susceptibility gene for non-alcoholic CP (Zou et al. 2020) and has been suggested to regulate Ca^{2+} uptake and pancreatic inflammation (Masamune et al. 2020).

Cancer

TRPV6 is considered to be a suitable target in cancer treatment because it increases intracellular Ca^{2+} levels and induces cell proliferation, metastasis, and inhibition of cancer cell apoptosis. TRPV6 channels are overexpressed in various types of epithelial cancers. Upregulation of constitutively active TRPV6 causes sustained elevation of intracellular Ca^{2+} and activates the calmodulin/calcineurin/nuclear factor of activated T-cells (NFAT) pathway in cancer cells (Lehen'kyi et al. 2007). Furthermore, reduction in *TRPV6* mRNA expression by siRNA reduces the proliferation rate and calcium transport of breast cancer cells (Bolanz et al. 2008). Therefore, TRPV6 is expected to be a new target of anti-cancer drugs for the treatment of solid tumors overexpressing TRPV6.

CBP-1008, a bi-specific ligand drug conjugate targeting folate receptor α (FRα) and TRPV6, is in early clinical development for the treatment of advanced solid tumors. A phase 1 trial in patients with ovarian cancer, triple-negative breast cancer, and non-small cell lung cancer is underway (NCT 04740398). These cancers highly express both FRα and TRPV6. Because FRα is selectively expressed on the apical membrane of these epithelial cancer cells but not in normal epithelial cells, FRα-targeting drugs such as CBP-1008 show high specificity for tumor cells. In this phase 1 clinical study, tumor responses correlated with FRα/TRPV6 receptor expression levels in solid tumors.

SOR-C13 is a 13-mer peptide antagonist of TRPV6 derived from the C-terminus of soricidin, a paralytic oligopeptide found in the northern short-tailed shrew (*Blarina brevicauda*). Phase 1 study of SOR-C13 has been completed for the treatment of advanced epithelial cancers. In particular, SOR-C13 shows a high response to pancreatic cancer (Fu et al. 2017). An *in vivo* study suggested that this compound significantly reduces the growth of ovarian tumors in a xenograft model (Xue et al. 2018). SOR-C13 has also

Table 7. Exogenous antagonists of TRPV6 channels and the pharmacological effects

Ligand	Pharmacological effects	Others
2-APB	Attenuate tumor growth Attenuate invasiveness in cancer cell lines	Activate TRPV1, TRPV2, TRPV3
cis-22a	Anti-proliferative effects	
CBP-1008	Anti-cancer	
SOR-C13	Anti-cancer	

been investigated as a potential treatment for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (*i.e.*, COVID-19).

Pharmacological effects of TRPV6 ligands

Exogenous antagonists

• **2-Aminoethoxydiphenyl borate (2-APB)**, a TRPV6 antagonist, reportedly binds to TRPV6 in a pocket formed by the cytoplasmic half of the S1–S4 transmembrane helix bundle (Singh et al. 2018). 2-APB inhibits TRPV6 activity in HEK293 cells (human embryonic kidney cells) transfected with human TRPV6, and this effect is sensitive to the concentration of extracellular calcium (Kovacs et al. 2012). 2-APB may serve as a potential compound for the development of therapeutic targets for TRPV6.

• **Others.** Phenyl-cyclohexyl-piperazine cis-22a was reported as the first sub-micromolar TRPV6 antagonist. Moreover, some selective TRPV6 antagonists, including analogs incorporating the structural features of capsaicin, have been reported (Cunha et al. 2020).

Future perspectives

In the history of TRP channels, the discovery of the first mammalian TRP channel was that of TRPC1 in 1995 (Kremeyer et al. 2010). Within a few years after TRPC1 discovery, representative and drugable TRP channels, such as TRPV1 and the camphor receptor TRPV3, have been discovered. The initial target of drug discovery research was TRP channels expressed in nociceptive neurons. First, clinical trials of TRPV1 antagonists targeting novel analgesic drugs were initiated, followed by the development of TRPA1 and TRPV3 antagonists (Szallasi et al. 2007; Brederson et al. 2013). However, most TRPV1 antagonists have been withdrawn from clinical studies, owing to complications involving hyperthermia and/or impaired noxious heat sensation (Moran et al. 2011; Brederson et al. 2013). Nevertheless, the development of second-generation antagonists having minimal or no adverse effects is ongoing.

An attractive insight of each TRP channel expects the novel therapeutic potential of drugs targeting TRP channels in various disease areas. TRPV1 agonists are expected to exert pharmacological effects for treating metabolic diseases, including diabetes and its complications, *via* the inhibition of oxidative stress and inflammation. In addition, TRPV4 antagonists may provide a therapeutic benefit to heart failure patients with pulmonary edema *via* the regulation of vascular permeability and pulmonary venous pressure. A thorough investigation of the risks and benefits of each TRPV agonist/antagonist over available therapeutic options should be carried out. Drug discovery research targeting TRPV channels and other TRP channels may lead to the development of first-in-class drugs.

Conflict of interest. The authors have no conflict of interest to declare.

References

Aguettaz E, Bois P, Cognard C, Sebille S (2017): Stretch-activated TRPV2 channels: Role in mediating cardiopathies. Prog. Biophys. Mol. Biol. **130**, 273-280 https://doi.org/10.1016/j.pbiomolbio.2017.05.007

Alexander R, Kerby A, Aubdool AA, Power AR, Grover S, Gentry C, Grant AD (2013): 4alpha-phorbol 12,13-didecanoate activates cultured mouse dorsal root ganglia neurons independently of TRPV4. Br. J. Pharmacol. **168**, 761-772 https://doi.org/10.1111/j.1476-5381.2012.02186.x

Ambrosino P, Soldovieri MV, Russo C, Taglialatela M (2013): Activation and desensitization of TRPV1 channels in sensory neurons by the PPARalpha agonist palmitoylethanolamide. Br. J. Pharmacol. **168**, 1430-1444 https://doi.org/10.1111/bph.12029

Anand P, Bley K (2011): Topical capsaicin for pain management: therapeutic potential and mechanisms of action of the new high-concentration capsaicin 8% patch. Br. J. Anaesth. **107**, 490-502 https://doi.org/10.1093/bja/aer260

Araya EI, Nones CFM, Ferreira LEN, Kopruszinski CM, Cunha JMD, Chichorro JG (2017): Role of peripheral and central TRPV1 receptors in facial heat hyperalgesia in streptozotocin-induced diabetic rats. Brain Res. **1670**, 146-155 https://doi.org/10.1016/j.brainres.2017.06.004

Atalay S, Jarocka-Karpowicz I, Skrzydlewska E (2019): Antioxidative and anti-inflammatory properties of cannabidiol. Antioxidants (Basel) **9**, 21 https://doi.org/10.3390/antiox9010021

Bae J, Wang Z, Li H, Lu L, Yu Q, Li Q, Tao Z (2018): Activation of TRPV4 increases neovascularization of rat prefabricated flaps. J. Reconstr. Microsurg. **34**, 35-40 https://doi.org/10.1055/s-0037-1607210

Bang S, Yoo S, Yang TJ, Cho H, Hwang SW (2010a): Farnesyl pyrophosphate is a novel pain-producing molecule via specific activation of TRPV3. J. Biol. Chem. **285**, 19362-19371 https://doi.org/10.1074/jbc.M109.087742

Bang S, Yoo S, Yang TJ, Cho H, Kim YG, Hwang SW (2010b): Resolvin D1 attenuates activation of sensory transient receptor potential channels leading to multiple anti-nociception. Br. J. Pharmacol. **161**, 707-720 https://doi.org/10.1111/j.1476-5381.2010.00909.x

Bang S, Yoo S, Yang TJ, Cho H, Hwang SW (2012): 17(R)-resolvin D1 specifically inhibits transient receptor potential ion channel vanilloid 3 leading to peripheral antinociception. Br. J. Pharmacol. **165**, 683-692 https://doi.org/10.1111/j.1476-5381.2011.01568.x

Baranowska-Kuczko M, Kozlowska H, Kloza M, Sadowska O, Kozlowski M, Kusaczuk M, Kasacka I, Malinowska B (2020):

Vasodilatory effects of cannabidiol in human pulmonary and rat small mesenteric arteries: modification by hypertension and the potential pharmacological opportunities. J. Hypertens. **38**, 896-911
https://doi.org/10.1097/HJH.0000000000002333

Barley NF, Howard A, O'Callaghan D, Legon S, Walters JR (2001): Epithelial calcium transporter expression in human duodenum. Am. J. Physiol. Gastrointest. Liver Physiol. **280**, G285-290
https://doi.org/10.1152/ajpgi.2001.280.2.G285

Baskaran P, Markert L, Bennis J, Zimmerman L, Fox J, Thyagarajan B (2019): Assessment of pharmacology, safety, and metabolic activity of capsaicin feeding in mice. Sci. Rep. **9**, 8588
https://doi.org/10.1038/s41598-019-45050-0

Behm DJ, Ogbonna A, Wu C, Burns-Kurtis CL, Douglas SA (2009): Epoxyeicosatrienoic acids function as selective, endogenous antagonists of native thromboxane receptors: identification of a novel mechanism of vasodilation. J. Pharmacol. Exp. Ther. **328**, 231-239
https://doi.org/10.1124/jpet.108.145102

Benitez-Del-Castillo JM, Moreno-Montanes J, Jimenez-Alfaro I, Munoz-Negrete FJ, Turman K, Palumaa K, Sadaba B, Gonzalez MV, Ruz V, Vargas B, et al. (2016): Safety and efficacy clinical trials for SYL1001, a novel short interfering RNA for the treatment of dry eye disease. Invest. Ophthalmol. Vis. Sci. **57**, 6447-6454
https://doi.org/10.1167/iovs.16-20303

Berna-Erro A, Izquierdo-Serra M, Sepulveda RV, Rubio-Moscardo F, Donate-Macian P, Serra SA, Carrillo-Garcia J, Peralvarez-Marin A, Gonzalez-Nilo F, Fernandez-Fernandez JM, et al. (2017): Structural determinants of 5',6'-epoxyeicosatrienoic acid binding to and activation of TRPV4 channel. Sci. Rep. **7**, 10522
https://doi.org/10.1038/s41598-017-11274-1

Bolanz KA, Hediger MA, Landowski CP (2008): The role of TRPV6 in breast carcinogenesis. Mol. Cancer Ther. **7**, 271-279
https://doi.org/10.1158/1535-7163.MCT-07-0478

Borrelli F, Romano B, Petrosino S, Pagano E, Capasso R, Coppola D, Battista G, Orlando P, Di Marzo V, Izzo AA (2015): Palmitoylethanolamide, a naturally occurring lipid, is an orally effective intestinal anti-inflammatory agent. Br. J. Pharmacol. **172**, 142-158
https://doi.org/10.1111/bph.12907

Boudaka A, Al-Suleimani M, Al-Lawati I, Baomar H, Al-Siyabi S, Zadjali F (2019): Downregulation of endothelial transient receptor potential vanilloid type 4 channel underlines impaired endothelial nitric oxide-mediated relaxation in the mesenteric arteries of hypertensive rats. Physiol. Res. **68**, 219-231
https://doi.org/10.33549/physiolres.933952

Boukalova S, Marsakova L, Teisinger J, Vlachova V (2010): Conserved residues within the putative S4-S5 region serve distinct functions among thermosensitive vanilloid transient receptor potential (TRPV) channels. J. Biol. Chem. **285**, 41455-41462
https://doi.org/10.1074/jbc.M110.145466

Brederson JD, Kym PR, Szallasi A (2013): Targeting TRP channels for pain relief. Eur. J. Pharmacol. **716**, 61-76
https://doi.org/10.1016/j.ejphar.2013.03.003

Campbell WB, Fleming I (2010): Epoxyeicosatrienoic acids and endothelium-dependent responses. Pflügers Arch. **459**, 881-895
https://doi.org/10.1007/s00424-010-0804-6

Cassano T, Villani R, Pace L, Carbone A, Bukke VN, Orkisz S, Avolio C, Serviddio G (2020): From cannabis sativa to cannabidiol: promising therapeutic candidate for the treatment of neurodegenerative diseases. Front. Pharmacol. **11**, 124
https://doi.org/10.3389/fphar.2020.00124

Caterina MJ, Schumacher MA, Tominaga M, Rosen TA, Levine JD, Julius D (1997): The capsaicin receptor: a heat-activated ion channel in the pain pathway. Nature **389**, 816-824
https://doi.org/10.1038/39807

Caterina MJ, Rosen TA, Tominaga M, Brake AJ, Julius D (1999): A capsaicin-receptor homologue with a high threshold for noxious heat. Nature **398**, 436-441
https://doi.org/10.1038/18906

Cheng X, Jin J, Hu L, Shen D, Dong XP, Samie MA, Knoff J, Eisinger B, Liu ML, Huang SM, et al. (2010): TRP channel regulates EGFR signaling in hair morphogenesis and skin barrier formation. Cell **141**, 331-343
https://doi.org/10.1016/j.cell.2010.03.013

Chopra PS, Rao PS (1992): Corrective surgery for tricuspid atresia: which modification of Fontan-Kreutzer procedure should be used? A review. Am. Heart J. **123**, 758-767
https://doi.org/10.1016/0002-8703(92)90517-y

Clapham DE (2003): TRP channels as cellular sensors. Nature **426**, 517-524
https://doi.org/10.1038/nature02196

Costa B, Giagnoni G, Franke C, Trovato AE, Colleoni M (2004): Vanilloid TRPV1 receptor mediates the antihyperalgesic effect of the nonpsychoactive cannabinoid, cannabidiol, in a rat model of acute inflammation. Br. J. Pharmacol. **143**, 247-250
https://doi.org/10.1038/sj.bjp.0705920

Costa B, Comelli F, Bettoni I, Colleoni M, Giagnoni G (2008): The endogenous fatty acid amide, palmitoylethanolamide, has anti-allodynic and anti-hyperalgesic effects in a murine model of neuropathic pain: involvement of CB(1), TRPV1 and PPARgamma receptors and neurotrophic factors. Pain **139**, 541-550
https://doi.org/10.1016/j.pain.2008.06.003

Couch DG, Cook H, Ortori C, Barrett D, Lund JN, O'Sullivan SE (2019): Palmitoylethanolamide and cannabidiol prevent inflammation-induced hyperpermeability of the human gut in vitro and in vivo-a randomized, placebo-controlled, double-blind controlled trial. Inflamm. Bowel Dis. **25**, 1006-1018
https://doi.org/10.1093/ibd/izz017

Cuba LF, Salum FG, Cherubini K, Figueiredo MAZ (2017): Cannabidiol: an alternative therapeutic agent for oral mucositis? J. Clin. Pharm. Ther. **42**, 245-250
https://doi.org/10.1111/jcpt.12504

Cui TT, Wang GX, Wei NN, Wang K (2018): A pivotal role for the activation of TRPV3 channel in itch sensations induced by the natural skin sensitizer carvacrol. Acta Pharmacol. Sin. **39**, 331-335
https://doi.org/10.1038/aps.2017.152

Cunha MR, Bhardwaj R, Carrel AL, Lindinger S, Romanin C, Parise-Filho R, Hediger MA, Reymond JL (2020): Natural product inspired optimization of a selective TRPV6 calcium channel inhibitor. RSC Med. Chem. **11**, 1032-1040
https://doi.org/10.1039/d0md00145g

Dang S, van Goor MK, Asarnow D, Wang Y, Julius D, Cheng Y, van der Wijst J (2019): Structural insight into TRPV5 channel function and modulation. Proc. Natl. Acad. Sci. USA **116**, 8869-8878
https://doi.org/10.1073/pnas.1820323116

den Dekker E, Hoenderop JG, Nilius B, Bindels RJ (2003): The epithelial calcium channels, TRPV5 & TRPV6: from identification towards regulation. Cell Calcium **33**, 497-507
https://doi.org/10.1016/s0143-4160(03)00065-4

Deng Z, Paknejad N, Maksaev G, Sala-Rabanal M, Nichols CG, Hite RK, Yuan P (2018): Cryo-EM and X-ray structures of TRPV4 reveal insight into ion permeation and gating mechanisms. Nat. Struct. Mol. Biol. **25**, 252-260
https://doi.org/10.1038/s41594-018-0037-5

Dias FC, Alves VS, Matias DO, Figueiredo CP, Miranda ALP, Passos GF, Costa R (2019): The selective TRPV4 channel antagonist HC-067047 attenuates mechanical allodynia in diabetic mice. Eur. J. Pharmacol. **856**, 172408
https://doi.org/10.1016/j.ejphar.2019.172408

Du J, Wang X, Li J, Guo J, Liu L, Yan D, Yang Y, Li Z, Zhu J, Shen B (2016): Increasing TRPV4 expression restores flow-induced dilation impaired in mesenteric arteries with aging. Sci. Rep. **6**, 22780
https://doi.org/10.1038/srep22780

Eubler K, Herrmann C, Tiefenbacher A, Kohn FM, Schwarzer JU, Kunz L, Mayerhofer A (2018): Ca(2+) signaling and IL-8 secretion in human testicular peritubular cells involve the cation channel TRPV2. Int. J. Mol. Sci. **19**, 2829
https://doi.org/10.3390/ijms19092829

Fallah A, Pierre R, Abed E, Moreau R (2013): Lysophosphatidylcholine-induced cytotoxicity in osteoblast-like MG-63 cells: involvement of transient receptor potential vanilloid 2 (TRPV2) channels. Mol. Membr. Biol. **30**, 315-326
https://doi.org/10.3109/09687688.2013.828855

Fang Y, Liu G, Xie C, Qian K, Lei X, Liu Q, Liu G, Cao Z, Fu J, Du H, et al. (2018): Pharmacological inhibition of TRPV4 channel suppresses malignant biological behavior of hepatocellular carcinoma via modulation of ERK signaling pathway. Biomed. Pharmacother. **101**, 910-919
https://doi.org/10.1016/j.biopha.2018.03.014

Fei XF, Wang BX, Li TJ, Tashiro S, Minami M, Xing DJ, Ikejima T (2003): Evodiamine, a constituent of Evodiae Fructus, induces anti-proliferating effects in tumor cells. Cancer Sci. **94**, 92-98
https://doi.org/10.1111/j.1349-7006.2003.tb01358.x

Feketa VV, Marrelli SP (2015): Systemic administration of the TRPV3 ion channel agonist Carvacrol induces hypothermia in conscious rodents. PLoS One **10**, e0141994
https://doi.org/10.1371/journal.pone.0141994

Fischer SPM, Brusco I, Brum ES, Fialho MFP, Camponogara C, Scussel R, Machado-de-Avila RA, Trevisan G, Oliveira SM (2020): Involvement of TRPV1 and the efficacy of alpha-spinasterol on experimental fibromyalgia symptoms in mice. Neurochem. Int. **134**, 104673
https://doi.org/10.1016/j.neuint.2020.104673

Fontan F, Baudet E (1971): Surgical repair of tricuspid atresia. Thorax **26**, 240-248
https://doi.org/10.1136/thx.26.3.240

Fu J, Du H, Zhang X, Xu X (2019): Pharmacological inhibition of transient receptor potential Vanilloid 4 (TRPV4) channel alleviates carbon tetrachloride-induced liver fibrosis in mice. J. Nippon Med. Sch. **86**, 258-262
https://doi.org/10.1272/jnms.JNMS.2019_86-407

Fu S, Hirte H, Welch S, Ilenchuk TT, Lutes T, Rice C, Fields N, Nemet A, Dugourd D, Piha-Paul S, et al. (2017): First-in-human phase I study of SOR-C13, a TRPV6 calcium channel inhibitor, in patients with advanced solid tumors. Invest. New Drugs **35**, 324-333
https://doi.org/10.1007/s10637-017-0438-z

Fujii N, Kenny GP, Amano T, Honda Y, Kondo N, Nishiyasu T (2019): Evidence for TRPV4 channel induced skin vasodilatation through NOS, COX, and KCa channel mechanisms with no effect on sweat rate in humans. Eur. J. Pharmacol. **858**, 172462
https://doi.org/10.1016/j.ejphar.2019.172462

Fujimura S, Mio K, Kuramochi M, Sekiguchi H, Ikezaki K, Mio M, Hengphasatporn K, Shigeta Y, Kubo T, Sasaki YC (2020): Agonist and antagonist-diverted twisting motions of a single TRPV1 channel. J. Phys. Chem. B **124**, 11617-11624
https://doi.org/10.1021/acs.jpcb.0c08250

Gao Y, Cao E, Julius D, Cheng Y (2016): TRPV1 structures in nanodiscs reveal mechanisms of ligand and lipid action. Nature **534**, 347-351
https://doi.org/10.1038/nature17964

Garcia-Sanz N, Fernandez-Carvajal A, Morenilla-Palao C, Planells-Cases R, Fajardo-Sanchez E, Fernandez-Ballester G, Ferrer-Montiel A (2004): Identification of a tetramerization domain in the C terminus of the vanilloid receptor. J. Neurosci. **24**, 5307-5314
https://doi.org/10.1523/JNEUROSCI.0202-04.2004

Garcia-Sanz N, Valente P, Gomis A, Fernandez-Carvajal A, Fernandez-Ballester G, Viana F, Belmonte C, Ferrer-Montiel A (2007): A role of the transient receptor potential domain of vanilloid receptor I in channel gating. J. Neurosci. **27**, 11641-11650
https://doi.org/10.1523/JNEUROSCI.2457-07.2007

Gavva NR, Klionsky L, Qu Y, Shi L, Tamir R, Edenson S, Zhang TJ, Viswanadhan VN, Toth A, Pearce LV, et al. (2004): Molecular determinants of vanilloid sensitivity in TRPV1. J. Biol. Chem. **279**, 20283-20295
https://doi.org/10.1074/jbc.M312577200

Gees M, Owsianik G, Nilius B, Voets T (2012): TRP channels. Compr. Physiol. **2**, 563-608
https://doi.org/10.1002/cphy.c110026

Geng S, Zheng Y, Meng M, Guo Z, Cao N, Ma X, Du Z, Li J, Duan Y, Du G (2016): Gingerol reverses the cancer-promoting effect of capsaicin by increased TRPV1 level in a urethane-induced lung carcinogenic model. J. Agric. Food Chem. **64**, 6203-6211
https://doi.org/10.1021/acs.jafc.6b02480

Gonzalez-Reyes LE, Ladas TP, Chiang CC, Durand DM (2013): TRPV1 antagonist capsazepine suppresses 4-AP-induced epileptiform activity in vitro and electrographic seizures in vivo. Exp. Neurol. **250**, 321-332
https://doi.org/10.1016/j.expneurol.2013.10.010

Gu Q, Lin RL, Hu HZ, Zhu MX, Lee LY (2005): 2-Aminoethoxydiphenyl borate stimulates pulmonary C neurons via the

activation of TRPV channels. Am. J. Physiol. Lung Cell Mol. Physiol. **288**, L932-941
https://doi.org/10.1152/ajplung.00439.2004

Harada K, Kitaguchi T, Kamiya T, Aung KH, Nakamura K, Ohta K, Tsuboi T (2017): Lysophosphatidylinositol-induced activation of the cation channel TRPV2 triggers glucagon-like peptide-1 secretion in enteroendocrine L cells. J. Biol. Chem. **292**, 10855-10864
https://doi.org/10.1074/jbc.M117.788653

Henry CO, Dalloneau E, Perez-Berezo MT, Plata C, Wu Y, Guillon A, Morello E, Aimar RF, Potier-Cartereau M, Esnard F, et al. (2016): In vitro and in vivo evidence for an inflammatory role of the calcium channel TRPV4 in lung epithelium: Potential involvement in cystic fibrosis. Am. J. Physiol. Lung Cell Mol. Physiol. **311**, L664-675
https://doi.org/10.1152/ajplung.00442.2015

Ho WS, Zheng X, Zhang DX (2015): Role of endothelial TRPV4 channels in vascular actions of the endocannabinoid, 2-arachidonoylglycerol. Br. J. Pharmacol. **172**, 5251-5264
https://doi.org/10.1111/bph.13312

Hoenderop JG, van Leeuwen JP, van der Eerden BC, Kersten FF, van der Kemp AW, Merillat AM, Waarsing JH, Rossier BC, Vallon V, Hummler E, et al. (2003): Renal Ca2+ wasting, hyperabsorption, and reduced bone thickness in mice lacking TRPV5. J. Clin. Invest. **112**, 1906-1914
https://doi.org/10.1172/JCI19826

Hogestatt ED, Zygmunt PM (2002): Cardiovascular pharmacology of anandamide. Prostaglandins Leukot. Essent. Fatty Acids **66**, 343-351
https://doi.org/10.1054/plef.2001.0346

Hu W, Ding Y, Li Q, Shi R, He Y (2020): Transient receptor potential vanilloid 4 channels as therapeutic targets in diabetes and diabetes-related complications. J. Diabetes Investig. **11**, 757-769
https://doi.org/10.1111/jdi.13244

Huang JK, Cheng HH, Huang CJ, Kuo CC, Chen WC, Liu SI, Hsu SS, Chang HT, Lu YC, Tseng LL, et al. (2006): Effect of capsazepine on cytosolic Ca(2+) levels and proliferation of human prostate cancer cells. Toxicol. In Vitro **20**, 567-574
https://doi.org/10.1016/j.tiv.2005.09.014

Huang YY, Wang ZK, Li J, Bai SW, Shen B, Du J, Xia XM, Wang FY (2018): The effect of serine phosphorylated claudin-7 on the epithelial barrier and the modulation by transient receptor potential vanilloid 4 in human colonic cells. Biomed. Pharmacother. **108**, 540-546
https://doi.org/10.1016/j.biopha.2018.09.070

Hughes TE, Del Rosario JS, Kapoor A, Yazici AT, Yudin Y, Fluck EC, 3rd, Filizola M, Rohacs T, Moiseenkova-Bell VY (2019): Structure-based characterization of novel TRPV5 inhibitors. eLife **8,** e49572
https://doi.org/10.7554/eLife.49572

Hughes TET, Pumroy RA, Yazici AT, Kasimova MA, Fluck EC, Huynh KW, Samanta A, Molugu SK, Zhou ZH, Carnevale V, et al. (2018): Structural insights on TRPV5 gating by endogenous modulators. Nat. Commun. **9**, 4198
https://doi.org/10.1038/s41467-018-06753-6

Hurd L, Kirwin SM, Boggs M, Mackenzie WG, Bober MB, Funanage VL, Duncan RL (2015): A mutation in TRPV4 results in altered chondrocyte calcium signaling in severe metatropic dysplasia. Am. J. Med. Genet. A **167A**, 2286-2293
https://doi.org/10.1002/ajmg.a.37182

Huynh KW, Cohen MR, Chakrapani S, Holdaway HA, Stewart PL, Moiseenkova-Bell VY (2014): Structural insight into the assembly of TRPV channels. Structure **22**, 260-268
https://doi.org/10.1016/j.str.2013.11.008

Ishikawa DT, Vizin RCL, Souza CO, Carrettiero DC, Romanovsky AA, Almeida MC (2019): Camphor, applied epidermally to the back, causes snout- and chest-grooming in rats: a response mediated by cutaneous TRP channels. Pharmaceuticals (Basel) **12,** 24
https://doi.org/10.3390/ph12010024

Kang JH, Goto T, Han IS, Kawada T, Kim YM, Yu R (2010): Dietary capsaicin reduces obesity-induced insulin resistance and hepatic steatosis in obese mice fed a high-fat diet. Obesity (Silver Spring) **18**, 780-787
https://doi.org/10.1038/oby.2009.301

Katanosaka Y, Iwasaki K, Ujihara Y, Takatsu S, Nishitsuji K, Kanagawa M, Sudo A, Toda T, Katanosaka K, Mohri S, et al. (2014): TRPV2 is critical for the maintenance of cardiac structure and function in mice. Nat. Commun. **5**, 3932
https://doi.org/10.1038/ncomms4932

Khaleel A, Wu MS, Wong HS, Hsu YW, Chou YH, Chen HY (2015): A single nucleotide polymorphism (rs4236480) in TRPV5 calcium channel gene is associated with stone multiplicity in calcium nephrolithiasis patients. Mediators Inflamm. **2015**, 375427
https://doi.org/10.1155/2015/375427

Khan K, Singh A, Mittal M, Sharan K, Singh N, Dixit P, Sanyal S, Maurya R, Chattopadhyay N (2012): [6]-Gingerol induces bone loss in ovary intact adult mice and augments osteoclast function via the transient receptor potential vanilloid 1 channel. Mol. Nutr. Food Res. **56**, 1860-1873
https://doi.org/10.1002/mnfr.201200200

Kitagawa Y, Tamai I, Hamada Y, Usui K, Wada M, Sakata M, Matsushita M (2013): Orally administered selective TRPV1 antagonist, JTS-653, attenuates chronic pain refractory to nonsteroidal anti-inflammatory drugs in rats and mice including post-herpetic pain. J. Pharmacol. Sci. **122**, 128-137
https://doi.org/10.1254/jphs.12276fp

Klausen TK, Pagani A, Minassi A, Ech-Chahad A, Prenen J, Owsianik G, Hoffmann EK, Pedersen SF, Appendino G, Nilius B (2009): Modulation of the transient receptor potential vanilloid channel TRPV4 by 4alpha-phorbol esters: a structure-activity study. J. Med. Chem. **52**, 2933-2939
https://doi.org/10.1021/jm9001007

Klein AH, Carstens MI, Carstens E (2013): Eugenol and carvacrol induce temporally desensitizing patterns of oral irritation and enhance innocuous warmth and noxious heat sensation on the tongue. Pain **154**, 2078-2087
https://doi.org/10.1016/j.pain.2013.06.025

Klein AH, Joe CL, Davoodi A, Takechi K, Carstens MI, Carstens E (2014): Eugenol and carvacrol excite first- and second-order trigeminal neurons and enhance their heat-evoked responses. Neuroscience **271**, 45-55
https://doi.org/10.1016/j.neuroscience.2014.04.019

Klein CJ, Shi Y, Fecto F, Donaghy M, Nicholson G, McEntagart ME, Crosby AH, Wu Y, Lou H, McEvoy KM, et al. (2011): TRPV4

mutations and cytotoxic hypercalcemia in axonal Charcot-Marie-Tooth neuropathies. Neurology **76**, 887-894 https://doi.org/10.1212/WNL.0b013e31820f2de3

Klein M, Goncalves Salum F, Cherubini K, Zancanaro de Figueiredo MA (2020): Cannabidiol as a novel therapeutic strategy for oral inflammatory diseases: a review of current knowledge and future perspectives. Altern. Ther. Health Med. **26**, 12-16

Koch SE, Gao X, Haar L, Jiang M, Lasko VM, Robbins N, Cai W, Brokamp C, Varma P, Tranter M, et al. (2012): Probenecid: novel use as a non-injurious positive inotrope acting via cardiac TRPV2 stimulation. J. Mol. Cell. Cardiol. **53**, 134-144 https://doi.org/10.1016/j.yjmcc.2012.04.011

Koch SE, Nieman ML, Robbins N, Slone S, Worley M, Green LC, Chen Y, Barlow A, Tranter M, Wang H, et al. (2018): Tranilast blunts the hypertrophic and fibrotic response to increased afterload independent of cardiomyocyte transient receptor potential vanilloid 2 channels. J. Cardiovasc. Pharmacol. **72**, 40-48 https://doi.org/10.1097/FJC.0000000000000588

Kovacs G, Montalbetti N, Simonin A, Danko T, Balazs B, Zsembery A, Hediger MA (2012): Inhibition of the human epithelial calcium channel TRPV6 by 2-aminoethoxydiphenyl borate (2-APB). Cell Calcium **52**, 468-480 https://doi.org/10.1016/j.ceca.2012.08.005

Kremeyer B, Lopera F, Cox JJ, Momin A, Rugiero F, Marsh S, Woods CG, Jones NG, Paterson KJ, Fricker FR, et al. (2010): A gain-of-function mutation in TRPA1 causes familial episodic pain syndrome. Neuron **66**, 671-680 https://doi.org/10.1016/j.neuron.2010.04.030

Krishna MS, Joy B, Sundaresan A (2015): Effect on oxidative stress, glucose uptake level and lipid droplet content by Apigenin 7, 4'-dimethyl ether isolated from Piper longum L. J. Food Sci. Technol. **52**, 3561-3570 https://doi.org/10.1007/s13197-014-1387-6

Laleh P, Yaser K, Alireza O (2019): Oleoylethanolamide: A novel pharmaceutical agent in the management of obesity-an updated review. J. Cell. Physiol. **234**, 7893-7902 https://doi.org/10.1002/jcp.27913

Landoure G, Zdebik AA, Martinez TL, Burnett BG, Stanescu HC, Inada H, Shi Y, Taye AA, Kong L, Munns CH, et al. (2010): Mutations in TRPV4 cause Charcot-Marie-Tooth disease type 2C. Nat. Genet. **42**, 170-174 https://doi.org/10.1038/ng.512

Lee SH, Raboune S, Walker JM, Bradshaw HB (2010): Distribution of endogenous farnesyl pyrophosphate and four species of lysophosphatidic acid in rodent brain. Int. J. Mol. Sci. **11**, 3965-3976 https://doi.org/10.3390/ijms11103965

Lehen'kyi V, Flourakis M, Skryma R, Prevarskaya N (2007): TRPV6 channel controls prostate cancer cell proliferation via Ca(2+)/NFAT-dependent pathways. Oncogene **26**, 7380-7385 https://doi.org/10.1038/sj.onc.1210545

Li Q, Li L, Wang F, Chen J, Zhao Y, Wang P, Nilius B, Liu D, Zhu Z (2013): Dietary capsaicin prevents nonalcoholic fatty liver disease through transient receptor potential vanilloid 1-mediated peroxisome proliferator-activated receptor delta activation. Pflügers Arch. **465**, 1303-1316 https://doi.org/10.1007/s00424-013-1274-4

Liao M, Cao E, Julius D, Cheng Y (2013): Structure of the TRPV1 ion channel determined by electron cryo-microscopy. Nature **504**, 107-112 https://doi.org/10.1038/nature12822

Liedtke W, Choe Y, Marti-Renom MA, Bell AM, Denis CS, Sali A, Hudspeth AJ, Friedman JM, Heller S (2000): Vanilloid receptor-related osmotically activated channel (VR-OAC), a candidate vertebrate osmoreceptor. Cell **103**, 525-535 https://doi.org/10.1016/s0092-8674(00)00143-4

Lin Z, Chen Q, Lee M, Cao X, Zhang J, Ma D, Chen L, Hu X, Wang H, Wang X, et al. (2012): Exome sequencing reveals mutations in TRPV3 as a cause of Olmsted syndrome. Am. J. Hum. Genet. **90**, 558-564 https://doi.org/10.1016/j.ajhg.2012.02.006

Lishko PV, Procko E, Jin X, Phelps CB, Gaudet R (2007): The ankyrin repeats of TRPV1 bind multiple ligands and modulate channel sensitivity. Neuron **54**, 905-918 https://doi.org/10.1016/j.neuron.2007.05.027

Liu AJ, Wang SH, Chen KC, Kuei HP, Shih YL, Hou SY, Chiu WT, Hsiao SH, Shih CM (2013a): Evodiamine, a plant alkaloid, induces calcium/JNK-mediated autophagy and calcium/mitochondria-mediated apoptosis in human glioblastoma cells. Chem. Biol. Interact. **205**, 20-28 https://doi.org/10.1016/j.cbi.2013.06.004

Liu AJ, Wang SH, Hou SY, Lin CJ, Chiu WT, Hsiao SH, Chen TH, Shih CM (2013b): Evodiamine induces transient receptor potential vanilloid-1-mediated protective autophagy in U87-MG astrocytes. Evid. Based Complement. Alternat. Med. **2013**, 354840 https://doi.org/10.1155/2013/354840

Liu N, Lu W, Dai X, Qu X, Zhu C (2022): The role of TRPV channels in osteoporosis. Mol. Biol. Rep. **49**, 577-585 https://doi.org/10.1007/s11033-021-06794-z

Liu X, Yang L, Bi Y, Wang LH, Huang H (2015): Effect of evodiamine in inducing apoptosis of gastric cancer SGC-7901 cells through mTOR signal pathway. Zhongguo Zhong Yao Za Zhi **40**, 3262-3266 (in Chinese)

Luo H, Rossi E, Saubamea B, Chasseigneaux S, Cochois V, Choublier N, Smirnova M, Glacial F, Perriere N, Bourdoulous S, et al. (2019): Cannabidiol increases proliferation, migration, tubulogenesis, and integrity of human brain endothelial cells through TRPV2 activation. Mol. Pharm. **16**, 1312-1326 https://doi.org/10.1021/acs.molpharmaceut.8b01252

Ma Y, Zhang P, Li J, Lu J, Ge J, Zhao Z, Ma X, Wan S, Yao X, Shen B (2015): Epoxyeicosatrienoic acids act through TRPV4-TRPC1-KCa1.1 complex to induce smooth muscle membrane hyperpolarization and relaxation in human internal mammary arteries. Biochim. Biophys. Acta **1852**, 552-559 https://doi.org/10.1016/j.bbadis.2014.12.010

Macpherson LJ, Hwang SW, Miyamoto T, Dubin AE, Patapoutian A, Story GM (2006): More than cool: promiscuous relationships of menthol and other sensory compounds. Mol. Cell. Neurosci. **32**, 335-343 https://doi.org/10.1016/j.mcn.2006.05.005

Malik S, Suchal K, Khan SI, Bhatia J, Kishore K, Dinda AK, Arya DS (2017): Apigenin ameliorates streptozotocin-induced diabetic nephropathy in rats via MAPK-NF-kappaB-TNF-alpha

and TGF-beta1-MAPK-fibronectin pathways. Am. J. Physiol. Renal Physiol. **313**, F414-F422
https://doi.org/10.1152/ajprenal.00393.2016

Maqboul A, Elsadek B (2018): Expression profiles of TRPV1, TRPV4, TLR4 and ERK1/2 in the dorsal root ganglionic neurons of a cancer-induced neuropathy rat model. PeerJ **6**, e4622
https://doi.org/10.7717/peerj.4622

Marichal-Cancino BA, Gonzalez-Hernandez A, MaassenVanDenBrink A, Ramirez-San Juan E, Villalon CM (2020): Potential mechanisms involved in palmitoylethanolamide-induced vasodepressor effects in rats. J. Vasc. Res. **57**, 152-163
https://doi.org/10.1159/000506158

Maruyama M, Sakai A, Suzuki H, Akimoto T (2015): Analysis of TRPV3 function in pain sensation using a gain-of-function mutant rat. Exp. Anim. **64**, S69–S135

Maruyama T, Kanaji T, Nakade S, Kanno T, Mikoshiba K (1997): 2APB, 2-aminoethoxydiphenyl borate, a membrane-penetrable modulator of Ins(1,4,5)P3-induced Ca2+ release. J. Biochem. **122**, 498-505
https://doi.org/10.1093/oxfordjournals.jbchem.a021780

Masamune A, Kotani H, Sorgel FL, Chen JM, Hamada S, Sakaguchi R, Masson E, Nakano E, Kakuta Y, Niihori T, et al. (2020): Variants that affect function of calcium channel trpv6 are associated with early-onset chronic pancreatitis. Gastroenterology **158**, 1626-1641e1628
https://doi.org/10.1053/j.gastro.2020.01.005

Matsumura T, Matsui M, Iwata Y, Asakura M, Saito T, Fujimura H, Sakoda S (2018): A pilot study of tranilast for cardiomyopathy of muscular dystrophy. Intern. Med. **57**, 311-318
https://doi.org/10.2169/internalmedicine.8651-16

Meents JE, Hoffmann J, Chaplan SR, Neeb L, Schuh-Hofer S, Wickenden A, Reuter U (2015): Two TRPV1 receptor antagonists are effective in two different experimental models of migraine. J. Headache Pain **16**, 57
https://doi.org/10.1186/s10194-015-0539-z

Messeguer A, Planells-Cases R, Ferrer-Montiel A (2006): Physiology and pharmacology of the vanilloid receptor. Curr. Neuropharmacol. **4**, 1-15
https://doi.org/10.2174/157015906775202995

Miyashita K, Oyama T, Sakuta T, Tokuda M, Torii M (2012): Anandamide induces matrix metalloproteinase-2 production through cannabinoid-1 receptor and transient receptor potential vanilloid-1 in human dental pulp cells in culture. J. Endod. **38**, 786-790
https://doi.org/10.1016/j.joen.2012.02.025

Moiseenkova-Bell VY, Stanciu LA, Serysheva, II, Tobe BJ, Wensel TG (2008): Structure of TRPV1 channel revealed by electron cryomicroscopy. Proc. Natl. Acad. Sci. USA **105**, 7451-7455
https://doi.org/10.1073/pnas.0711835105

Monet M, Gkika D, Lehen'kyi V, Pourtier A, Vanden Abeele F, Bidaux G, Juvin V, Rassendren F, Humez S, Prevarsakaya N (2009): Lysophospholipids stimulate prostate cancer cell migration via TRPV2 channel activation. Biochim. Biophys. Acta **1793**, 528-539
https://doi.org/10.1016/j.bbamcr.2009.01.003

Montell C (2001): Physiology, phylogeny, and functions of the TRP superfamily of cation channels. Sci. STKE **2001**, re1
https://doi.org/10.1126/stke.2001.90.re1

Montell C, Rubin GM (1989): Molecular characterization of the Drosophila trp locus: a putative integral membrane protein required for phototransduction. Neuron **2**, 1313-1323
https://doi.org/10.1016/0896-6273(89)90069-x

Moqrich A, Hwang SW, Earley TJ, Petrus MJ, Murray AN, Spencer KS, Andahazy M, Story GM, Patapoutian A (2005): Impaired thermosensation in mice lacking TRPV3, a heat and camphor sensor in the skin. Science **307**, 1468-1472
https://doi.org/10.1126/science.1108609

Moran MM, McAlexander MA, Biro T, Szallasi A (2011): Transient receptor potential channels as therapeutic targets. Nat. Rev. Drug Discov. **10**, 601-620
https://doi.org/10.1038/nrd3456

Motte J, Ambrosius B, Gruter T, Bachir H, Sgodzai M, Pedreiturria X, Pitarokoili K, Gold R (2018): Capsaicin-enriched diet ameliorates autoimmune neuritis in rats. J. Neuroinflammation **15**, 122
https://doi.org/10.1186/s12974-018-1165-x

Muller D, Hoenderop JG, Meij IC, van den Heuvel LP, Knoers NV, den Hollander AI, Eggert P, Garcia-Nieto V, Claverie-Martin F, Bindels RJ (2000): Molecular cloning, tissue distribution, and chromosomal mapping of the human epithelial Ca2+ channel (ECAC1). Genomics **67**, 48-53
https://doi.org/10.1006/geno.2000.6203

Nabissi M, Morelli MB, Amantini C, Liberati S, Santoni M, Ricci-Vitiani L, Pallini R, Santoni G (2015): Cannabidiol stimulates Aml-1a-dependent glial differentiation and inhibits glioma stem-like cells proliferation by inducing autophagy in a TRPV2-dependent manner. Int. J. Cancer **137**, 1855-1869
https://doi.org/10.1002/ijc.29573

Nahama A, Ramachandran R, Cisternas AF, Ji H (2020): The role of afferent pulmonary innervation in ARDS associated with COVID-19 and potential use of resiniferatoxin to improve prognosis: A review. Med. Drug Discov. **5**, 100033
https://doi.org/10.1016/j.medidd.2020.100033

Naik JS, Osmond JM, Walker BR, Kanagy NL (2016): Hydrogen sulfide-induced vasodilation mediated by endothelial TRPV4 channels. Am. J. Physiol. Heart Circ. Physiol. **311**, H1437-H1444
https://doi.org/10.1152/ajpheart.00465.2016

Naticchioni M, Karani R, Smith MA, Onusko E, Robbins N, Jiang M, Radzyukevich T, Fulford L, Gao X, Apel R, et al. (2015): Transient receptor potential vanilloid 2 regulates myocardial response to exercise. PLoS One **10**, e0136901
https://doi.org/10.1371/journal.pone.0136901

Nguyen TL, Nam YS, Lee SY, Kim HC, Jang CG (2010): Effects of capsazepine, a transient receptor potential vanilloid type 1 antagonist, on morphine-induced antinociception, tolerance, and dependence in mice. Br. J. Anaesth. **105**, 668-674
https://doi.org/10.1093/bja/aeq212

Nilius B, Vennekens R, Prenen J, Hoenderop JG, Droogmans G, Bindels RJ (2001): The single pore residue Asp542 determines Ca2+ permeation and Mg2+ block of the epithelial Ca2+ channel. J. Biol. Chem. **276**, 1020-1025
https://doi.org/10.1074/jbc.M006184200

Ogasawara M, Matsunaga T, Takahashi S, Saiki I, Suzuki H (2002): Anti-invasive and metastatic activities of evodiamine. Biol. Pharm. Bull. **25**, 1491-1493
https://doi.org/10.1248/bpb.25.1491

Okumi H, Tashima K, Matsumoto K, Namiki T, Terasawa K, Horie S (2012): Dietary agonists of TRPV1 inhibit gastric acid secretion in mice. Planta Med. **78**, 1801-1806 https://doi.org/10.1055/s-0032-1315387

Onusko E, McDermott MR, Robbins N, Liu G, Kranias EG, Rubinstein J, Koch SE (2020): Probenecid treatment improves outcomes in a novel mouse model of peripartum cardiomyopathy. PLoS One **15**, e0230386 https://doi.org/10.1371/journal.pone.0230386

Ou-Yang Q, Li B, Xu M, Liang H (2018): TRPV4 promotes the migration and invasion of glioma cells via AKT/Rac1 signaling. Biochem. Biophys. Res. Commun. **503**, 876-881 https://doi.org/10.1016/j.bbrc.2018.06.090

Pabbidi RM, Yu SQ, Peng S, Khardori R, Pauza ME, Premkumar LS (2008): Influence of TRPV1 on diabetes-induced alterations in thermal pain sensitivity. Mol. Pain **4**, 9 https://doi.org/10.1186/1744-8069-4-9

Pan Z, Wang Z, Yang H, Zhang F, Reinach PS (2011): TRPV1 activation is required for hypertonicity-stimulated inflammatory cytokine release in human corneal epithelial cells. Invest. Ophthalmol. Vis. Sci. **52**, 485-493 https://doi.org/10.1167/iovs.10-5801

Paterniti I, Di Paola R, Campolo M, Siracusa R, Cordaro M, Bruschetta G, Tremolada G, Maestroni A, Bandello F, Esposito E, et al. (2015): Palmitoylethanolamide treatment reduces retinal inflammation in streptozotocin-induced diabetic rats. Eur. J. Pharmacol. **769**, 313-323 https://doi.org/10.1016/j.ejphar.2015.11.035

Peier AM, Reeve AJ, Andersson DA, Moqrich A, Earley TJ, Hergarden AC, Story GM, Colley S, Hogenesch JB, McIntyre P, et al. (2002): A heat-sensitive TRP channel expressed in keratinocytes. Science **296**, 2046-2049 https://doi.org/10.1126/science.1073140

Peng JB, Brown EM, Hediger MA (2001): Structural conservation of the genes encoding CaT1, CaT2, and related cation channels. Genomics **76**, 99-109 https://doi.org/10.1006/geno.2001.6606

Peng JB, Chen XZ, Berger UV, Weremowicz S, Morton CC, Vassilev PM, Brown EM, Hediger MA (2000): Human calcium transport protein CaT1. Biochem. Biophys. Res. Commun. **278**, 326-332 https://doi.org/10.1006/bbrc.2000.3716

Petrosino S, Cristino L, Karsak M, Gaffal E, Ueda N, Tuting T, Bisogno T, De Filippis D, D'Amico A, Saturnino C, et al. (2010): Protective role of palmitoylethanolamide in contact allergic dermatitis. Allergy **65**, 698-711 https://doi.org/10.1111/j.1398-9995.2009.02254.x

Petrosino S, Verde R, Vaia M, Allara M, Iuvone T, Di Marzo V (2018): Anti-inflammatory properties of cannabidiol, a nonpsychotropic cannabinoid, in experimental allergic contact dermatitis. J. Pharmacol. Exp. Ther. **365**, 652-663 https://doi.org/10.1124/jpet.117.244368

Portavella M, Rodriguez-Espinosa N, Galeano P, Blanco E, Romero JI, Holubiec MI, Rodriguez de Fonseca F, Fernandez-Espejo E (2018): Oleoylethanolamide and palmitoylethanolamide protect cultured cortical neurons against hypoxia. Cannabis Cannabinoid Res. **3**, 171-178 https://doi.org/10.1089/can.2018.0013

Proulx K, Cota D, Castaneda TR, Tschop MH, D'Alessio DA, Tso P, Woods SC, Seeley RJ (2005): Mechanisms of oleoylethanolamide-induced changes in feeding behavior and motor activity. Am. J. Physiol. Regul. Integr. Comp. Physiol. **289**, R729-737 https://doi.org/10.1152/ajpregu.00029.2005

Pumroy RA, Samanta A, Liu Y, Hughes TE, Zhao S, Yudin Y, Rohacs T, Han S, Moiseenkova-Bell VY (2019): Molecular mechanism of TRPV2 channel modulation by cannabidiol. eLife **8,** e48792 https://doi.org/10.7554/eLife.48792

Qian K, Wang G, Cao R, Liu T, Qian G, Guan X, Guo Z, Xiao Y, Wang X (2016): Capsaicin suppresses cell proliferation, induces cell cycle arrest and ros production in bladder cancer cells through FOXO3a-mediated pathways. Molecules **21,** 1406 https://doi.org/10.3390/molecules21101406

Qu YJ, Zhang X, Fan ZZ, Huai J, Teng YB, Zhang Y, Yue SW (2016): Effect of TRPV4-p38 MAPK Pathway on neuropathic pain in rats with chronic compression of the dorsal root ganglion. Biomed. Res. Int. **2016**, 6978923 https://doi.org/10.1155/2016/6978923

Ramer R, Bublitz K, Freimuth N, Merkord J, Rohde H, Haustein M, Borchert P, Schmuhl E, Linnebacher M, Hinz B (2012): Cannabidiol inhibits lung cancer cell invasion and metastasis via intercellular adhesion molecule-1. FASEB J. **26**, 1535-1548 https://doi.org/10.1096/fj.11-198184

Rapoport AM (2012): The therapeutic future in headache. Neurol. Sci. **33** (Suppl. 1), S119-125 https://doi.org/10.1007/s10072-012-1056-3

Ren B, Qin W, Wu F, Wang S, Pan C, Wang L, Zeng B, Ma S, Liang J (2016): Apigenin and naringenin regulate glucose and lipid metabolism, and ameliorate vascular dysfunction in type 2 diabetic rats. Eur. J. Pharmacol. **773**, 13-23 https://doi.org/10.1016/j.ejphar.2016.01.002

Robbins N, Koch SE, Rubinstein J (2013): Targeting TRPV1 and TRPV2 for potential therapeutic interventions in cardiovascular disease. Transl. Res. **161**, 469-476 https://doi.org/10.1016/j.trsl.2013.02.003

Robbins N, Koch SE, Tranter M, Rubinstein J (2012): The history and future of probenecid. Cardiovasc. Toxicol. **12**, 1-9 https://doi.org/10.1007/s12012-011-9145-8

Robbins N, Gilbert M, Kumar M, McNamara JW, Daly P, Koch SE, Conway G, Effat M, Woo JG, Sadayappan S, et al. (2018): Probenecid improves cardiac function in patients with heart failure with reduced ejection fraction in vivo and cardiomyocyte calcium sensitivity in vitro. J. Am. Heart Assoc. **7,** e007148 https://doi.org/10.1161/JAHA.117.007148

Ross RA (2003): Anandamide and vanilloid TRPV1 receptors. Br. J. Pharmacol. **140**, 790-801 https://doi.org/10.1038/sj.bjp.0705467

Rubinstein J, Woo JG, Garcia AM, Alsaied T, Li J, Lunde PK, Moore RA, Laasmaa M, Sammons A, Mays WA, et al. (2020): probenecid improves cardiac function in subjects with a fontan circulation and augments cardiomyocyte calcium homeostasis. Pediatr. Cardiol. **41**, 1675-1688 https://doi.org/10.1007/s00246-020-02427-7

Sakuta H, Lin CH, Yamada M, Kita Y, Tokuoka SM, Shimizu T, Noda M (2020): Nax-positive glial cells in the organum vasculosum laminae terminalis produce epoxyeicosatrienoic acids

to induce water intake in response to increases in [Na(+)] in body fluids. Neurosci. Res. **154**, 45-51
https://doi.org/10.1016/j.neures.2019.05.006

Samad MB, Mohsin M, Razu BA, Hossain MT, Mahzabeen S, Unnoor N, Muna IA, Akhter F, Kabir AU, Hannan JMA (2017): [6]-Gingerol, from Zingiber officinale, potentiates GLP-1 mediated glucose-stimulated insulin secretion pathway in pancreatic beta-cells and increases RAB8/RAB10-regulated membrane presentation of GLUT4 transporters in skeletal muscle to improve hyperglycemia in Lepr(db/db) type 2 diabetic mice. BMC Complement. Altern. Med. **17**, 395
https://doi.org/10.1186/s12906-017-1903-0

Santoni G, Amantini C, Maggi F, Marinelli O, Santoni M, Nabissi M, Morelli MB (2020): The TRPV2 cation channels: from urothelial cancer invasiveness to glioblastoma multiforme interactome signature. Lab. Invest. **100**, 186-198
https://doi.org/10.1038/s41374-019-0333-7

Saotome K, Singh AK, Yelshanskaya MV, Sobolevsky AI (2016): Crystal structure of the epithelial calcium channel TRPV6. Nature **534**, 506-511
https://doi.org/10.1038/nature17975

Sartim AG, Brito BM, Gobira PH, Joca SRL (2019): Attenuation of glutamatergic and nitrergic system contributes to the antidepressant-like effect induced by capsazepine in the forced swimming test. Behav. Pharmacol. **30**, 59-66
https://doi.org/10.1097/FBP.0000000000000416

Scott VE, Patel H, Wetter J, Edlmayer R, Neelands T, Miller L, Huang S, Gauld S, Todorovic V, Gomtsian A, et al. (2016): Defining a mechanistic link between TRPV3 activity and psoriasis through IL-1α and EGFR signaling pathways. J. Investig. Dermatol. **136**, S94

Seebohm G, Schreiber JA (2021): Beyond hot and spicy: TRPV channels and their pharmacological modulation. Cell. Physiol. Biochem. **55**, 108-130
https://doi.org/10.33594/000000358

Selescu T, Ciobanu AC, Dobre C, Reid G, Babes A (2013): Camphor activates and sensitizes transient receptor potential melastatin 8 (TRPM8) to cooling and icilin. Chem. Senses **38**, 563-575
https://doi.org/10.1093/chemse/bjt027

Shibata M, Tang C (2020): Implications of transient receptor potential cation channels in migraine pathophysiology. Neurosci. Bull. **37**, 103-116
https://doi.org/10.1007/s12264-020-00569-5

Shirakawa H, Nakagawa T, Kaneko S (2010): Pathophysiological roles of transient receptor potential channels in glial cells. Yakugaku Zasshi (Journal of the Pharmaceutical Society of Japan) **130**, 281-287
https://doi.org/10.1248/yakushi.130.281

Singh AK, Saotome K, McGoldrick LL, Sobolevsky AI (2018): Structural bases of TRP channel TRPV6 allosteric modulation by 2-APB. Nat. Commun. **9**, 2465
https://doi.org/10.1038/s41467-018-04828-y

Skrzypski M, Kakkassery M, Mergler S, Grotzinger C, Khajavi N, Sassek M, Szczepankiewicz D, Wiedenmann B, Nowak KW, Strowski MZ (2013): Activation of TRPV4 channel in pancreatic INS-1E beta cells enhances glucose-stimulated insulin secretion via calcium-dependent mechanisms. FEBS Lett. **587**, 3281-3287
https://doi.org/10.1016/j.febslet.2013.08.025

Smith GD, Gunthorpe MJ, Kelsell RE, Hayes PD, Reilly P, Facer P, Wright JE, Jerman JC, Walhin JP, Ooi L, et al. (2002): TRPV3 is a temperature-sensitive vanilloid receptor-like protein. Nature **418**, 186-190
https://doi.org/10.1038/nature00894

Stamatelou KK, Francis ME, Jones CA, Nyberg LM, Curhan GC (2003): Time trends in reported prevalence of kidney stones in the United States: 1976-1994. Kidney Int. **63**, 1817-1823
https://doi.org/10.1046/j.1523-1755.2003.00917.x

Strotmann R, Harteneck C, Nunnenmacher K, Schultz G, Plant TD (2000): OTRPC4, a nonselective cation channel that confers sensitivity to extracellular osmolarity. Nat. Cell. Biol. **2**, 695-702
https://doi.org/10.1038/35036318

Sun W, Uchida K, Takahashi N, Iwata Y, Wakabayashi S, Goto T, Kawada T, Tominaga M (2016): Activation of TRPV2 negatively regulates the differentiation of mouse brown adipocytes. Pflügers Arch. **468**, 1527-1540
https://doi.org/10.1007/s00424-016-1846-1

Suzuki M, Mizuno A, Kodaira K, Imai M (2003): Impaired pressure sensation in mice lacking TRPV4. J. Biol. Chem. **278**, 22664-22668
https://doi.org/10.1074/jbc.M302561200

Suzuki Y, Chitayat D, Sawada H, Deardorff MA, McLaughlin HM, Begtrup A, Millar K, Harrington J, Chong K, Roifman M, et al. (2018): TRPV6 variants interfere with maternal-fetal calcium transport through the placenta and cause transient neonatal hyperparathyroidism. Am. J. Hum. Genet. **102**, 1104-1114
https://doi.org/10.1016/j.ajhg.2018.04.006

Suzuki Y, Sawada H, Tokumasu T, Suzuki S, Ninomiya S, Shirai M, Mukai T, Saito CT, Nishimura G, Tominaga M (2020): Novel TRPV6 mutations in the spectrum of transient neonatal hyperparathyroidism. J. Physiol. Sci. **70**, 33
https://doi.org/10.1186/s12576-020-00761-2

Szallasi A, Blumberg PM (1999): Vanilloid (Capsaicin) receptors and mechanisms. Pharmacol. Rev. **51**, 159-212

Szallasi A, Cortright DN, Blum CA, Eid SR (2007): The vanilloid receptor TRPV1: 10 years from channel cloning to antagonist proof-of-concept. Nat. Rev. Drug Discov. **6**, 357-372
https://doi.org/10.1038/nrd2280

Szymaszkiewicz A, Wlodarczyk J, Wasilewski A, Di Marzo V, Storr M, Fichna J, Zielinska M (2020): Desensitization of transient receptor potential vanilloid type-1 (TRPV1) channel as promising therapy of irritable bowel syndrome: characterization of the action of palvanil in the mouse gastrointestinal tract. Naunyn Schmiedebergs Arch. Pharmacol. **393**, 1357-1364
https://doi.org/10.1007/s00210-020-01829-x

Takayama Y, Uta D, Furue H, Tominaga M (2015): Pain-enhancing mechanism through interaction between TRPV1 and anoctamin 1 in sensory neurons. Proc. Natl. Acad. Sci. USA **112**, 5213-5218
https://doi.org/10.1073/pnas.1421507112

Toth A, Blumberg PM, Boczan J (2009): Anandamide and the vanilloid receptor (TRPV1). Vitam. Horm. **81**, 389-419
https://doi.org/10.1016/S0083-6729(09)81015-7

Townsley MI, Morisseau C, Hammock B, King JA (2010): Impact of epoxyeicosatrienoic acids in lung ischemia-reperfusion injury. Microcirculation **17**, 137-146

https://doi.org/10.1111/j.1549-8719.2009.00013.x
Tsuchiya Y, Fujita R, Saitou A, Wajima N, Aizawa F, Iinuma A (2014): [6]-Gingerol induces electrogenic sodium absorption in the rat colon via the capsaicin receptor TRPV1. J. Nutr. Sci. Vitaminol. (Tokyo) **60**, 403-407
https://doi.org/10.3177/jnsv.60.403
Tsuchiya Y, Kawamata K (2018): [6]-Gingerol induces amiloride-sensitive sodium absorption in the rat colon via the capsaicin receptor TRPV1 in colonic mucosa. J. Nutr. Sci. Vitaminol. (Tokyo) **64**, 287-291
https://doi.org/10.3177/jnsv.64.287
Tsushima H, Mori M (2006): Antidipsogenic effects of a TRPV4 agonist, 4alpha-phorbol 12,13-didecanoate, injected into the cerebroventricle. Am. J. Physiol. Regul. Integr. Comp. Physiol. **290**, R1736-1741
https://doi.org/10.1152/ajpregu.00043.2005
Vinayagam R, Xu B (2015): Antidiabetic properties of dietary flavonoids: a cellular mechanism review. Nutr. Metab. (Lond) **12**, 60
https://doi.org/10.1186/s12986-015-0057-7
Vizin RC, Scarpellini Cda S, Ishikawa DT, Correa GM, de Souza CO, Gargaglioni LH, Carrettiero DC, Bicego KC, Almeida MC (2015): TRPV4 activates autonomic and behavioural warmth-defence responses in Wistar rats. Acta Physiol. (Oxf) **214**, 275-289
https://doi.org/10.1111/apha.12477
Vogt-Eisele AK, Weber K, Sherkheli MA, Vielhaber G, Panten J, Gisselmann G, Hatt H (2007): Monoterpenoid agonists of TRPV3. Br. J. Pharmacol. **151**, 530-540
https://doi.org/10.1038/sj.bjp.0707245
Walker KM, Urban L, Medhurst SJ, Patel S, Panesar M, Fox AJ, McIntyre P (2003): The VR1 antagonist capsazepine reverses mechanical hyperalgesia in models of inflammatory and neuropathic pain. J. Pharmacol. Exp. Ther. **304**, 56-62
https://doi.org/10.1124/jpet.102.042010
Wang B, Wu Q, Liao J, Zhang S, Liu H, Yang C, Dong Q, Zhao N, Huang Z, Guo K, et al. (2019a): Propofol induces cardioprotection against ischemia-reperfusion injury via suppression of transient receptor potential Vanilloid 4 channel. Front. Pharmacol. **10**, 1150
https://doi.org/10.3389/fphar.2019.01150
Wang T, Wang Y, Kontani Y, Kobayashi Y, Sato Y, Mori N, Yamashita H (2008): Evodiamine improves diet-induced obesity in a uncoupling protein-1-independent manner: involvement of antiadipogenic mechanism and extracellularly regulated kinase/mitogen-activated protein kinase signaling. Endocrinology **149**, 358-366
https://doi.org/10.1210/en.2007-0467
Wang T, Wang Y, Yamashita H (2009): Evodiamine inhibits adipogenesis via the EGFR-PKCalpha-ERK signaling pathway. FEBS Lett. **583**, 3655-3659
https://doi.org/10.1016/j.febslet.2009.10.046
Wang X, Miyares RL, Ahern GP (2005): Oleoylethanolamide excites vagal sensory neurones, induces visceral pain and reduces short-term food intake in mice via capsaicin receptor TRPV1. J. Physiol. **564**, 541-547
https://doi.org/10.1113/jphysiol.2004.081844
Wang Z, Sun L, Yu H, Zhang Y, Gong W, Jin H, Zhang L, Liang H (2012): Binding mode pediction of evodiamine within vanilloid receptor TRPV1. Int. J. Mol. Sci. **13**, 8958-8969
https://doi.org/10.3390/ijms13078958
Wang Z, Zhou L, An D, Xu W, Wu C, Sha S, Li Y, Zhu Y, Chen A, Du Y, et al. (2019b): TRPV4-induced inflammatory response is involved in neuronal death in pilocarpine model of temporal lobe epilepsy in mice. Cell Death Dis. **10**, 386
https://doi.org/10.1038/s41419-019-1612-3
Wei J, Ching LC, Zhao JF, Shyue SK, Lee HF, Kou YR, Lee TS (2013): Essential role of transient receptor potential vanilloid type 1 in evodiamine-mediated protection against atherosclerosis. Acta Physiol. (Oxf) **207**, 299-307
https://doi.org/10.1111/apha.12005
Wei X, Gao P, Pu Y, Li Q, Yang T, Zhang H, Xiong S, Cui Y, Li L, Ma X, et al. (2017): Activation of TRPV4 by dietary apigenin antagonizes renal fibrosis in deoxycorticosterone acetate (DOCA)-salt-induced hypertension. Clin. Sci. (Lond) **131**, 567-581
https://doi.org/10.1042/CS20160780
Wissenbach U, Bodding M, Freichel M, Flockerzi V (2000): Trp12, a novel Trp related protein from kidney. FEBS Lett. **485**, 127-134
https://doi.org/10.1016/s0014-5793(00)02212-2
Woudenberg-Vrenken TE, Bindels RJ, Hoenderop JG (2009): The role of transient receptor potential channels in kidney disease. Nat. Rev. Nephrol. **5**, 441-449
https://doi.org/10.1038/nrneph.2009.100
Wu Q, Lu K, Zhao Z, Wang B, Liu H, Zhang S, Liao J, Zeng Y, Dong Q, Zhao N, et al. (2019): Blockade of transient receptor potential Vanilloid 4 enhances antioxidation after myocardial ischemia/reperfusion. Oxid. Med. Cell. Longev. **2019**, 7283683
https://doi.org/10.1155/2019/7283683
Xie H, Lu WC (2018): Inhibition of transient receptor potential vanilloid 4 decreases the expressions of caveolin-1 and caveolin-2 after focal cerebral ischemia and reperfusion in rats. Neuropathology **38**, 337-346
https://doi.org/10.1111/neup.12469
Xu H, Ramsey IS, Kotecha SA, Moran MM, Chong JA, Lawson D, Ge P, Lilly J, Silos-Santiago I, Xie Y, et al. (2002): TRPV3 is a calcium-permeable temperature-sensitive cation channel. Nature **418**, 181-186
https://doi.org/10.1038/nature00882
Xue H, Wang Y, MacCormack TJ, Lutes T, Rice C, Davey M, Dugourd D, Ilenchuk TT, Stewart JM (2018): Inhibition of transient receptor potential vanilloid 6 channel, elevated in human ovarian cancers, reduces tumour growth in a xenograft model. J. Cancer **9**, 3196-3207
https://doi.org/10.7150/jca.20639
Yamamoto-Kasai E, Yasui K, Shichijo M, Sakata T, Yoshioka T (2013): Impact of TRPV3 on the development of allergic dermatitis as a dendritic cell modulator. Exp. Dermatol. **22**, 820-824
https://doi.org/10.1111/exd.12273
Yao E, Zhang G, Huang J, Yang X, Peng L, Huang X, Luo X, Ren J, Huang R, Yang L, et al. (2019): Immunomodulatory effect of oleoylethanolamide in dendritic cells via TRPV1/AMPK activation. J. Cell. Physiol. **234**, 18392-18407
https://doi.org/10.1002/jcp.28474
Ye Y, Wang H, Chu JH, Chou GX, Yu ZL (2011): Activation of p38 MAPK pathway contributes to the melanogenic property of apigenin in B16 cells. Exp. Dermatol. **20**, 755-757

https://doi.org/10.1111/j.1600-0625.2011.01297.x
Yin Y, Dong Y, Vu S, Yang F, Yarov-Yarovoy V, Tian Y, Zheng J (2019): Structural mechanisms underlying activation of TRPV1 channels by pungent compounds in gingers. Br. J. Pharmacol. **176**, 3364-3377
https://doi.org/10.1111/bph.14766
Yoshioka T, Imura K, Asakawa M, Suzuki M, Oshima I, Hirasawa T, Sakata T, Horikawa T, Arimura A (2009): Impact of the Gly573Ser substitution in TRPV3 on the development of allergic and pruritic dermatitis in mice. J. Invest. Dermatol. **129**, 714-722
https://doi.org/10.1038/jid.2008.245
Yu LY, Shi WL, Guo XG (2017): Cardio-protective role of gingerol along with prominent anti-diabetic cardiomyopathy action in a streptozotocin-induced diabetes mellitus rat model. Cell J. **19**, 469-475
https://doi.org/10.22074/cellj.2017.4509
Yu SQ, Ma S, Wang DH (2018): Activation of TRPV1 Prevents salt-induced kidney damage and hypertension after renal ischemia-reperfusion injury in rats. Kidney Blood Press. Res. **43**, 1285-1296
https://doi.org/10.1159/000492412
Yuan XL, Zhang P, Liu XM, Du YM, Hou XD, Cheng S, Zhang ZF (2017): Cytological assessments and transcriptome profiling demonstrate that evodiamine inhibits growth and induces apoptosis in a renal carcinoma cell line. Sci. Rep. **7**, 12572
https://doi.org/10.1038/s41598-017-12918-y
Zhang Q, Henry G, Chen Y (2021): Emerging role of transient receptor potential vanilloid 4 (TRPV4) ion channel in acute and chronic itch. Int. J. Mol. Sci. **22**, 7591
https://doi.org/10.3390/ijms22147591
Zhang Y, Wang J, Wang C, Li Z, Liu X, Zhang J, Lu J, Wang D (2018): Pharmacological basis for the use of evodiamine in Alzheimer's disease: Antioxidation and antiapoptosis. Int. J. Mol. Sci. **19,** 1527
https://doi.org/10.3390/ijms19051527
Zhong G, Long H, Chen F, Yu Y (2021): Oxoglaucine mediates Ca(2+) influx and activates autophagy to alleviate osteoarthritis through the TRPV5/calmodulin/CAMK-II pathway. Br. J. Pharmacol. **178**, 2931-2947
https://doi.org/10.1111/bph.15466
Zou WB, Wang YC, Ren XL, Wang L, Deng SJ, Mao XT, Li ZS, Liao Z (2020): TRPV6 variants confer susceptibility to chronic pancreatitis in the Chinese population. Hum. Mutat. **41**, 1351-1357
https://doi.org/10.1002/humu.24032
Zubcevic L, Borschel WF, Hsu AL, Borgnia MJ, Lee SY (2019): Regulatory switch at the cytoplasmic interface controls TRPV channel gating. eLife **8**, e47746

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